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EFFECT OF DIETARY RESTRICTION ON TOXICOLOGY AND CARCINOGENESIS STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

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

FOREWORD

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

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

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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ABSTRACT

Studies were conducted to compare outcomes when four chemicals were evaluated under typical NTP bioassay conditions as well as under protocols employing dietary restriction. Specific experiments were designed to evaluate the effect of diet restriction on the sensitivity of the bioassay toward chemical-induced chronic toxicity and carcinogenicity and to evaluate the effect of weight-matched control groups on the sensitivity of the bioassays. Two chemicals, butyl benzyl phthalate and *t*-butylhydroquinone, were administered in feed; one chemical, salicylazosulfapyridine, was administered in corn oil by gavage; and one chemical, scopolamine hydrobromide trihydrate, was administered in distilled water by gavage. In each of four protocols, the effects of the chemical were assessed by a comparison between a group exposed to a single dose concentration of the study chemical and a nonexposed control group. F344/N rats and B6C3F$_1$ mice were fed NIH-07 diet either *ad libitum* or in amounts that restricted mean body weights according to the following design requirements. For the core bioassay, groups of 50 to 60 *ad libitum*-fed animals were allotted to a control group and three dosed groups for approximately 104 weeks or up to 128 weeks (*t*-butylhydroquinone study). The comparison between the control group and the group receiving the highest dose was used to represent the outcome of the bioassay under *ad libitum* feeding protocols. In a second comparison, outcomes from the group receiving the highest dose were compared with a weight-matched group of 50 to 60 untreated controls; the weight-matched controls received feed in amounts restricted so that the mean body weight matched the mean body weight of the dosed group.

Two additional groups of 48 to 60 animals (one control and one dosed group) were offered feed in amounts that limited the mean body weight of the control group to approximately 85% that of the controls fed *ad libitum* under the first protocol. Animals assigned to this dietary restriction paradigm were evaluated after 104 weeks or 130 weeks (*t*-butylhydroquinone). A fourth protocol was employed to evaluate whether an additional period of exposure (up to 1 year) would influence the neoplasm profile of animals fed a restricted diet. Two groups of approximately 50 animals (one control and one dosed group) in the butyl benzyl phthalate, salicylazosulfapyridine, and scopolamine hydrobromide trihydrate studies received restricted diets, as under the third protocol, for 3 years or until survival in either group was reduced to 20%.

Butyl benzyl phthalate caused an increased incidence of pancreatic acinar cell neoplasms in *ad libitum*-fed male rats relative to *ad libitum*-fed and weight-matched controls. This change did not occur in rats in the restricted feed protocol after 2 years; however, acinar cell adenomas were observed in three exposed, feed-restricted males at 30 months. Feed restriction is known to influence the incidence of pancreatic acinar cell neoplasms and may have prevented the full expression of this chemical-induced effect. Butyl benzyl phthalate also caused an increased incidence of urinary bladder neoplasms in female rats in the 32-month restricted feed protocol. The incidences of urinary bladder neoplasms were not significantly increased in female rats in any of the 2-year protocols, suggesting that the length of study, and not body weight, was the primary factor in the detection of this carcinogenic response.

Salicylazosulfapyridine caused an increased incidence of urinary bladder papillomas in male rats fed *ad libitum* relative to *ad libitum*-fed and weight-matched controls. This increase was associated with an increased incidence of urinary bladder calculi; the incidences of urinary bladder concretions, dilatation, and hyperplasia were also increased in dosed males. The incidences of urinary bladder papillomas and calculi were not increased in male rats receiving salicylazosulfapyridine that were fed restricted diets.

In male mice, salicylazosulfapyridine caused an increased incidence of liver neoplasms relative to the *ad libitum*-fed and weight-matched controls. This increase did not occur in the restricted feed protocols.

Liver neoplasms in mice are greatly influenced by body weight, and the marked mean body weight reduction observed in dosed male mice in the restricted feed protocols may have overridden the carcinogenic response.

Neither *t*-butylhydroquinone nor scopolamine hydrobromide trihydrate caused increased neoplasm incidences under any of the experimental protocols.

Results consistently show that feed restriction caused decreased incidences of neoplasms and nonneoplastic lesions at a variety of anatomic sites in control and dosed animals. Furthermore, the sensitivity of the bioassay to detect a carcinogenic response was altered by dietary restriction: two of the four chemicals caused increased incidences of neoplasms at three sites when evaluated under a standard *ad libitum* feeding protocol for 104 weeks. When control and dosed groups were subjected to dietary restriction, none of these three sites was detected as a target of carcinogenesis after 2 to 3 years. Rather, one different site of carcinogenesis was detected after 32 months. When dosed animals in the *ad libitum* feeding protocol were compared to weight-matched control groups, three sites were identified as targets of carcinogenesis and corresponded to the three sites discovered under the *ad libitum* feeding protocol. The magnitude of the response was greater when the weight-matched controls protocol was used. Dietary restriction of dosed and control animals decreased the sensitivity of these carcinogenesis bioassays.

Regarding the future use of dietary restriction regimens in long-term studies, only limited conclusions can be drawn because only four chemicals were evaluated and none of these proved to be a strong carcinogen. However, the results of these studies are consistent with previous findings that dietary restriction increases survival rates and decreases the incidences of neoplasms and nonneoplastic lesions at a variety of sites in rats and mice. This association between reduced body weights and decreased neoplasm incidences underlines the necessity that the doses selected for chronic studies not exceed "minimally toxic doses" so that no marked body weight reductions (or increases) will occur in the dosed groups. Such body weight changes complicate the detection of carcinogenic effects.

The following tables summarize and compare the findings from *ad libitum*-fed, weight-matched, and feed-restricted groups for each chemical.

A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the Dietary Restriction Study of Butyl Benzyl Phthalate

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (2 Years)	Restricted Feed (Lifetime[b])
MALE RATS				
Doses	0 or 12,000 ppm in feed	0 or 12,000 ppm in feed	0 or 12,000 ppm in feed	0 or 12,000 ppm in feed
Body weights[c]	417 g, 379 g	377 g, 379 g	355 g, 336 g	363 g, 340 g
Survival rates	28/50, 22/50	34/50, 22/50	34/50, 31/50	10/50, 13/50
Nonneoplastic effects	Pancreas (acinus): hyperplasia (4/50, 12/50)	Pancreas (acinus): hyperplasia (2/50, 12/50)	None	None
Neoplastic effects	Pancreas (acinus): adenoma (3/50, 10/50)	Pancreas (acinus): adenoma (0/50, 10/50)	None	None
FEMALE RATS				
Doses	0 or 24,000 ppm in feed	0 or 24,000 ppm in feed	0 or 24,000 ppm in feed	0 or 24,000 ppm in feed
Body weights	225 g, 199 g	203 g, 199 g	187 g, 175 g	189 g, 175 g
Survival rates	25/50, 29/50	41/50, 29/50	35/50, 39/50	10/50, 11/50
Nonneoplastic effects	Urinary bladder: transitional epithelium, hyperplasia (4/50, 10/50)	Urinary bladder: transitional epithelium, hyperplasia (0/50, 10/50)	Urinary bladder: transitional epithelium, hyperplasia (0/50, 14/50)	Urinary bladder: transitional epithelium, hyperplasia (0/49, 16/50)
Neoplastic effects	None	None	None	Urinary bladder: papilloma or carcinoma (1/49, 6/50)

[a] Includes exposed group from *ad libitum* feeding protocol
[b] Survival fell to 20% at 30 months (males) or 32 months (females)
[c] Body weight data are presented as the average of weekly mean body weights for weeks 14 through 52.

Summary of the Dietary Restriction Study of *t*-Butylhydroquinone

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (30 Months)
MALE RATS			
Doses	0 or 5,000 ppm in feed	0 or 5,000 ppm in feed	0 or 5,000 ppm in feed
Body weights[b]	425 g, 390 g	378 g, 390 g	365 g, 361 g
Survival rates	8/60, 14/60	12/60, 14/60	10/60, 22/60
Nonneoplastic effects	None	None	None
Neoplastic effects	None	None	None
FEMALE RATS			
Doses	0 or 5,000 ppm in feed	0 or 5,000 ppm in feed	0 or 5,000 ppm in feed
Body weights	232 g, 211 g	213 g, 211 g	196 g, 196 g
Survival rates	10/60, 17/60	22/60, 17/60	18/60, 24/60
Nonneoplastic effects	None	None	None
Neoplastic effects	None	None	None

[a] Includes exposed group from *ad libitum* feeding protocol
[b] Body weight data are presented as the average of weekly mean body weights for weeks 14 through 52.

Summary of the Dietary Restriction Studies of Salicylazosulfapyridine

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (2 Years)	Restricted Feed (30 Months)
MALE RATS				
Doses	0 or 337.5 mg/kg in corn oil by gavage	0 or 337.5 mg/kg in corn oil by gavage	0 or 337.5 mg/kg in corn oil by gavage	0 or 337.5 mg/kg in corn oil by gavage
Body weights[b]	410 g, 399 g	408 g, 399 g	346 g, 330 g	348 g, 329 g
Survival rates	35/50, 23/50	31/50, 23/50	34/51, 39/50	10/49, 24/50
Nonneoplastic effects	Urinary bladder: calculus (0/50, 27/50); concretion (0/50, 10/50); dilatation (0/50, 7/50); mucosa, hyperplasia (0/50, 41/50)	Urinary bladder: calculus (0/50, 27/50); concretion (0/50, 10/50); dilatation (1/50, 7/50); mucosa, hyperplasia (0/50, 41/50)	Urinary bladder: transitional epithelium, hyperplasia (0/51, 7/50)	Urinary bladder: transitional epithelium, hyperplasia (0/49, 8/49)
	Kidney: concretion (0/50, 33/50); hydronephrosis (0/50, 28/50); mineralization (3/50, 13/50); renal tubule dilatation (0/50, 11/50); transitional epithelium, hyperplasia (10/50, 43/50)	Kidney: concretion (0/50, 33/50); hydronephrosis (0/50, 28/50); mineralization (6/50, 13/50); renal tubule dilatation (1/50, 11/50); transitional epithelium, hyperplasia (5/50, 43/50)	Kidney: concretion (0/51, 22/50); mineralization (2/51, 11/50); transitional epithelium, hyperplasia (3/51, 18/50)	Kidney: concretion (0/49, 35/50); nephropathy (39/49, 48/50); transitional epithelium, hyperplasia (1/49, 37/50)
	Spleen: hematopoietic cell proliferation (14/50, 23/50); hemosiderin pigmentation (14/50, 30/50)	Spleen: hematopoietic cell proliferation (9/50, 23/50); hemosiderin pigmentation (20/50, 30/50)	Spleen: hemosiderin pigmentation (12/51, 35/50)	Spleen: hemosiderin pigmentation (15/49, 33/49)
Neoplastic effects	Urinary bladder: papilloma (0/50, 6/50)	Urinary bladder: papilloma (0/50, 6/50)	None	None

Summary of the Dietary Restriction Studies of Salicylazosulfapyridine (continued)

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (2 Years)	Restricted Feed (3 Years)
MALE MICE				
Doses	0 or 2,700 mg/kg in corn oil by gavage	0 or 2,700 mg/kg in corn oil by gavage	0 or 2,700 mg/kg in corn oil by gavage	0 or 2,700 mg/kg in corn oil by gavage
Body weights	45.0 g, 38.3 g	39.4 g, 38.3 g	39.2 g, 32.0 g	38.4 g, 32.2 g
Survival rates	40/50, 46/50	45/50, 46/50	42/52, 44/50	20/48, 34/50
Nonneoplastic effects	Liver: clear cell focus (2/50, 11/50); eosinophilic focus (6/50, 22/50)	Liver: clear cell focus (2/50, 11/50); eosinophilic focus (1/50, 22/50)	None	None
Neoplastic effects	Liver: hepatocellular adenoma (13/50, 42/50)	Liver: hepatocellular adenoma (8/50, 42/50)	None	None

[a] Includes dosed group from *ad libitum* feeding protocol
[b] Body weight data are presented as the average of weekly mean body weights for weeks 14 through 52.

Summary of the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (2 Years)	Restricted Feed (3 Years)
MALE MICE				
Doses	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage
Body weights[b]	45.0 g, 36.0 g	35.9 g, 36.0 g	31.3 g, 29.1 g	31.9 g, 29.2 g
Survival rates	40/50, 39/50	41/50, 39/50	49/50, 48/50	28/50, 37/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None
FEMALE MICE				
Doses	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage
Body weights	43.2 g, 34.8 g	32.3 g, 34.8 g	29.2 g, 27.8 g	29.9 g, 27.2 g
Survival rates	33/51, 38/51	36/50, 38/51	47/50, 44/50	20/50, 19/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None

[a] Includes dosed group from *ad libitum* feeding protocol
[b] Body weight data are presented as the average of weekly mean body weights for weeks 14 through 52.

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 the effect of dietary restriction on toxicity and carcinogenesis studies in F344/N rats and B6C3F$_1$ mice on 20 June 1995 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 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 20 June 1995, the draft Technical Report on the effect of dietary restriction on toxicology and carcinogenesis studies in F344/N rats and B6C3F$_1$ mice 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. F.W. Kari, NIEHS, introduced the studies by noting that it has been recognized since the turn of the century that body weight reductions or feed restriction with concomitant decreases in body weight results in increased longevity and decreased incidences of a variety of neoplasms and nonneoplastic lesions. He showed an abbreviated list of literature reports indicating that this phenomenon is not unique to a particular species, strain, sex, tumor site, or carcinogen. Dr. Kari then reviewed the primary objectives and overall design of the studies with the four chemicals, butyl benzyl phthalate, *t*-butylhydroquinone, salicylazosulfapyridine, and scopolamine hydrobromide trihydrate, and described the four basic comparisons made in the studies. Dr. Kari provided an overview of the results, discussing discordance or disparities between the outcomes under the various protocols. Dr. Kari then discussed neoplasm sites particularly with regard to biological plausibility of weight reduction versus chemical exposure as determinants of incidence for certain neoplasms.

Dr. Goldsworthy, the principal reviewer, stated that the experimental results were predictable, given the preexisting literature and especially the limited responses seen with the four chemicals. The study corroborates earlier evidence that increased survival and decreased incidences of certain neoplasms occur in studies with dietary restriction. His major criticism was that the selected chemicals limited the number of insights and conclusions that could be made. He said that both weak and strong carcinogens should have been used and that the chosen chemicals should have targeted tissues that are sensitive to dietary restriction and that have low spontaneous neoplasm incidences, where changes due to dietary restriction in untreated animals normally could not be observed. He said this was not the case in the current studies, and it was not clear how the chemicals were chosen. Dr. Goldsworthy pointed out that the studies were properly conducted, and he thought that some of the interesting insights of the studies were obtained by examining the limited responses or subtle differences that were detected. These insights were important because there is a need both in the literature and in future studies for determining the effects of dietary restriction on very small and variable changes after long-term chemical administration.

Dr. Weindruch, a special reviewer, prefaced his comments by saying they should be viewed as those of a gerontologist with a long-term interest in the retardation of aging and diseases by dietary restriction. His main scientific concern involved the lack of a precise definition of the *ad libitum* feed intake and that the methods described did not lend confidence that the intake was precisely measured. In his experience with many strains of rats and mice, *ad libitum* feed intake varied considerably between animals. Thus, with a target of 15% mean body weight reduction, there would be a large range of individual intake values, and the use of group housing added to this problem. Dr. Weindruch spoke against the stated implication that dietary restriction "works" by preventing obesity, and he spoke for diets enriched in vitamins, minerals, and amino acids so as to balance the intakes of dietary essentials among rodents fed different levels of calories and undergoing toxicology testing. Finally, he said that the scientific rationale for the choices of the test chemicals, doses, and routes of administration needs to be stated clearly in this Technical Report.

Dr. Hart, the second special reviewer, said his foremost criticism had to do with the choice of test chemicals, commenting that if he were going to test a new paradigm for conducting bioassays, he would not randomly choose four chemicals for evaluation. Dr. Hart commented that the use of a maximum tolerated dose determined in *ad libitum*-fed animals to calculate doses in animals fed restricted diets is misleading at best, as toxic endpoints can be more severely impacted by feed restriction than by carcinogenicity. He said that using weight-restricted controls fails to take into consideration the impact that

altered caloric intake can have on a number of key physiological, metabolic, biochemical, and molecular parameters, e.g., polydipsia, increased renal clearance, or alteration of key drug metabolizing enzymes in feed-restricted animals. Dr. Hart found disconcerting a perceived lack of concern by the investigators that the data, in his view, fly in the face of 50 years of similar studies, conducted in over 20 laboratories, using over 30 different model carcinogens, which have shown that in general, dietary restriction delays the onset or reduces the severity of neoplastic changes but does not completely eliminate such changes. He felt it is also important to note that where chemically induced neoplasms appeared to be eliminated in the current studies, the mean body weights of the dosed groups were significantly less than those of the corresponding feed-restricted control groups. This compromised the assumption that the neoplasms had really been eliminated. Dr. Hart stated that his main point and, as he viewed it, the main point of this Technical Report is that if dietary restriction is used, it should be moderate. Furthermore, to enhance interstudy reproducibility, a more physiological normalizer such as adjusting dietary intake to achieve an idealized body weight curve will be needed. He proposed that a small workshop be convened to discuss and decide what an idealized body weight curve is, how to achieve it, and how to monitor it. The findings and recommendations could be reported back to the NTP Board.

Dr. Kari acknowledged the suggestions concerned with using more idealized conditions. However, he stated that the primary purpose of the dietary restriction studies was to create a data base that would help to clarify results retrospectively when there were alterations in body weight (presumably due to primary or secondary chemical effects) and to guide the interpretation of prospective studies in which alterations in body weight are expected. Thus, the experimental conditions in these dietary restriction studies needed to mimic those used in the bioassays, such as group housing and standardized diet. He said there is a definite lack of consensus in the literature as to the best experimental conditions, and it is important to have a data base that allows interpretations of effects that are often subtle. With regard to the chemicals selected for study, Dr. Kari said selection was based in part on neoplasms and nonneoplastic lesions expected to be induced by the particular chemicals selected, based on the information available at the time of selection. The chemicals in this set of studies were representative of the majority of chemicals tested by NTP; indeed, potent multisite carcinogens are exceptional.

Dr. Hart noted that the fact that the dietary restriction paradigm works under diverse conditions suggests that body weight is a factor to be considered in making an evaluation of toxicity. He thought the NTP study could serve as a good baseline; however, better model compounds are needed to test the paradigm. Dr. Weindruch said the driving force is the caloric intake *per se*. Dr. Karol stated that it is important to look at the mechanisms of effects seen in dietary restriction studies.

Dr. K. Keenan, Merck Research Laboratories, said his laboratory is already using dietary restriction; however, it is called "proper nutrition" in studies with Sprague-Dawley rats. He said the percent restriction is irrelevant, but what is important is the number of kilocalories consumed per rat per day. He showed data from studies in his laboratory and the Wistar Institute correlating kilocalories per day the with the percentages of animals bearing neoplasms and neoplasms per rat. He stated that *ad libitum* feeding is one of the most adverse events to which an animal can be subjected. Dr. Keenan concluded by summarizing the positive effects (and the lack of adverse effects) of moderate dietary restriction on animal health, longevity, and spontaneous and chemical-induced neoplasm incidences at his laboratory.

Dr. Miller stated that she supported bringing together experts in nutrition, geriatrics, and toxicology to focus on the issues around dietary restriction and toxicology studies. Dr. G.W. Lucier, NIEHS, agreed it would be a good idea for the NTP to sponsor a workshop to address these issues. The findings and recommendations could be commented on in an open meeting, perhaps through the NTP Board. Chemical selection would be an important issue. Dr. J.R. Bucher, NIEHS, commented on the increasing body weights of F344/N rats in NTP studies and the debate about whether the NTP will have to go to a more expensive and technically difficult dietary restriction regimen for all of its studies. Dr. G.N. Rao, NIEHS, said that the key to stopping or reversing the upward drift of animal body weights is to go back to the production

colonies or to establish a colony to effect controls over growth patterns. Dr. A. Turturro, NCTR, observed that breeding back will not necessarily yield the same animal. He said the large variability between individual animals within studies must somehow be controlled or reduced. Dr. W.T. Allaben, NCTR, reported that as an outcome of a conference in 1994, the FDA has put together a draft white paper looking at the issue of diet, variability of test outcomes, and the value of caloric restriction in controlling for that variability; this document will soon be presented for public comment. Dr. Kari said it is important that false negatives and false positives are not masked. Returning to the concept of a workshop, Dr. Lucier commented that the impact of dietary restriction on additional toxicologic endpoints needs to be addressed. Dr. Hart said that the term "dietary control" might be preferable to "dietary restriction." He said the FDA would cosponsor a workshop, and Dr. Karol indicated that the Society of Toxicology would be interested in serving as a cosponsor. Dr. Keenan said the Society of Toxicologic Pathologists was planning a symposium in June 1996, and he suggested that better integration among sponsoring groups was needed.

INTRODUCTION

It is well documented that dietary restriction with concomitant body weight reduction significantly increases longevity and decreases the incidence of background and chemical-, physical-, and biological-induced tumors in rats and mice (Tannenbaum, 1940; Ross and Bras, 1973; Gross and Dreyfuss, 1984; Pollard *et al.*, 1984; Weindruch and Walford, 1988). The interrelationships between body weights, survival rates, and neoplasm incidences suggest that practical benefits as well as problematic confounding factors may be introduced when feed intake, body weights, or both are intentionally or unintentionally altered in toxicity and carcinogenicity bioassays for chemical hazard identification.

Typically, chronic studies involve feeding rodents *ad libitum* while exposing them to several concentrations of a chemical for up to 2 years. In dietary restriction paradigms, the feed presented to control and dosed animals is restricted to amounts that result in reduced body weights relative to those of animals fed *ad libitum*. Because diet restriction fosters leaner animals that live longer than more obese animals (Maeda *et al.*, 1985; Yu *et al.*, 1985), experiments conducted with dietary restriction may permit higher survival rates, thereby allowing more opportunities for chemical exposure and more time for treatment-related lesions to develop. It follows that these influences might enhance statistical power and increase the ability to resolve chemical effects in toxicity and carcinogenesis studies.

These potentially beneficial influences could be confounded by the propensity of dietary restriction to generally decrease tumor incidence. A chemical observed to be toxic or carcinogenic in animals fed *ad libitum* might not produce the same effects in diet-restricted or otherwise leaner animals. This discordance could cause difficulties in comparing tumor outcomes within and between studies. For example, observations collected for over a decade from the NTP show that some background tumor rates have comigrated with increasing body weights (Haseman and Rao, 1992; Haseman, 1993). Theoretically, comparisons between otherwise identical studies conducted several years apart could yield disparate results influenced primarily by the body weight of the animals.

STUDY RATIONALE

Chemical-associated body weight depression in 13-week toxicity studies is routinely used in conjunction with other factors to select exposures for 2-year toxicity and carcinogenicity studies. By design, the highest dose concentrations selected for some toxicity studies cause body weight depression. Comparisons in an experiment in which dose-related decreases in feed intake or body weight occur are potentially confounded by the influence of body weight on survival and disease processes. As fewer neoplasms would be expected in the leaner animals than in similarly dosed but heavier animals, carcinogenic activity might be underestimated.

To begin assessing the merits and limitations of different dietary regimens in bioassays, studies were undertaken to compare the outcomes of four chemicals evaluated under typical NTP bioassay conditions as well as under protocols including dietary restriction. Specifically, these experiments were designed to evaluate the effect of dietary restriction (to achieve a body weight reduction of approximately 15% compared to animals fed *ad libitum*) and to evaluate the effect of weight-matched control groups on the sensitivity of the bioassays. The results, based on these data, show a marked difference in bioassay outcome depending upon the protocol used.

Studies were designed to compare the toxicity and carcinogenicity of four chemicals, each evaluated under three (*t*-butylhydroquinone study only) or four different protocols. In each protocol, the effects of the chemical were assessed by a comparison between a group administered a single concentration of the chemical and a control group (Figure 1). The

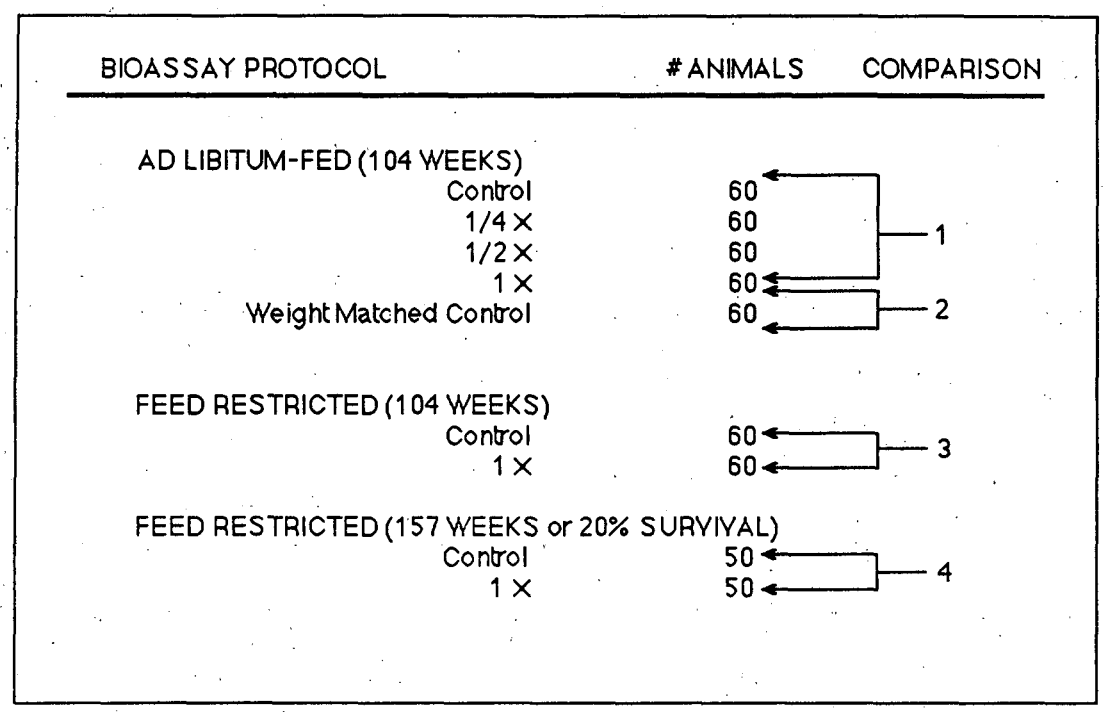


FIGURE 1
General Design of Feed Restriction Studies

concentrations were chosen based upon outcomes of 13-week studies conducted under *ad libitum* feeding protocols.

For the core bioassay, groups of about 60 animals, fed *ad libitum*, were allotted to control and dosed groups (nominally 0, 1/4X, 1/2X, and 1X) for approximately 104 weeks or up to 128 weeks (*t*-butylhydroquinone study). The comparison between the control group and the group receiving the highest dose (1X) was used to represent the outcome of the bioassay under *ad libitum* feeding protocols (Figure 1, Comparison 1).

In a second experiment, the 1X group was instead compared with a weight-matched group of 60 untreated controls (Figure 1, Comparison 2). The daily feed allotment for this control group was restricted so that the mean body weight matched the mean body weight of the 1X group.

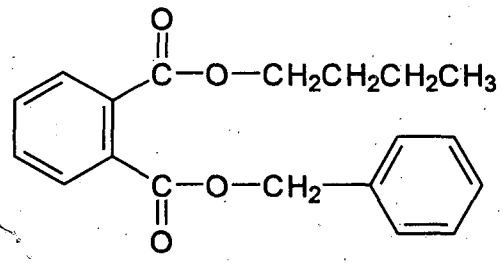
Two additional groups of about 60 animals (one control and one treated group) were offered feed in amounts that limited the mean body weight of the control group to approximately 85% that of the controls fed *ad libitum* under the first protocol. Animals assigned to this third dietary restriction paradigm were evaluated after 104 weeks (Figure 1, Comparison 3).

Because animals fed a restricted diet are expected to live longer than animals fed *ad libitum*, concurrent evaluations could result in comparisons at disproportionate times in their respective lifespans, thereby

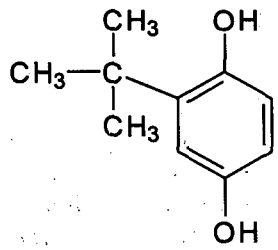
masking age-dependent effects. Therefore, a fourth protocol was employed to evaluate the influence of an additional year of chemical exposure on the neoplasm profile of animals fed a restricted diet. Two groups of 50 animals (one control and one dosed group) received restricted diets, as under the third protocol, for 3 years or until survival in either group was reduced to 20% (Figure 1, Comparison 4).

The protocols described above and shown in Figure 1 were used in the evaluation of four chemicals, butyl benzyl phthalate, salicylazosulfapyridine, *t*-butylhydroquinone, and scopolamine hydrobromide trihydrate. Dietary restriction protocols were not imposed across all dose groups of the four gender/species combinations typically used by the NTP; however, male and female rats and mice are represented in these studies, as are the two principal modes of oral exposure (dosed feed and gavage). Butyl benzyl phthalate was administered to male and female rats in feed. *t*-Butylhydroquinone was administered to F_1 male and female rats in feed; in this study, rats were exposed *in utero* and during lactation through F_0 (parental) exposure as well as during the adult stages of life. Salicylazosulfapyridine was administered to male rats and male mice by gavage in corn oil. Scopolamine hydrobromide trihydrate was administered to male and female mice by gavage in water. For the dosed feed studies, animals were offered a single concentration of the chemical (1X mg/kg body weight) blended in NIH-07 mash-type diet. For the gavage studies, a single concentration of the chemical (1X mg/mL vehicle) was mixed in corn oil or distilled water and administered to the animals at a dose of 5 mL corn oil or distilled water per kilogram body weight (rats) or 10 mL/kg (mice); control animals received the gavage vehicle only. Thus, for feed and gavage exposures, animals treated under *ad libitum* feeding or dietary restriction protocols received similar quantities of a given chemical on a body weight basis.

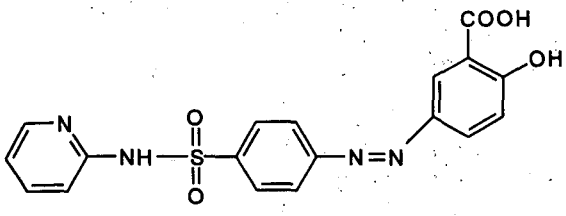
Butyl benzyl phthalate, *t*-butylhydroquinone, salicylazosulfapyridine, and scopolamine hydrobromide trihydrate (Figure 2) were administered in feed or by gavage for 2 years under the standard NTP *ad libitum* feeding protocol; these studies are presented in NTP Technical Reports 445, 457, 458, and 459 (NTP, 1997a,b,c,d). Additional animal groups were included to permit comparisons of the sensitivity of assays incorporating *ad libitum* feeding, matching the mean body weights of controls to those of dosed animals, and restricting the diet to achieve body weights that were approximately 85% those of controls fed *ad libitum*. The results of these comparisons are presented in this Technical Report.



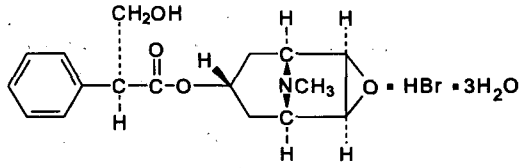
BUTYL BENZYL PHTHALATE
CAS No. 85-68-7
Chemical Formula: $C_{19}H_{20}O_4$
Molecular Weight: 312.39



***t*-BUTYLHYDROQUINONE**
CAS No. 1948-33-0
Chemical Formula: $C_{10}H_{14}O_2$
Molecular Weight: 166.22



SALICYLAZOSULFAPYRIDINE
CAS No. 599-79-1
Chemical Formula: $C_{18}H_{14}N_4O_5S$
Molecular Weight: 398.39



SCOPOLAMINE HYDROBROMIDE TRIHYDRATE
CAS No. 6533-68-2
Chemical Formula: $C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$
Molecular Weight: 438.31

FIGURE 2
Chemical Structures and Information for Compounds Used to Determine the Effects of Dietary Restriction on Toxicology and Carcinogenesis Studies in Rats and Mice

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Butyl benzyl phthalate was obtained from Chem Central (Kansas City, MO). *t*-Butylhydroquinone was obtained from U.O.P., Inc. (Des Plaines, IL). Salicylazosulfapyridine was obtained from Pharmacia, Inc. (Piscataway, NJ). Scopolamine hydrobromide trihydrate was obtained from Henley and Company, Inc. (New York, NY). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of these studies are on file at the National Institute of Environmental Health Sciences (NIEHS). Detailed information on the analyses of each chemical is also provided in the Technical Reports (NTP, 1997a,b,c,d).

The identity of each chemical was confirmed by infrared, ultraviolet, and nuclear magnetic resonance spectroscopy. The purity of each chemical was determined by elemental analysis, Karl Fischer water analysis, functional group titrations, and one or more chromatographic methods. Butyl benzyl phthalate and *t*-butylhydroquinone were each determined to have a purity of approximately 99%. Salicylazosulfapyridine was determined to have a purity of at least 98%. Scopolamine hydrobromide trihydrate was determined to have a purity of approximately 89% (with 11% water). The stability of each bulk chemical was monitored by the study laboratory; no degradation of any of the bulk chemicals was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Detailed information on dose preparation and analyses for butyl benzyl phthalate, *t*-butylhydroquinone, salicylazosulfapyridine, and scopolamine hydrobromide trihydrate are provided in the Technical Reports (NTP, 1997a,b,c,d). For the butyl benzyl phthalate and *t*-butylhydroquinone studies, the bulk chemical was mixed with feed. For the salicylazosulfapyridine studies, the bulk chemical was mixed with corn oil; scopolamine hydrobromide trihydrate was mixed with distilled water.

Dose formulations for each chemical were periodically analyzed by the study laboratories. Dose formulations were generally within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratories. Periodic analyses by the study laboratory of the corn oil vehicle used in the salicylazosulfapyridine studies demonstrated that peroxide levels were generally within the acceptable limit of 3 mEq/kg; two lots that were slightly outside the acceptable limit were replaced as quickly as possible.

STUDY DESIGNS

Diets and Feeding

NIH-07 open formula diet (4.0126 cal/g), obtained from Zeigler Brothers, Inc. (Gardners, PA) was offered either *ad libitum* or in restricted quantities. For the butyl benzyl phthalate and *t*-butylhydroquinone feed studies, a mash formulation was used; for the salicylazosulfapyridine and scopolamine hydrobromide trihydrate gavage studies, feed was processed into precise 1-gram pellets, thereby facilitating the presentation of restricted amounts of feed by eliminating the requirement for weighing.

For the core *ad libitum* feeding protocol (Figure 1, Comparison 1), the control and dosed groups were allowed unlimited access to feed. Apparent feed intake, as measured by disappearance of feed from feed hoppers (cage averages), was generally measured weekly for the first 26 weeks and monthly thereafter. In all studies, individual animal body weights were determined weekly for the first 13 weeks and monthly thereafter. Feed spillage was not determined; therefore, values reported for feed intake represent uncorrected indexes of actual consumption.

The daily feed allotment for the weight-matched control groups was restricted so that the mean body weights of these groups would match those of the corresponding 1X groups (Figure 1, Comparison 2). The first 2 weeks of each study were used to establish baseline averages for body weights and feed intake; consequently, dietary restriction was not imposed during this period. Thereafter, daily feed offerings to the weight-matched control groups were determined from the ratio of the mean body weight of dosed animals to that of the *ad libitum* controls multiplied by the feed intake of the *ad libitum* controls. For example, if the mean body weight of the 1X group was 90% that of the *ad libitum* controls at a given weighing period, the amount of feed presented to the weight-matched controls the following week was 90% that of the average feed intake of the *ad libitum* controls during the week of the given weighing. The new weekly target value for feed intake was then divided by seven to obtain a daily value, then multiplied by the number of animals per cage and rounded to the nearest gram. The resultant feed mass was put into the cage feed hoppers daily. Corrections for body weight changes, if necessary, were made weekly for the first 13 weeks and monthly thereafter. Corrections for changes in the number of rats per cage due to mortality were made as these changes occurred.

In an analogous manner, feed-restricted control groups (Figure 1, Comparisons 3 and 4) were offered a quantity of feed sufficient to produce a 15% reduction in body weight compared to the *ad libitum* controls. Feed-restricted, dosed groups were offered an amount of feed identical to that given the feed-restricted controls. This portion of each study was begun 2 weeks after the *ad libitum* feeding portion so that baseline values for body weights and feed intake could be established.

Mean body weight at 1 year was used as an indicator of the growth of the animals. By this time, the animals generally had had sufficient time to be influenced by adverse effects of the chemical but not to be greatly influenced by the variety of changes associated with morbidity and mortality in older animals (Turturro *et al.*, 1993).

Butyl Benzyl Phthalate Study

Groups of 60 male rats were fed diets containing 0 or 12,000 ppm butyl benzyl phthalate; groups of 60 female rats were fed diets containing 0 or 24,000 ppm butyl benzyl phthalate. Ten male and ten female rats from each group were evaluated at 15 months for histopathology and organ weights.

Male and female F344/N rats were obtained from Simonsen Laboratories (Gilroy, CA) for use in the dietary restriction study. Rats were quarantined for 10 or 11 days before the beginning of the study. Prior to the beginning of treatment, five male and five female rats were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program.

Rats were housed five per cage. Water was available *ad libitum*. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1.

t-Butylhydroquinone Study

The design of the *t*-butylhydroquinone study is similar to the design of the butyl benzyl phthalate study, except that 70 male and 70 female rats were used and the exposure began *in utero*. Five-week-old female F344/N rats were maintained for 5 to 7 weeks and were then housed two per cage. At this time, females began receiving 0 or 5,000 ppm *t*-butylhydroquinone in feed; after 2 weeks, one male rat was cohoused with each pair of females. When pregnancy was ascertained by vaginal smear, the females were housed individually; females continued to receive the same diet during pregnancy and through weaning of the pups. The litters were culled to four males and four females on day 4 postpartum. During the fourth week postpartum (from day 28 to day 35), two males and two females were selected at random from each litter until 70 males and 70 females per exposure concentration were selected. These rats received the

same concentration of *t*-butylhydroquinone as their dams had received for up to 130 weeks. At 3 months, 10 males and 10 females per group were evaluated for histopathology and organ weights.

Male and female F344/N rats used for breeding were obtained from Taconic Laboratory (Germantown, NY) for use in the dietary restriction study. Rats were quarantined for 18 days before the beginning of the study. Prior to the beginning of treatment, 10 male and 10 female rats were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program.

F_1 rats were housed five per cage. Water was available *ad libitum*. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1.

Salicylazosulfapyridine Studies

Groups of 60 male rats received 0 or 337.5 mg salicylazosulfapyridine per kilogram body weight in corn oil by gavage. Groups of 60 male mice received 0 or 2,700 mg/kg salicylazosulfapyridine in corn oil by gavage. Ten rats and ten mice from each group were evaluated at 15 months for histopathology and organ weights.

Male F344/N rats and $B6C3F_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the dietary restriction studies. Rats and mice were quarantined for 11 to 13 days before the beginning of the studies. Prior to the beginning of treatment, five rats and five mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were approximately 6 to 7 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program.

Rats were housed five per cage and mice were housed individually. Water was available *ad libitum*. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1.

Scopolamine Hydrobromide Trihydrate Study

Groups of up to 70 male and 70 female mice received 0 or 25 mg scopolamine hydrobromide trihydrate per kilogram body weight in deionized water by gavage. (Ten males and nine females in each group fed *ad libitum* were evaluated for scopolamine hydrobromide trihydrate levels in plasma and were discarded without further evaluation; results of these analyses are included in NTP, 1997a). Ten male and ten female mice from each group were evaluated at 15 months for histopathology and organ weights.

Male and female $B6C3F_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. Mice were quarantined for 14 days before the beginning of the studies. Prior to the beginning of treatment, five male and five female mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program.

Mice were housed individually. Water was available *ad libitum*. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights were recorded as described in Table 1.

A complete necropsy and microscopic examination were performed on rats and mice. At each interim evaluation necropsy, selected organs of rats and mice were weighed (see Table 1). 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 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

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. A quality assessment pathologist reviewed selected organs in each study. In the butyl benzyl phthalate study, the organs examined included the adrenal gland, kidney, liver, mammary gland (females), pancreas, pituitary gland (pars distalis), spleen, thyroid gland (males), urinary bladder, and uterus. In the *t*-butylhydroquinone study, the organs examined included the bone marrow (females), clitoral gland, forestomach (males), kidney (males), liver, mammary gland, nose, pituitary gland, preputial gland, spleen, and thyroid gland (males). In the salicylazosulfapyridine studies, selected neoplasms and nonneoplastic lesions were examined. In the scopolamine hydrobromide trihydrate study, the organs and tissues examined included the bone marrow (females), forestomach, liver, lung, kidney, pancreatic islets (males), pituitary gland (females), preputial gland, teeth (males), thyroid gland, and uterus.

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. Thus, the final diagnoses represent a consensus of quality assessment pathologists, the PWG chairperson, 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 diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals 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 chemical-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A3, B1, B3, C1, C3, D1, D3, E1, E3, F1, F3, G1, G3, H1, and H3 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A2, B2, C2, D2, E2, F2, G2, and H2) 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., skin, intestine, harderian gland, and mammary gland) 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 A2, B2, C2, D2, E2, F2, G2, and H2 also give the survival-adjusted tumor rate for each group and each site-specific tumor, i.e., the Kaplan-Meier estimate of the tumor incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

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

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test (Gart *et al.*, 1979), a procedure based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation of all studies and for lesions detected in animals treated under the restricted-feed protocols, the Fisher exact test, a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Organ and body weight data, which have approximately normal distributions, were analyzed with Student's *t*-test.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

Quality Assurance Methods

The studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. 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, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

TABLE 1
Experimental Design and Materials and Methods in the Study of the Effect of Dietary Restriction on Toxicology and Carcinogenesis Studies in F344/N Rats and B6C3F$_1$ Mice

Butyl Benzyl Phthalate	*t*-Butylhydroquinone	Salicylazo-sulfapyridine	Scopolamine Hydrobromide Trihydrate
Study Laboratory			
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Battelle Columbus (Columbus, OH)
Strain and Species			
Rats: F344/N	Rats: F344/N	Rats: F344/N males Mice: B6C3F$_1$ males	Mice: B6C3F$_1$
Animal Source			
Simonsen Laboratories, Inc. (Gilroy, CA)	F$_0$: Taconic Laboratory (Germantown, NY) F$_1$: Bred at study laboratory	Simonsen Laboratories, Inc. (Gilroy, CA)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies			
10-11 days	F$_0$: 18 days	Rats: 11-12 days Mice: 11-13 days	14 days
Average Age When Studies Began			
6 weeks	F$_1$ *ad libitum*-fed and weight-matched: 5 weeks F$_1$ feed-restricted: 5 weeks	6 to 7 weeks	6 weeks
Date of First Dose			
Ad libitum-fed and weight-matched: 26 June 1989 Feed-restricted: 17 July 1989	F$_1$ *ad libitum*-fed and weight-matched: 29 January 1990 F$_1$ feed-restricted: 12 February 1990	*Ad libitum*-fed and weight-matched: 12 December 1988 (rats), 3 January 1989 (mice) Feed-restricted: 27 December 1988 (rats), 16 January 1989 (mice)	*Ad libitum*-fed and weight-matched: 22 September 1988 Feed-restricted: 6 October 1988
Duration of Dosing			
Ad libitum-fed and weight-matched: 105 (male) or 106 weeks (female) (7 days/week) Feed-restricted: 105 weeks (male and female), 128 weeks (male), or 140 weeks (female) (7 days/week)	F$_1$ *ad libitum*-fed and weight-matched: 122 (male) or 128 weeks (female) (7 days/week) F$_1$ feed-restricted: 130 weeks (7 days/week)	*Ad libitum*-fed and weight-matched: 103 weeks (5 days/week) Feed-restricted: 104, 130 (rats), or 156 weeks (mice) (5 days/week)	*Ad libitum*-fed and weight-matched: 104 weeks (5 days/week) Feed-restricted: 104 or 157 weeks (5 days/week)

TABLE 1
Experimental Design and Materials and Methods in the Study of the Effect of Dietary Restriction on Toxicology and Carcinogenesis Studies in F344/N Rats and B6C3F$_1$ Mice (continued)

Butyl Benzyl Phthalate	*t*-Butylhydroquinone	Salicylazo-sulfapyridine	Scopolamine Hydrobromide Trihydrate
Necropsy Dates			
Ad libitum-fed and weight-matched: 15-Month interim evaluation - 26-27 September 1990 Termination - 24-26 June (male) and 1-3 July (female) 1991 Feed-restricted: 15-Month interim evaluation - 16 October 1990 2-Year termination - 15-17 July 1991 30/32-Month termination - 30 December 1991 (male) and 19 March 1992 (female)	F$_1$ *ad libitum*-fed and weight-matched: 3-Month interim evaluation - 30 April (male) and 1 May (female) 1990 Termination - 3 June (male) and 14-15 July (female) 1992 F$_1$ feed-restricted: 3-Month interim evaluation - 14 May 1990 Termination - 10-12 August 1992	*Ad libitum*-fed and weight-matched: 15-Month interim evaluation - 12-13 March 1990 (rats) 3 April 1990 (mice) Termination - 10-14 December 1990 (rats) 31 December 1990- 4 January 1991 (mice) Feed-restricted: 15-Month interim evaluation - 27 March 1990 (rats) 17 April 1990 (mice) 2-Year termination - 26-27 December 1990 (rats) 14-15 January 1991 (mice) 30-Month/3-year termination - 24 June 1991 (rats) 13 January 1992 (mice)	*Ad libitum*-fed and weight-matched: 15-Month interim evaluation - 21-22 December 1989 Termination - 17-20 September (male) and 17-21 September (female) 1990 Feed-restricted: 15-Month interim evaluation - 4 January 1990 2-Year termination - 27-28 September 1990 3-Year termination - 26-27 September 1991
Average Age at Necropsy			
Ad libitum-fed and weight-matched: 110 weeks (male); 111 weeks (female) Feed-restricted: 110 or 134 weeks (male); 110 or 145 weeks (female)	F$_1$ *ad libitum*-fed and weight-matched: 127 weeks (male); 133 weeks (female) F$_1$ feed-restricted: 135 weeks	*Ad libitum*-fed and weight-matched: 110-112 weeks Feed-restricted: 110 or 136 weeks (rats) 110 or 162 weeks (mice)	*Ad libitum*-fed and weight-matched: 110 weeks Feed-restricted: 110 or 162 weeks
Size of Study Groups			
15-Month interim evaluation - 10 males and 10 females Termination - 50 males and 50 females	F$_1$: 3-Month interim evaluation - 10 males and 10 females F$_1$: Termination - 60 males and 60 females	15-Month interim evaluation - 10 males Termination - 50 males	15-Month interim evaluation - 10 males and 10 females Termination - 50 males and 50 females

TABLE 1
Experimental Design and Materials and Methods in the Study of the Effect of Dietary Restriction on Toxicology and Carcinogenesis Studies in F344/N Rats and B6C3F$_1$ Mice (continued)

Butyl Benzyl Phthalate	*t*-Butylhydroquinone	Salicylazo-sulfapyridine	Scopolamine Hydrobromide Trihydrate
Method of Distribution			
Animals were distributed randomly into groups of approximately equal initial mean body weight.	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study
Animals per Cage			
5	F_1: 5	Rats: 5 Mice: 1	1
Method of Animal Identification			
Tail tattoo	Tail tattoo	Rats: Tail tattoo Mice: Toe clip	Toe clip
Diet			
NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed daily	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study, changed twice weekly	NIH-07 open formula pellets (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum* and changed weekly, or 1-gram pellets, available in fixed amounts and changed daily
Water Distribution			
Tap water (Birmingham municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study	Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*
Cages			
Polycarbonate (Lab Products, Inc., Maywood, NJ), changed twice weekly	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study, except changed weekly for mice	Polycarbonate (Lab Products, Inc., Maywood, NJ), rotated every 2 weeks
Bedding			
Sani-Chips® hardwood chips (P.J. Murphy Forest Products, Montville, NJ), changed twice weekly	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study, except changed weekly for mice	Same as butyl benzyl phthalate study, except changed weekly

TABLE 1
Experimental Design and Materials and Methods in the Study of the Effect of Dietary Restriction on Toxicology and Carcinogenesis Studies in F344/N Rats and B6C3F$_1$ Mice (continued)

Butyl Benzyl Phthalate	*t*-Butylhydroquinone	Salicylazo-sulfapyridine	Scopolamine Hydrobromide Trihydrate
Cage Filters			
Remay® spun-bonded polyester (Andico, Birmingham, AL), changed every 2 weeks	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study	DuPont 2024 spun-bonded polyester (Snow Filtration, Cincinnati, OH), changed every 2 weeks
Racks			
Stainless steel (Lab Products, Inc., Maywood, NJ), changed every 2 weeks	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study	Same as butyl benzyl phthalate study
Animal Room Environment			
Ad libitum-fed and weight-matched: Temperature - 13.1° to 29.2° C Relative humidity - 22% to 89% Feed-restricted: Temperature - 13.3° to 28.6° C Relative humidity - 18% to 91% All groups: Fluorescent light - 12 hours/day Room air - minimum of 10 changes/hour	F$_1$ *ad libitum*-fed and weight-matched: Temperature - 17.3° to 28.8° C Relative humidity - 17% to 85% F$_1$ feed-restricted: Temperature - 14.2° to 26.7° C Relative humidity - 19% to 90% All F$_1$ groups: Fluorescent light - 12 hours/day Room air - minimum of 10 changes/hour	*Ad libitum*-fed and weight-matched: Temperature - 13.5° to 25.9° C (rats), 13.4° to 26.3° C (mice) Relative humidity - 20% to 90% (rats), 15% to 87% (mice) Feed-restricted: Temperature - 16.2° to 29.4° C (rats), 17.3° to 29.7° C (mice) Relative humidity - 21% to 90% (rats), 22% to 85% (mice) All groups: Fluorescent light - 12 hours/day Room air - minimum of 10 changes/hour	*Ad libitum*-fed and weight-matched: Temperature - 20.0° to 24.4° C Relative humidity - 30% to 73% Feed-restricted: Temperature - 18.3° to 26.7° C Relative humidity - 15% to 79% All groups: Fluorescent light - 12 hours/day Room air - minimum of 10 changes/hour
Doses			
0 or 12,000 ppm (males) and 0 or 24,000 ppm (females) in feed that was available *ad libitum* or in restricted amounts	0 or 5,000 ppm in feed, available *ad libitum* or in restricted amounts	Rats: 0 or 337.5 mg/kg body weight in corn oil by gavage at a volume of 5 mL/kg body weight Mice: 0 or 2,700 mg/kg body weight in corn oil by gavage at a volume of 10 mL/kg body weight	0 or 25 mg/kg body weight in deionized water by gavage at a volume of 10 mL/kg body weight

TABLE 1
Experimental Design and Materials and Methods in the Study of the Effect of Dietary Restriction on Toxicology and Carcinogenesis Studies in F344/N Rats and B6C3F$_1$ Mice (continued)

Butyl Benzyl Phthalate	*t*-Butylhydroquinone	Salicylazo-sulfapyridine	Scopolamine Hydrobromide Trihydrate
Type and Frequency of Observation			
Observed twice daily. Animals were weighed and clinical findings were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies. Feed consumption by rats fed *ad libitum* was recorded weekly by cage for 26 weeks and monthly thereafter; feed consumption for other groups was recorded daily for 15 months and monthly thereafter.	F_1: Observed twice daily. Animals were weighed and clinical findings were recorded initially; on lactation days 4, 11, 18, and 28; at the beginning of adult exposures; weekly for 13 weeks; monthly thereafter; and at the end of the studies. Feed consumption by control rats fed *ad libitum* and weight-matched controls was recorded weekly by cage for 26 weeks and monthly thereafter. Feed consumption for restricted-feed groups was recorded weekly for 36 weeks and monthly thereafter. Feed consumption for other groups was recorded monthly.	Observed twice daily. Animals were weighed and clinical findings were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies. Feed consumption by control rats (by cage) and mice (by animal) fed *ad libitum* was recorded weekly for 26 weeks and monthly thereafter. Feed consumption by other rat groups was recorded monthly. Feed consumption by weight-matched and feed restricted mouse groups was recorded daily for 21 months, then 5 days a week for 1 week each month. For dosed mice fed *ad libitum*, feed consumption was recorded 5 days a week for 1 week each month.	Observed twice daily. Clinical findings were recorded initially, monthly thereafter, and at the end of the studies. Animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies. Feed consumption was not recorded.
Method of Sacrifice			
CO_2 asphyxiation	CO_2 asphyxiation	CO_2 asphyxiation	Anesthetization with CO_2:O_2 followed by exsanguination by cardiac puncture (for groups with blood analyses); CO_2:O_2 asphyxiation (all other groups)

TABLE 1
Experimental Design and Materials and Methods in the Study of the Effect of Dietary Restriction on Toxicology and Carcinogenesis Studies in F344/N Rats and B6C3F$_1$ Mice (continued)

Butyl Benzyl Phthalate	*t*-Butylhydroquinone	Salicylazo-sulfapyridine	Scopolamine Hydrobromide Trihydrate
Necropsy			
Necropsy was performed on all rats. Organs weighed at the 15-month interim evaluation were right epididymis, right kidney, liver, and right testis.	Necropsy was performed on all F$_1$ rats. Organs weighed at the 3-month interim evaluation were right epididymis, right kidney, liver, and right testis.	Necropsy was performed on all animals. Organs weighed at the 15-month interim evaluations were right kidney, liver, spleen, right testis, and right thyroid gland.	Necropsy was performed on all mice. Organs weighed at the 15-month interim evaluation were right epididymis, right kidney, liver, and right testis.
Histopathology			
Complete histopathology was performed on all rats. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, eyes (if grossly abnormal), heart, kidney, large intestine (cecum, colon, and rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pharynx (if grossly abnormal), pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, spleen, small intestine (duodenum, jejunum, and ileum), spinal cord and sciatic nerve (if neurologic signs were present), stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathology was performed on all rats. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, eyes (if grossly abnormal), heart, kidney, large intestine (cecum, colon, and rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pharynx (if grossly abnormal), pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, spleen, small intestine (duodenum, jejunum, and ileum), spinal cord and sciatic nerve (if neurologic signs were present), stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, epididymis, esophagus, eyes (if grossly abnormal), gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, pancreas, parathyroid gland, pharynx (if grossly abnormal), pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, spleen, small intestine (duodenum, jejunum, and ileum), spinal cord and sciatic nerve (if neurologic signs were present), stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, and urinary bladder.	Complete histopathology was performed on all mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, eyes (if grossly abnormal), gallbladder, heart, kidney, large intestine (cecum, colon, and rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pharynx (if grossly abnormal), pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, spleen, small intestine (duodenum, jejunum, and ileum), spinal cord and sciatic nerve (if neurologic signs were present), stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

BUTYL BENZYL PHTHALATE FEED STUDY

AD LIBITUM FEEDING AND WEIGHT-MATCHED CONTROLS PROTOCOLS

Survival

Estimates of 2-year survival probabilities for male and female rats fed *ad libitum* and the weight-matched control rats are shown in Table 2 and in the Kaplan-Meier survival curves in Figure 3. The survival rates of exposed male and female rats were similar to those of the controls fed *ad libitum* but less than those of the weight-matched controls.

Body Weights

Mean body weights are given in Figure 4 and in Appendix J, Table J1. At 1 year, the mean body weight of exposed males was approximately 92% that of the controls fed *ad libitum* and 104% that of the weight-matched controls. The mean body weight of females in the 24,000 ppm group was 80% that of the controls fed *ad libitum* and 108% that of the weight-matched controls at 1 year. From 1 year through the end of the study, the mean body weight of exposed males remained within 8% that of the controls fed *ad libitum* and within 7% that of the weight-matched controls; the mean body weight of exposed females fell to 73% that of the controls fed *ad libitum* by the end of the study, but remained within 9% that of the weight-matched controls through the end of the study, indicating that the weight-matching protocol was successfully employed.

Feed Consumption, Clinical Findings, and Organ Weights

Feed consumption by exposed males was similar to that by the controls during the study; females in the 24,000 ppm group consumed less feed than the *ad libitum*-fed controls from week 38 through the end of the study (Table K1). There were no clinical findings related to butyl benzyl phthalate administration.

The absolute and relative right kidney and liver weights of exposed males and females were greater than those of the weight-matched controls (Table I1a).

TABLE 2
Survival of Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
Male			
Animals initially in study	60	60	60
15-Month interim evaluation[a]	10	10	10
Moribund	19	15	26
Natural deaths	3	1	2
Animals surviving to study termination	28	33	22
Other[a]		1	
Percent probability of survival at the end of study[b]	57	68	44
Mean survival (days)[c]	625	648	632
Survival analysis[d]			P=0.520
Survival analysis[e]			P=0.036
	***Ad Libitum*-Fed Control**	**Weight-Matched Control**	**24,000 ppm**
Female			
Animals initially in study	60	60	60
15-Month interim evaluation[a]	10	10	10
Moribund	23	7	20
Natural deaths	2	2	1
Animals surviving to study termination	25	41	29
Percent probability of survival at the end of study	50	82	59
Mean survival (days)	651	672	645
Survival analysis			P=0.759N
Survival analysis			P=0.011

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The results of the life table pairwise comparisons (Cox, 1972) with the controls fed *ad libitum* are in the exposed group column. A lower mortality in the exposed group is indicated by N.
[e] Result of life table pairwise comparison with the weight-matched controls

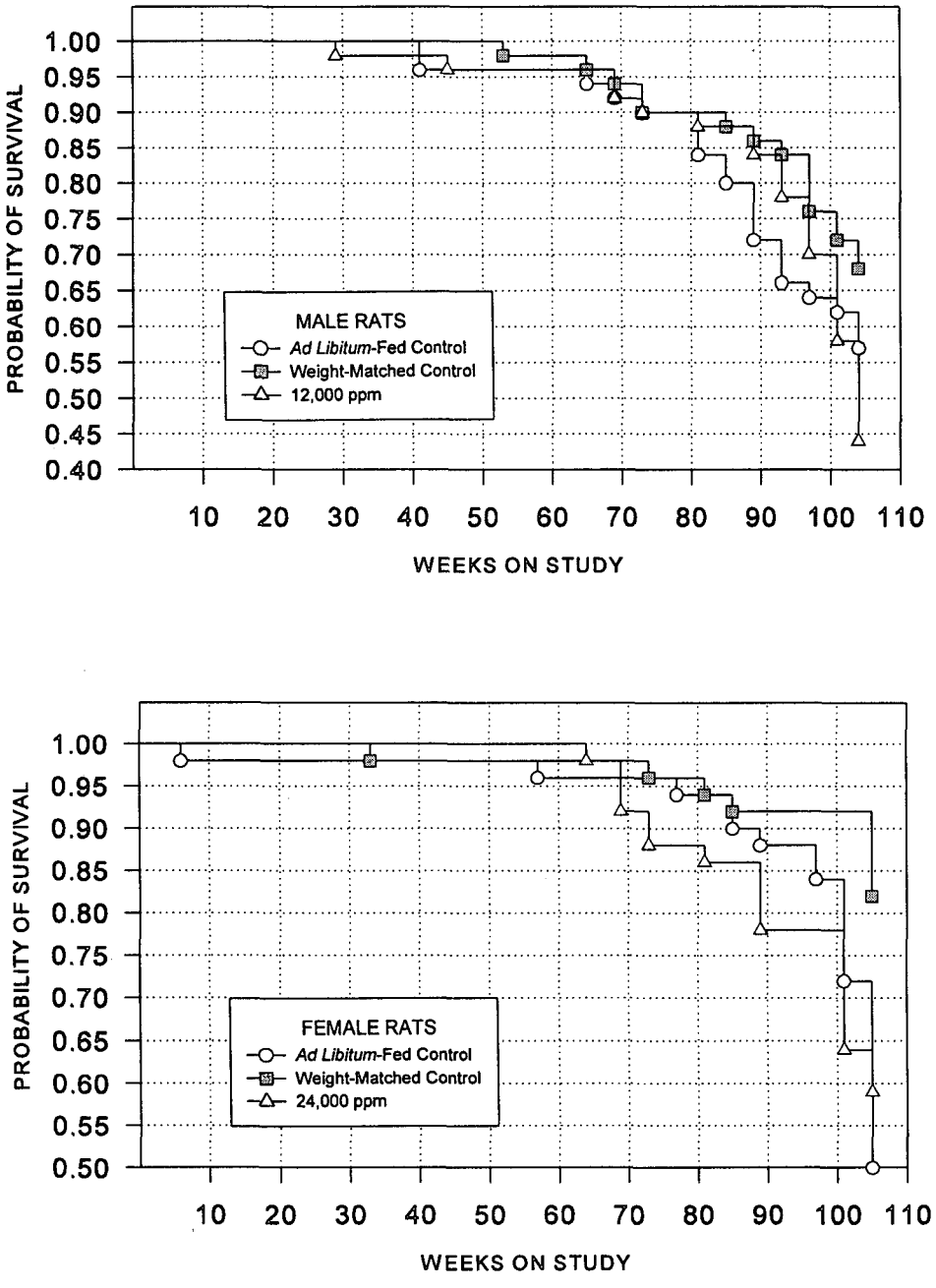


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Rats Administered Butyl Benzyl Phthalate in Feed for 2 Years: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

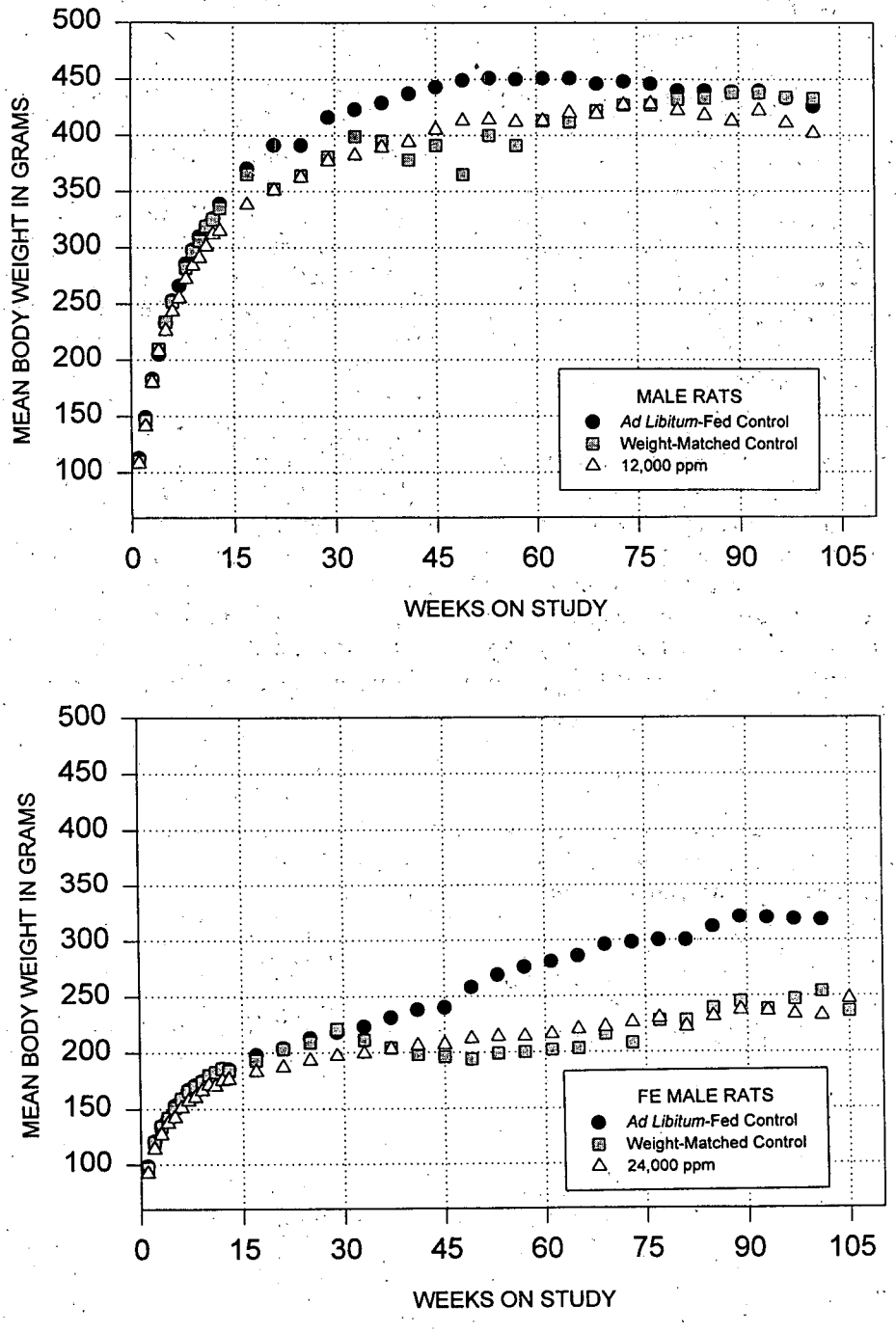


FIGURE 4
Growth Curves for Male and Female Rats Administered Butyl Benzyl Phthalate in Feed for 2 Years: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and of neoplasms and/or nonneoplastic lesions of the pancreas, adrenal medulla, urinary bladder, preputial gland, and mammary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A for male rats and Appendix B for female rats. Pathologic descriptions of neoplasms and nonneoplastic lesions occurring in rats in the butyl benzyl phthalate study are provided in NTP Technical Report 458 (NTP, 1997c).

Pancreas: The incidence of adenoma of the acinus was significantly greater in exposed males than in the *ad libitum*-fed or weight-matched controls (Tables 3 and A2a). No adenomas occurred in the weight-matched controls; however, one male each in the weight-matched control and 12,000 ppm groups had an acinar cell carcinoma. The incidence of adenoma in exposed males exceeded the overall NTP historical control incidence of these neoplasms in untreated control male rats fed *ad libitum*; no incidences of pancreatic carcinomas were recorded for historical control males. The incidence of hyperplasia of the pancreatic acinus was greater in exposed males than in the *ad libitum*-fed or weight-matched controls.

Adrenal Medulla: Exposed males had significantly greater combined incidences of benign or malignant pheochromocytoma than those in the weight-matched controls (Tables 3 and A2a). The exposed group incidences of these neoplasms were similar to those in the controls fed *ad libitum*. The incidence of benign pheochromocytoma and the combined incidence of benign or malignant pheochromocytoma in exposed males were within the historical control range for these neoplasms in untreated males fed *ad libitum*; the incidences of these neoplasms in the weight-matched controls fell below the historical control range for untreated males. The incidence of hyperplasia was greater in exposed males than in the *ad libitum*-fed or weight-matched controls (Table 3).

TABLE 3
Incidences of Neoplasms and Nonneoplastic Lesions of the Pancreas and Adrenal Medulla in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
Pancreas, Acinus[a]	50	50	50
Focal Hyperplasia[b]	4	2	12
Adenoma			
Overall rate[c]	3/50 (6%)	0/50 (0%)	10/50 (20%)
Adjusted rate[d]	10.7%	0.0%	41.0%
Terminal rate[e]	3/28 (11%)	0/33 (0%)	8/22 (36%)
First incidence (days)	729 (T)	–[f]	709
Logistic regression test[g]			P=0.016
Logistic regression test[h]			P<0.001
Carcinoma			
Overall rate	0/50 (0%)	1/50 (2%)	1/50 (2%)

(continued)

TABLE 3
Incidences of Neoplasms and Nonneoplastic Lesions of the Pancreas and Adrenal Medulla in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
Pancreas, Acinus (continued)			
Adenoma or Carcinoma[i]			
Overall rate	3/50 (6%)	1/50 (2%)	11/50 (22%)
Adjusted rate	10.7%	3.0%	42.7%
Terminal rate	3/28 (11%)	1/33 (3%)	8/22 (36%)
First incidence (days)	729 (T)	730 (T)	674
Logistic regression test			P=0.014
Logistic regression test			P<0.001
Adrenal Medulla	50	50	50
Hyperplasia	6	6	12
Benign Pheochromocytoma			
Overall rate	9/50 (18%)	3/50 (6%)	8/50 (16%)
Adjusted rate	28.2%	8.5%	25.4%
Terminal rate	6/28 (21%)	2/33 (6%)	3/22 (14%)
First incidence (days)	607	678	639
Logistic regression test			P=0.475N
Logistic regression test			P=0.086
Malignant Pheochromocytoma			
Overall rate	2/50 (4%)	1/50 (2%)	2/50 (4%)
Benign or Malignant Pheochromocytoma[j]			
Overall rate	10/50 (20%)	3/50 (6%)	10/50 (20%)
Adjusted rate	30.1%	8.5%	33.3%
Terminal rate	6/28 (21%)	2/33 (6%)	5/22 (23%)
First incidence (days)	607	678	639
Logistic regression test			P=0.573N
Logistic regression test			P=0.028

(T)Terminal sacrifice
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Number of animals with neoplasms per number of animals with tissue examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] Not applicable; no neoplasms in animal group
[g] In the exposed group column are the P values corresponding to the pairwise comparisons between the *ad libitum*-fed controls and the exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in the exposed group is indicated by N.
[h] Result of pairwise comparison between the weight-matched controls and the exposed group
[i] Historical incidence for 2-year NTP feed studies with untreated control groups fed *ad libitum* (mean ± standard deviation): 19/1,191 (1.6% ± 2.4%); range, 0%-10%.
[j] Historical incidence: 398/1,182 (33.7% ± 10.4%); range, 12%-63%.

Urinary Bladder: Exposed females had a greater incidence of hyperplasia of the urinary bladder transitional epithelium (10/50) than did the *ad libitum*-fed controls (4/50) or the weight-matched controls (0/50) (Table B3a).

Mononuclear Cell Leukemia: The incidences of mononuclear cell leukemia in exposed males and females were greater than those in the weight-matched controls (Tables 4, A2a, and B2a) but similar to the incidences in the controls fed *ad libitum* and within the historical control ranges for leukemia (all types) in untreated rats.

TABLE 4
Incidences of Mononuclear Cell Leukemia in Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
Male			
Mononuclear Cell Leukemia[a]			
Overall rate[b]	31/50 (62%)	15/50 (30%)	30/50 (60%)
Adjusted rate[c]	71.8%	34.9%	65.6%
Terminal rate[d]	16/28 (57%)	6/33 (18%)	7/22 (32%)
First incidence (days)	479	422	180
Life table test[e]			P=0.478
Life table test[f]			P=0.002
	***Ad Libitum*-Fed Control**	**Weight-Matched Control**	**24,000 ppm**
Female			
Mononuclear Cell Leukemia[g]			
Overall rate	21/50 (42%)	13/50 (26%)	19/50 (38%)
Adjusted rate	51.7%	28.6%	46.1%
Terminal rate	7/25 (28%)	9/41 (22%)	8/29 (28%)
First incidence (days)	368	551	452
Life table test			P=0.398N
Life table test			P=0.034

[a] Historical incidence for 2-year NTP feed studies with untreated control groups fed *ad libitum* (mean ± standard deviation): 562/1,203 (46.7% ± 10.7%); range, 18%-62%. Includes lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemias.
[b] Number of animals with neoplasms per number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the exposed group column are the P values corresponding to the pairwise comparisons between the *ad libitum*-fed controls and the exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. A lower incidence in the exposed group is indicated by N.
[f] Result of pairwise comparison between the weight-matched controls and the exposed group
[g] Historical incidence: 322/1,202 (26.8% ± 9.0%); range, 14%-52%. Includes lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemias.

Preputial Gland: The combined incidence of preputial gland adenomas and carcinomas was significantly less in exposed males than in the controls fed *ad libitum* and the weight-matched controls (Tables 5 and A2a); these neoplasms occurred in five controls fed *ad libitum* and in six weight-matched controls, but in no exposed males.

Mammary Gland: The incidence of mammary gland fibroadenomas and the combined incidence of fibroadenoma, adenoma, or carcinoma in exposed females were significantly less than those in the controls fed *ad libitum*; the incidences of these neoplasms in exposed females were similar to those in weight-matched control females (Tables 5 and B2a). Two *ad libitum*-fed control females with fibroadenomas also had adenomas; another control female with fibroadenoma and one additional control female also had carcinomas. Additionally, exposed females had a lower incidence of mammary gland hyperplasia than that of the controls fed *ad libitum*; the incidence in exposed females was greater than that in the weight-matched controls (Table 5).

TABLE 5
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
Male			
Preputial Gland			
Adenoma			
Overall rate[a]	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted rate[b]	12.8%	8.5%	0.0%
Terminal rate[c]	2/28 (7%)	2/33 (6%)	0/22 (0%)
First incidence (days)	644	678	–[d]
Logistic regression test[e]			P=0.059N
Logistic regression test[f]			P=0.136N
Carcinoma			
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.7%	8.2%	0.0%
Terminal rate	0/28 (0%)	2/33 (6%)	0/22 (0%)
First incidence (days)	614	607	–
Logistic regression test			P=0.504N
Logistic regression test			P=0.124N
Adenoma or Carcinoma[g]			
Overall rate	5/50 (10%)	6/50 (12%)	0/50 (0%)
Adjusted rate	15.1%	16.4%	0.0%
Terminal rate	2/28 (7%)	4/33 (12%)	0/22 (0%)
First incidence (days)	614	607	–
Logistic regression test			P=0.032N
Logistic regression test			P=0.020N

(continued)

TABLE 5
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
Female			
Mammary Gland[h]	50	50	50
Hyperplasia[i]	30	9	17
Fibroadenoma			
Overall rate	28/50 (56%)	7/50 (14%)	11/50 (22%)
Adjusted rate	71.0%	16.5%	28.9%
Terminal rate	14/25 (56%)	6/41 (15%)	5/29 (17%)
First incidence (days)	587	722	487
Logistic regression test			P<0.001N
Logistic regression test			P=0.225
Adenoma			
Overall rate	2/50 (4%)	0/50 (0%)	0/50 (0%)
Carcinoma			
Overall rate	2/50 (4%)	0/50 (0%)	0/50 (0%)
Fibroadenoma, Adenoma, or Carcinoma[j]			
Overall rate	29/50 (58%)	7/50 (14%)	11/50 (22%)
Adjusted rate	71.8%	16.5%	28.9%
Terminal rate	14/25 (56%)	6/41 (15%)	5/29 (17%)
First incidence (days)	587	722	487
Logistic regression test			P<0.001N
Logistic regression test			P=0.225

[a] Number of animals with neoplasms per number of animals examined. Denominator is number of animals examined microscopically for preputial gland and number of animals necropsied for mammary gland.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence in animals surviving until the end of the study
[d] Not applicable; no neoplasms in animal group
[e] In the exposed group column are the P values corresponding to the pairwise comparisons between the *ad libitum*-fed controls and the exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in the exposed group is indicated by N.
[f] Result of pairwise comparison between the weight-matched controls and the exposed group
[g] Historical incidence for 2-year NTP feed studies with untreated control groups fed *ad libitum* (mean ± standard deviation): 84/1,164 (7.2% ± 5.6%); range, 0%-24%.
[h] Number of animals necropsied
[i] Number of animals with lesion
[j] Historical incidence: 507/1,202 (42.2% ± 13.5%); range, 8%-64%.

2-YEAR AND LONG-TERM RESTRICTED FEED PROTOCOLS

Survival

Estimates of 2-year and long-term survival probabilities for male and female rats fed restricted diets for up to 32 months are shown in Table 6 and in the Kaplan-Meier survival curves in Figure 5. The survival rates of exposed males and females were similar to those of the controls at 2 years and at the end of the study. Survival was reduced to 20% during week 129 for males and week 140 for females.

Body Weights

Mean body weights are given in Figure 6 and in Table J2. At 1 year, the mean body weights of exposed male rats in each restricted feed protocol were 95% those of the respective controls; the mean body weights of exposed females in the 2-year and long-term protocols were 93% and 91% those of the controls, respectively, at 1 year. From 1 year through the end of the study, the mean body weights of exposed males remained within 10% of the controls; exposed females in the 2-year restricted feed protocol weighed 23% less than the controls at the end of exposure, and exposed females in the long-term restricted feed protocol weighed 29% less than the controls at the end of exposure.

Feed Consumption, Clinical Findings, and Organ Weights

Feed consumption data are shown in Table K2. There were no clinical findings related to butyl benzyl phthalate administration. At the 15-month interim evaluation, exposed males had significantly greater absolute and relative right kidney weights than those of the controls (Table I1b).

TABLE 6
Survival of Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and Long-Term Restricted Feed Protocols

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
Male				
Animals initially in study	60	60	50	50
15-Month interim evaluation[a]	10	10	0	0
Accidental death[a]	1	0	0	0
Moribund	14	17	37	29
Natural deaths	1	2	3	8
Animals surviving to study termination	34	31	10	13
Percent probability of survival at the end of study[b]	70	62	20	26
Mean survival (days)[c]	656	655	763	730
Survival analysis[d]		P=0.537		P=0.731N

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Female				
Animals initially in study	60	60	50	50
15-Month interim evaluation[a]	10	10	0	0
Moribund	11	10	34	38
Natural deaths	4	1	6	1
Animals surviving to study termination	35	39	10	11
Percent probability of survival at the end of study	71	78	20	22
Mean survival (days)	654	666	803	845
Survival analysis		P=0.473N		P=0.522N

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table pairwise comparison (Cox, 1972) with the controls is in the exposed group column. A lower mortality in the exposed group is indicated by N.

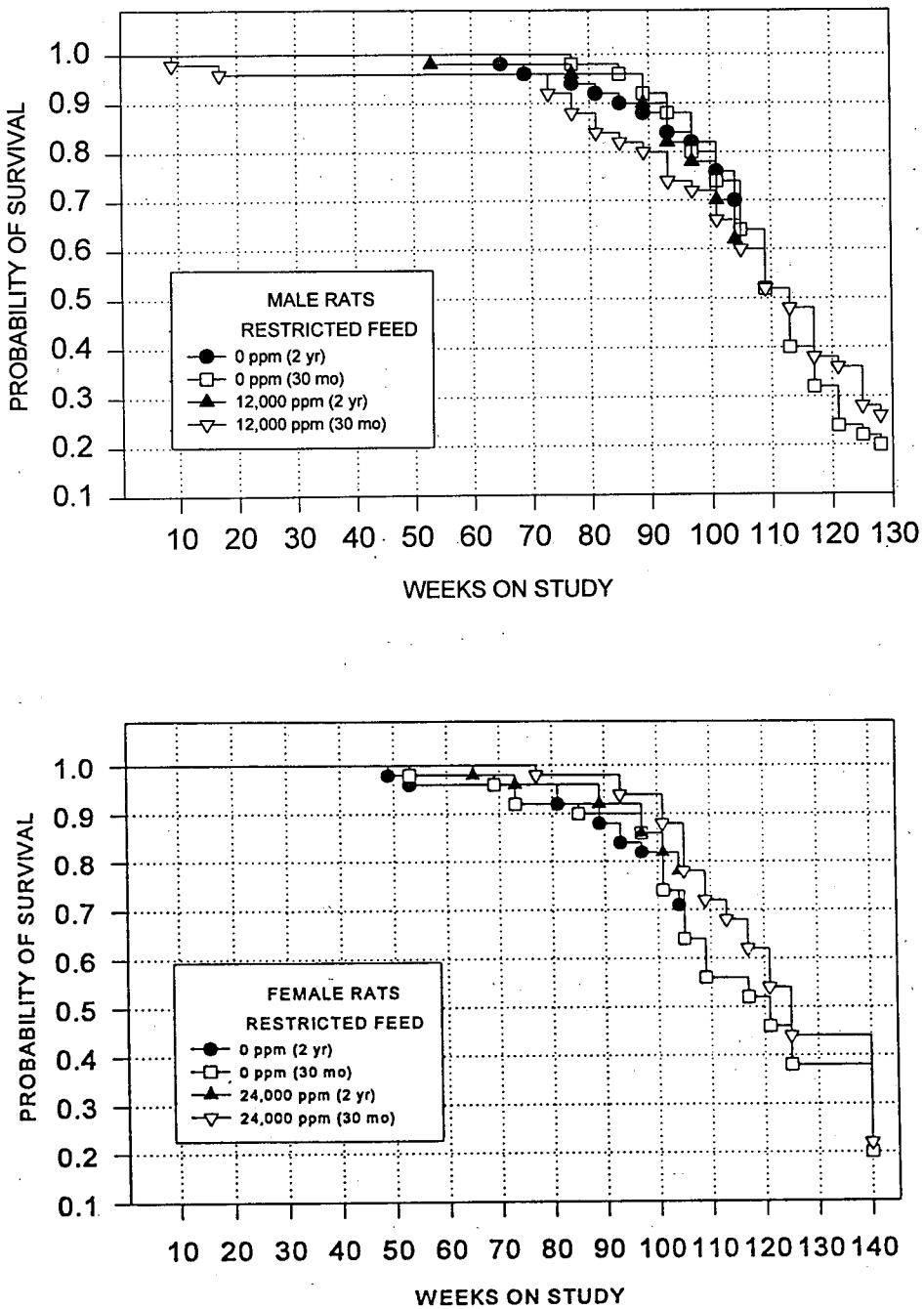


FIGURE 5
Kaplan-Meier Survival Curves for Male and Female Rats Administered Butyl Benzyl Phthalate in Feed for up to 32 Months: 2-Year and Long-Term Restricted Feed Protocols

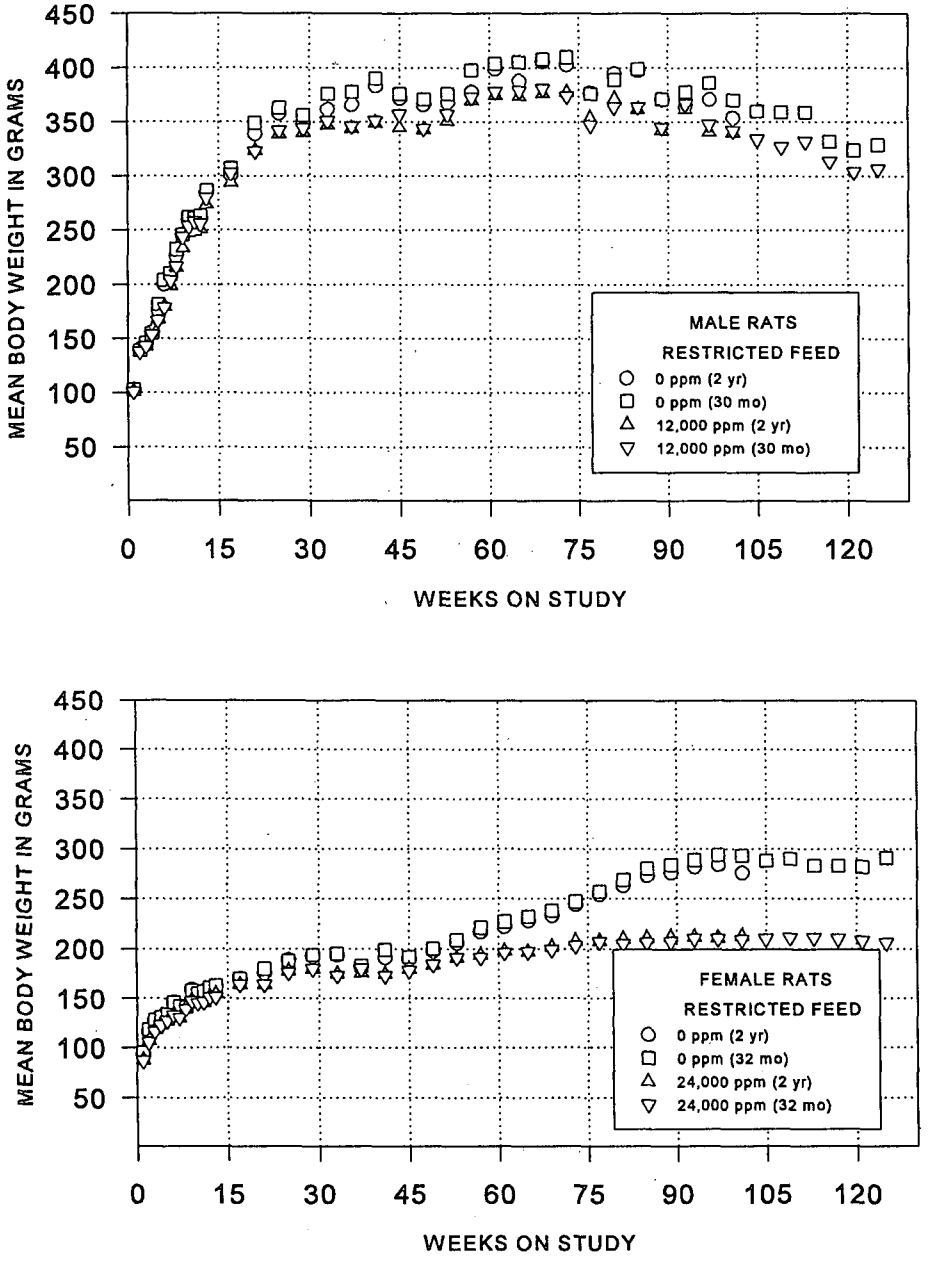


FIGURE 6
Growth Curves for Male and Female Rats Administered Butyl Benzyl Phthalate in Feed for up to 32 Months: 2-Year and Long-Term Restricted Feed Protocols

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the urinary bladder, clitoral gland, mammary gland, pituitary gland, and skin. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A for male rats and Appendix B for female rats.

Urinary Bladder: At 2 years and at 32 months, exposed females had significantly greater incidences of hyperplasia of the urinary bladder transitional epithelium than did the controls (Tables 7 and B3b). At 32 months, exposed female rats had a slightly greater incidence of papilloma or carcinoma (combined) of the urinary bladder transitional epithelium than the controls (Tables 7 and B2b); two exposed females had papillomas, and four exposed females had carcinomas. One control female had a papilloma at 32 months. Papillomas also occurred in two exposed females at 2 years. One exposed male had a papilloma at 2 years; at 30 months, one exposed male had a papilloma and a carcinoma (Table 7). No control males had urinary bladder neoplasms.

Clitoral Gland: The incidence of clitoral gland carcinoma and the combined incidence of clitoral gland adenoma or carcinoma in exposed females were less than those in the controls at 32 months (Tables 8 and B2b).

Mammary Gland: At 2 years and at 32 months, the incidences of fibroadenoma and the combined incidences of fibroadenoma or carcinoma in exposed females were significantly less than those in the controls (Tables 8 and B2b).

Pituitary Gland: The incidences of adenoma of the pars distalis in exposed females were less than those in the controls at 2 years and at 32 months (Tables 8 and B2b). Additionally, one control female had a carcinoma of the pars distalis at 32 months.

Skin: Four control females had fibromas of the subcutaneous tissue at 32 months; no fibromas were observed in exposed females (Tables 8 and B2b).

TABLE 7
Incidences of Neoplasms and Nonneoplastic Lesions
of the Urinary Bladder Transitional Epithelium in Rats in the Dietary Restriction Study
of Butyl Benzyl Phthalate: 2-Year and Long-Term Restricted Feed Protocols

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
Male				
Number Examined Microscopically	50	50	50	50
Hyperplasia[a]	1	2	0	1
Papilloma				
Overall rate[b]	0/50 (0%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Female				
Number Examined Microscopically	50	50	49	50
Hyperplasia	0	14**	0	16**
Papilloma				
Overall rate	0/50 (0%)	2/50 (4%)	1/49 (2%)	2/50 (4%)
Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	4/50 (8%)
Adjusted rate[c]			0.0%	29.0%
Terminal rate[d]			0/10 (0%)	3/11 (27%)
First incidence (days)			-[e]	719
Logistic regression test[f]				P=0.079
Papilloma or Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	1/49 (2%)	6/50 (12%)
Adjusted rate			2.6%	41.0%
Terminal rate			0/10 (0%)	4/11 (36%)
First incidence (days)			694	719
Logistic regression test				P=0.077

** Significantly different (P≤0.01) from the control group by the Fisher exact test
[a] Number of animals with lesion
[b] Number of animals with neoplasms per number of animals with urinary bladder examined microscopically
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] Not applicable; no neoplasms in animal group
[f] In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.

TABLE 8
Incidences of Selected Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and Long-Term Restricted Feed Protocols

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Clitoral Gland				
Adenoma				
Overall rate[a]	3/50 (6%)	3/50 (6%)	5/50 (10%)	2/49 (4%)
Adjusted rate[b]	16.4%	8.8%	16.2%	11.7%
Terminal rate[c]	2/35 (6%)	3/39 (8%)	0/10 (0%)	1/11 (9%)
First incidence (days)	677	731 (T)	649	779
Logistic regression test[d]		P=0.636N		0.253N
Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	0/49 (0%)
Adjusted rate			38.5%	0.0%
Terminal rate			3/10 (30%)	0/11 (0%)
First incidence (days)			829	-[e]
Logistic regression test				0.021N
Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	10/50 (20%)	2/49 (4%)
Adjusted rate	16.4%	8.8%	48.5%	11.7%
Terminal rate	2/35 (6%)	3/39 (8%)	3/10 (30%)	1/11 (9%)
First incidence (days)	677	731 (T)	649	779
Logistic regression test		P=0.636N		P=0.012N
Mammary Gland				
Fibroadenoma				
Overall rate	12/50 (24%)	2/50 (4%)	21/50 (42%)	5/50 (10%)
Adjusted rate	44.9%	5.0%	78.9%	26.1%
Terminal rate	12/35 (34%)	1/39 (3%)	5/10 (50%)	2/11 (18%)
First incidence (days)	730 (T)	600	687	796
Logistic regression test		P=0.003N		P<0.001N
Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate			14.8%	9.1%
Terminal rate			0/10 (0%)	1/11 (9%)
First incidence (days)			694	977 (T)
Logistic regression test				P=0.173N
Fibroadenoma or Carcinoma				
Overall rate	13/50 (26%)	2/50 (4%)	24/50 (48%)	6/50 (12%)
Adjusted rate	46.4%	5.0%	81.5%	34.4%
Terminal rate	12/35 (34%)	1/39 (3%)	5/10 (50%)	3/11 (27%)
First incidence (days)	712	600	687	796
Logistic regression test		P=0.002N		P<0.001N

(continued)

TABLE 8
Incidences of Selected Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and Long-Term Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Pituitary Gland (Pars Distalis)				
Adenoma				
Overall rate	15/50 (30%)	6/49 (12%)	25/50 (50%)	16/50 (32%)
Adjusted rate	45.8%	14.9%	85.4%	81.8%
Terminal rate	12/35 (34%)	4/39 (10%)	7/10 (70%)	8/11 (73%)
First incidence (days)	564	600	478	731
Logistic regression test		P=0.023N		P=0.018N
Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Skin (Subcutaneous Tissue)				
Fibroma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate			28.0%	0.0%
Terminal rate			2/10 (20%)	0/11 (0%)
First incidence (days)			687	-
Logistic regression test				P=0.048N

(T)Terminal sacrifice
[a] Number of animals with neoplasms per number of animals examined. Denominator is number of animals examined microscopically for clitoral gland and pituitary gland and number of animals necropsied for mammary gland and skin.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence in animals surviving until the end of the study
[d] In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposed group is indicated by N.
[e] Not applicable; no neoplasms in animal group

t-BUTYLHYDROQUINONE FEED STUDY

AD LIBITUM FEEDING AND WEIGHT-MATCHED CONTROLS PROTOCOLS

Survival

Estimates of 30-month survival probabilities for male and female rats fed *ad libitum* and the weight-matched control rats are shown in Table 9 and in the Kaplan-Meier survival curves in Figure 7. The survival rates of males and females administered 5,000 ppm were greater than those of the controls fed *ad libitum* and similar to those of the weight-matched controls. Survival was reduced to 20% during week 123 for exposed males and week 129 for exposed females.

Body Weights

Mean body weights are given in Figure 8 and in Table J3. The mean body weight of males in the 5,000 ppm group was 92% that of the controls fed *ad libitum* and 103% that of the weight-matched controls at 1 year; the mean body weight of exposed males remained within 8% that of the controls fed *ad libitum* and within 5% of the weight-matched controls from week 53 until the end of the study. The mean body weight of females in the 5,000 ppm group was 90% that of the controls fed *ad libitum* and 104% that of the weight-matched controls at 1 year. From week 53 until the end of the study, exposed females weighed 8% to 15% less than the controls fed *ad libitum* and 2% to 11% more than the weight-matched controls.

Feed Consumption, Clinical Findings, and Organ Weights

Feed consumption by exposed animals was similar to that by the controls fed *ad libitum* (Table K3). Clinical findings included skin discoloration in exposed males and females and urine stain on the fur of exposed females.

At the 3-month interim evaluation, exposed females had a lower absolute right kidney weight than that of the controls fed *ad libitum* (Table I2a). The absolute right kidney weight of exposed males and the absolute and relative liver weights of exposed males and females were greater than those of the weight-matched controls.

TABLE 9
Survival of Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Male			
Animals initially in study	70	70	70
3-Month interim evaluation[a]	10	10	10
Moribund	48	41	42
Natural deaths	4	7	4
Animals surviving to study termination	8	12	14
Percent probability of survival at the end of study[b]	13	20	23
Mean survival (days)[c]	621	657	629
Survival analysis[d]			P=0.361N
Survival analysis[e]			P=0.619
Female			
Animals initially in study	70	70	70
3-Month interim evaluation[a]	10	10	10
Moribund	40	31	36
Natural deaths	10	7	7
Animals surviving to study termination	10	22	17
Percent probability of survival at the end of study	17	37	28
Mean survival (days)	636	697	693
Survival analysis			P=0.030N
Survival analysis			P=0.481

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The results of the life table pairwise comparisons (Cox, 1972) with the controls fed *ad libitum* are in the exposed group column. A lower mortality in the exposed group is indicated by N.
[e] Result of life table pairwise comparison with the weight-matched controls

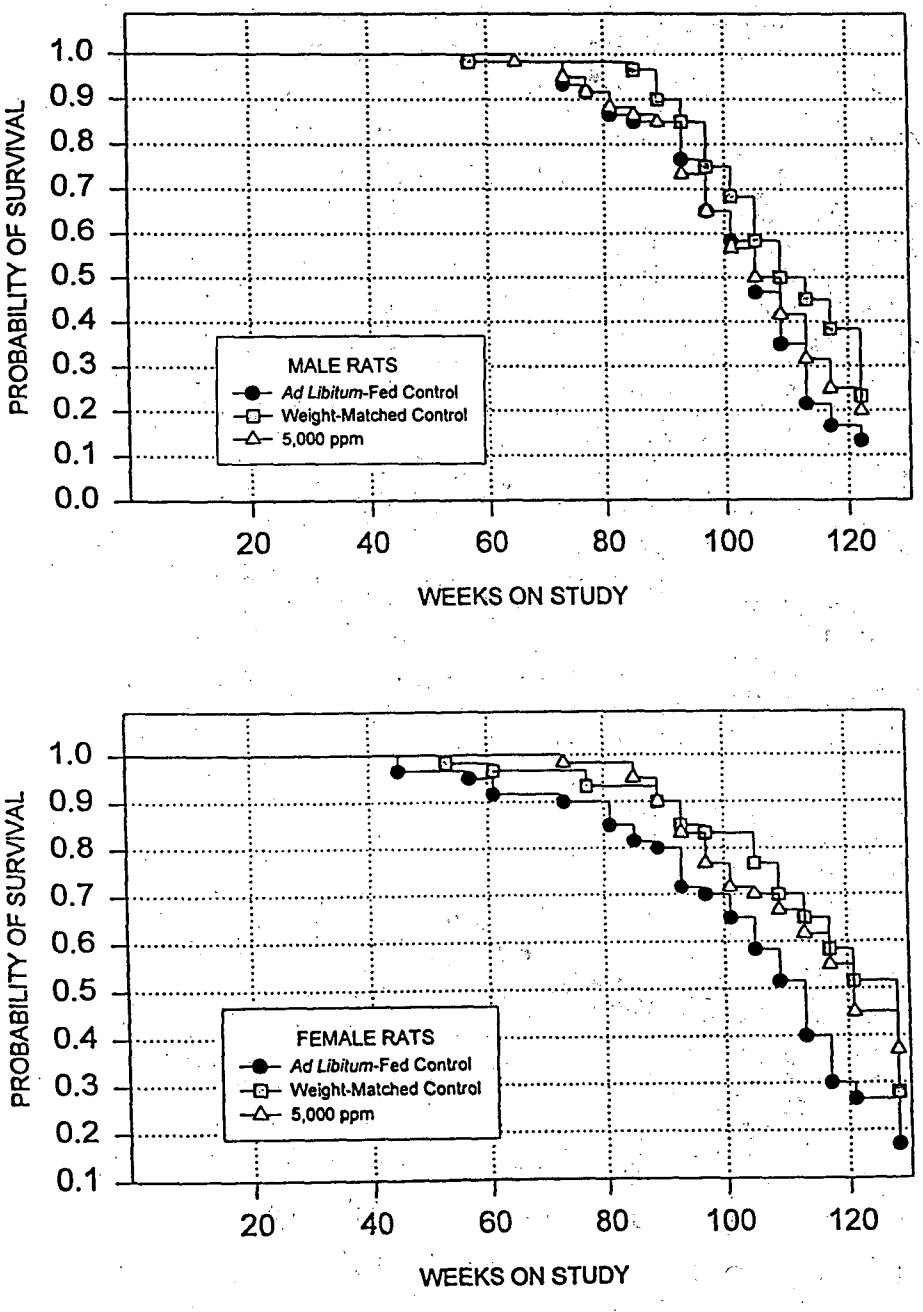


FIGURE 7
Kaplan-Meier Survival Curves for Male and Female Rats Administered *t*-Butylhydroquinone in Feed for up to 30 Months: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

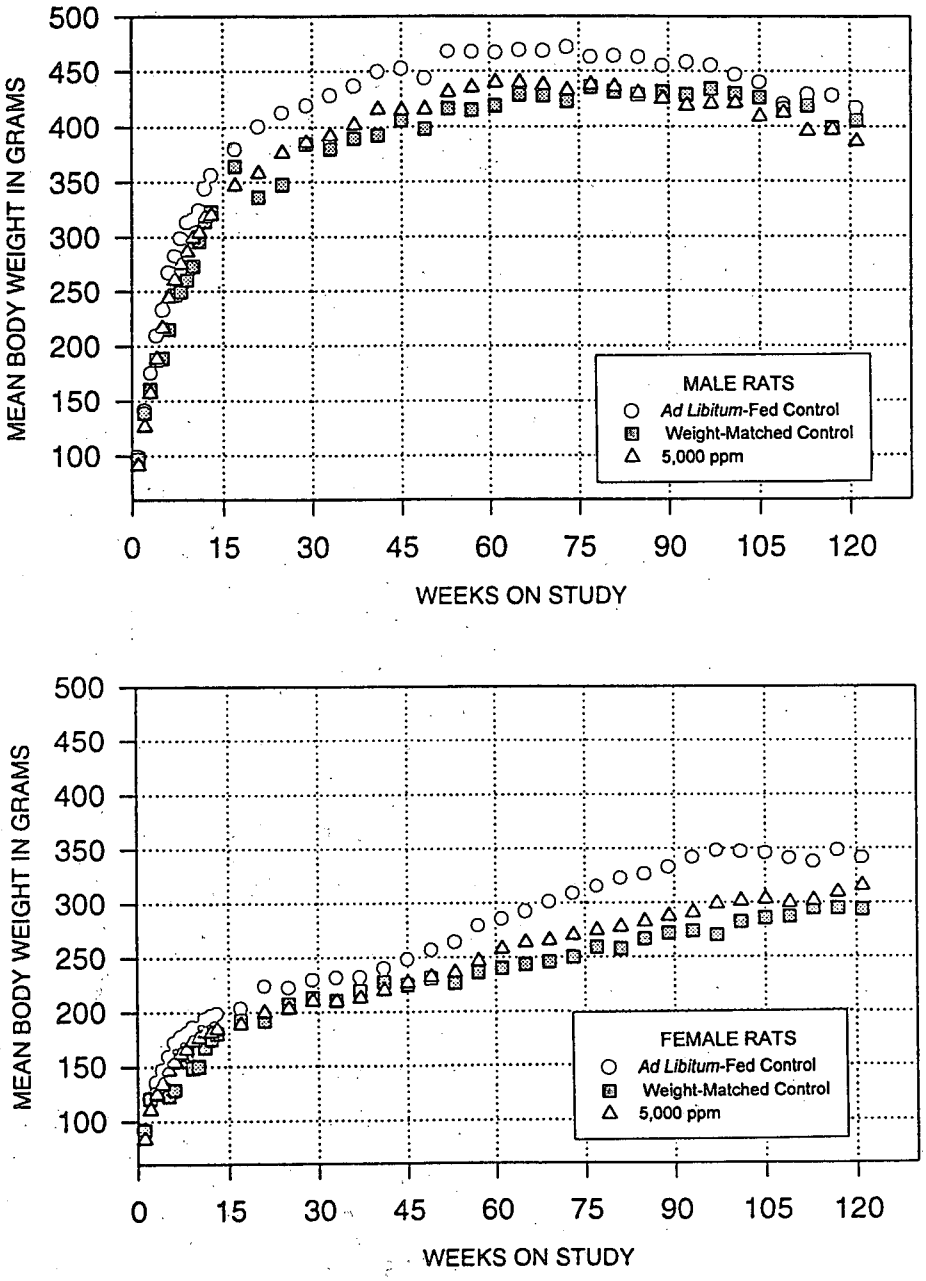


FIGURE 8
Growth Curves for Male and Female Rats Administered *t*-Butylhydroquinone in Feed for up to 30 Months: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms of the preputial gland, clitoral gland, pancreas, pituitary gland, and mammary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix C for male rats and Appendix D for female rats. Pathologic descriptions of neoplasms and nonneoplastic lesions occurring in rats in the *t*-butylhydroquinone study are provided in NTP Technical Report 459 (NTP, 1997d).

Preputial Gland: Males exposed to *t*-butylhydroquinone had significantly greater incidences of preputial gland carcinoma and adenoma or carcinoma (combined) than did the weight-matched controls (Tables 10 and C2a); there were no significant differences in the incidences of these neoplasms between exposed males and controls fed *ad libitum*.

Clitoral Gland: Exposed females had significantly greater incidences of clitoral gland carcinoma and adenoma or carcinoma (combined) than did the weight-matched controls (Tables 10 and D2a); the incidences of these neoplasms in exposed females were similar to those in the controls fed *ad libitum*.

TABLE 10
Incidences of Preputial and Clitoral Gland Neoplasms in Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Male			
Preputial Gland			
Adenoma			
Overall rate[a]	5/60 (8%)	0/60 (0%)	3/60 (5%)
Adjusted rate[b]	31.1%	0.0%	18.4%
Terminal rate[c]	2/8 (25%)	0/12 (0%)	2/14 (14%)
First incidence (days)	528	-[d]	786
Logistic regression test[e]			P=0.312N
Logistic regression test[f]			P=0.084
Carcinoma			
Overall rate	2/60 (3%)	0/60 (0%)	5/60 (8%)
Adjusted rate	3.6%	0.0%	18.4%
Terminal rate	0/8 (0%)	0/12 (0%)	1/14 (7%)
First incidence (days)	381	-	520
Logistic regression test			P=0.200
Logistic regression test			P=0.040
Adenoma or Carcinoma			
Overall rate	7/60 (12%)	0/60 (0%)	8/60 (13%)
Adjusted rate	33.6%	0.0%	34.2%
Terminal rate	2/8 (25%)	0/12 (0%)	3/14 (21%)
First incidence (days)	381	-	520
Logistic regression test			P=0.556
Logistic regression test			P=0.004

(continued)

TABLE 10
Incidences of Preputial and Clitoral Gland Neoplasms in Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Female			
Clitoral Gland			
Adenoma			
Overall rate	6/58 (10%)	4/59 (7%)	7/60 (12%)
Adjusted rate	38.3%	14.5%	27.0%
Terminal rate	3/10 (30%)	2/22 (9%)	2/17 (12%)
First incidence (days)	579	817	628
Logistic regression test			P=0.513N
Logistic regression test			P=0.247
Carcinoma			
Overall rate	6/58 (10%)	2/59 (3%)	8/60 (13%)
Adjusted rate	43.2%	4.0%	29.0%
Terminal rate	4/10 (40%)	0/22 (0%)	2/17 (12%)
First incidence (days)	649	648	750
Logistic regression test			P=0.579N
Logistic regression test			P=0.050
Adenoma or Carcinoma			
Overall rate	12/58 (21%)	6/59 (10%)	14/60 (23%)
Adjusted rate	74.9%	17.9%	47.4%
Terminal rate	7/10 (70%)	2/22 (9%)	4/17 (24%)
First incidence (days)	579	648	628
Logistic regression test			P=0.402N
Logistic regression test			P=0.040

[a] Number of animals with neoplasms per number of animals with tissue examined microscopically
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence in animals surviving until the end of the study
[d] Not applicable; no neoplasms in animal group
[e] In the exposed group column are the P values corresponding to the pairwise comparisons between the *ad libitum*-fed controls and the exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in the exposed group is indicated by N.
[f] Result of pairwise comparison between the weight-matched controls and the exposed group

Pancreas: Three control males fed *ad libitum* had adenomas of the pancreatic acinus; this neoplasm did not occur in the exposed males or in the weight-matched controls (Tables 11 and C2a).

Pituitary Gland, Pars Distalis: The incidences of adenoma and adenoma or carcinoma (combined) were significantly less in exposed males than in the controls fed *ad libitum* or the weight-matched controls (Tables 11 and C2a).

Mammary Gland: Exposed females had significantly lower incidences of fibroadenoma; fibroadenoma or adenoma (combined); and fibroadenoma, adenoma, or carcinoma (combined) than did the controls fed *ad libitum* (Tables 11 and D2a). Additionally, there were fewer mammary gland carcinomas in exposed females than in the controls fed *ad libitum*, although the difference was not statistically significant. There were no significant differences between the incidences of these neoplasms in exposed females and the weight-matched controls.

TABLE 11
Incidences of Selected Neoplasms in Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Male			
Pancreas			
Adenoma			
Overall rate[a]	3/60 (5%)	0/60 (0%)	0/60 (0%)
Adjusted rate[b]	37.5%	0.0%	0.0%
Terminal rate[c]	3/8 (38%)	0/12 (0%)	0/14 (0%)
First incidence (days)	857 (T)	–[d]	–
Logistic regression test[e]			P=0.038N
Logistic regression test[f]			–
Pituitary Gland (Pars Distalis)			
Adenoma			
Overall rate	19/60 (32%)	19/59 (32%)	6/60 (10%)
Adjusted rate	63.8%	72.4%	30.2%
Terminal rate	2/8 (25%)	7/12 (58%)	3/14 (21%)
First incidence (days)	528	638	668
Logistic regression test			P=0.002N
Logistic regression test			P=0.007N
Adenoma or Carcinoma			
Overall rate	19/60 (32%)	20/59 (34%)	7/60 (12%)
Adjusted rate	63.8%	74.2%	31.6%
Terminal rate	2/8 (25%)	7/12 (58%)	3/14 (21%)
First incidence (days)	528	638	627
Logistic regression test			P=0.006N
Logistic regression test			P=0.008N

(continued)

TABLE 11
Incidences of Selected Neoplasms in Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Female			
Mammary Gland			
Fibroadenoma			
Overall rate	43/60 (72%)	23/60 (38%)	27/60 (45%)
Adjusted rate	100.0%	62.8%	74.4%
Terminal rate	10/10 (100%)	10/22 (45%)	9/17 (53%)
First incidence (days)	418	600	596
Logistic regression test			P<0.001N
Logistic regression test			P=0.252
Adenoma			
Overall rate	3/60 (5%)	3/60 (5%)	2/60 (3%)
Fibroadenoma or Adenoma			
Overall rate	45/60 (75%)	25/60 (42%)	27/60 (45%)
Adjusted rate	100.0%	66.6%	74.4%
Terminal rate	10/10 (100%)	11/22 (50%)	9/17 (53%)
First incidence (days)	418	600	596
Logistic regression test			P<0.001N
Logistic regression test			P=0.389
Carcinoma			
Overall rate	8/60 (13%)	1/60 (2%)	4/60 (7%)
Adjusted rate	29.3%	2.1%	10.5%
Terminal rate	1/10 (10%)	0/22 (0%)	0/17 (0%)
First incidence (days)	540	729	690
Logistic regression test			P=0.177N
Logistic regression test			P=0.181
Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	48/60 (80%)	26/60 (43%)	30/60 (50%)
Adjusted rate	100.0%	67.3%	76.3%
Terminal rate	10/10 (100%)	11/22 (50%)	9/17 (53%)
First incidence (days)	418	600	596
Logistic regression test			P<0.001N
Logistic regression test			P=0.264

(T)Terminal sacrifice
[a] Number of animals with neoplasms per number of animals examined. Denominator is number of animals examined microscopically for pancreas, pituitary gland, and adrenal gland and number of animals necropsied for mammary gland.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence in animals surviving until the end of the study
[d] Not applicable; no neoplasms in animal group
[e] In the exposed group column are the P values corresponding to the pairwise comparisons between the *ad libitum*-fed controls and the exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in the exposed group is indicated by N.
[f] Result of pairwise comparison between the weight-matched controls and the exposed group

30-MONTH RESTRICTED FEED PROTOCOL

Survival

Estimates of 30-month survival probabilities for male and female rats fed restricted diets are shown in Table 12 and in the Kaplan-Meier survival curves in Figure 9. The survival rates of exposed rats were greater than those of the controls.

Body Weights

Mean body weights of rats fed restricted diets are shown in Figure 10 and Table J4. The mean body weights of exposed rats were similar to those of the controls throughout the study.

Feed Consumption, Clinical Findings, and Organ Weights

Feed consumption data are shown in Table K4. Clinical findings included hair discoloration in exposed males and females and urine stain on the fur of exposed females. Exposed males evaluated at 3 months had greater absolute and relative liver weights than those of the controls (Table I2b).

TABLE 12
Survival of Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: 30-Month Restricted Feed Protocol

	0 ppm	5,000 ppm
Male		
Animals initially in study	70	70
3-Month interim evaluation[a]	10	10
Moribund	43	33
Natural deaths	7	5
Animals surviving to study termination	10	22
Percent probability of survival at the end of study[b]	17	37
Mean survival (days)[c]	658	718
Survival analysis[d]		P=0.003N
Female		
Animals initially in study	70	70
3-Month interim evaluation[a]	10	10
Moribund	39	32
Natural deaths	3	4
Animals surviving to study termination	18	24
Percent probability of survival at the end of study	30	40
Mean survival (days)	705	718
Survival analysis		P=0.259N

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table pairwise comparison (Cox, 1972) with the controls is in the exposed group column. A lower mortality in the exposed group is indicated by N.

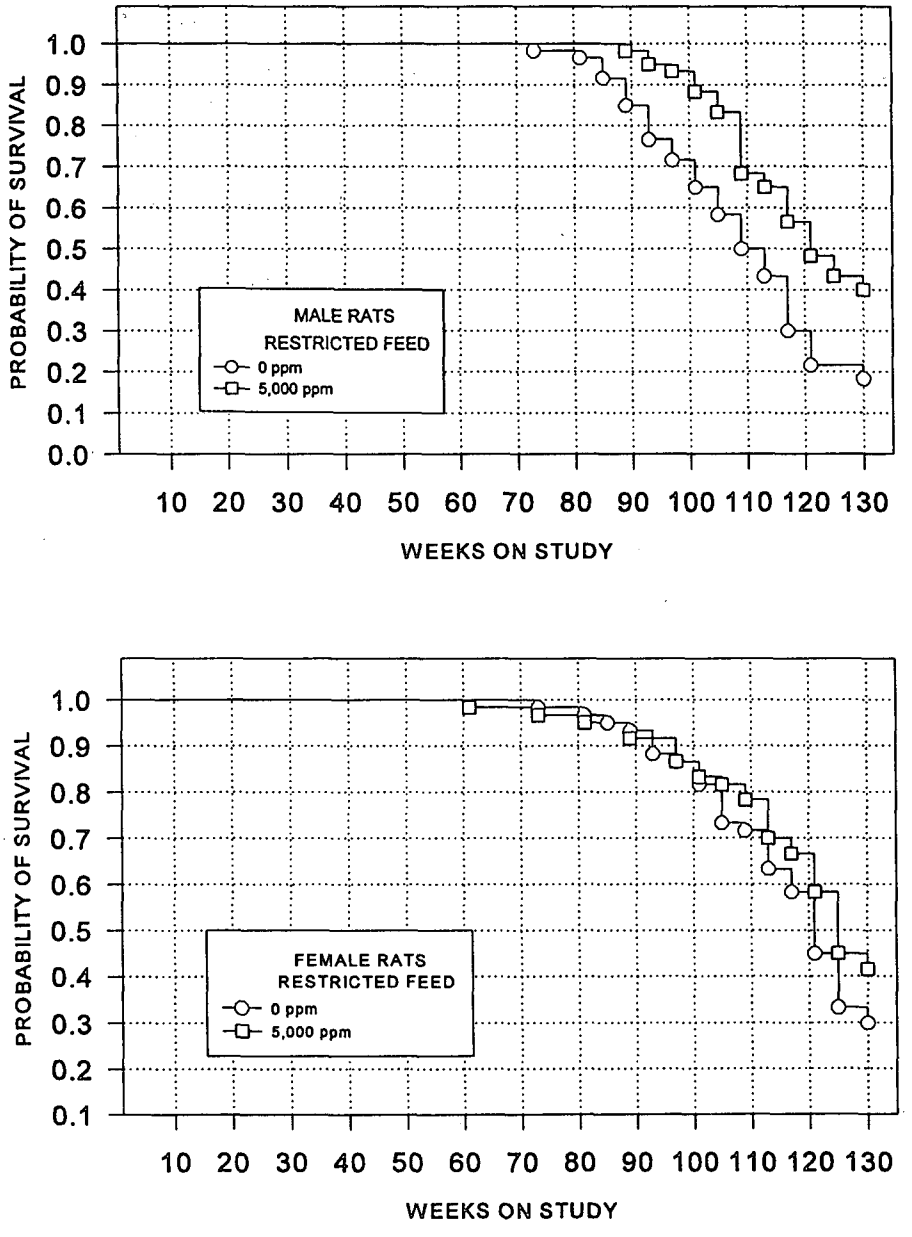


FIGURE 9
Kaplan-Meier Survival Curves for Male and Female Rats Administered *t*-Butylhydroquinone in Feed for 30 Months: Restricted Feed Protocol

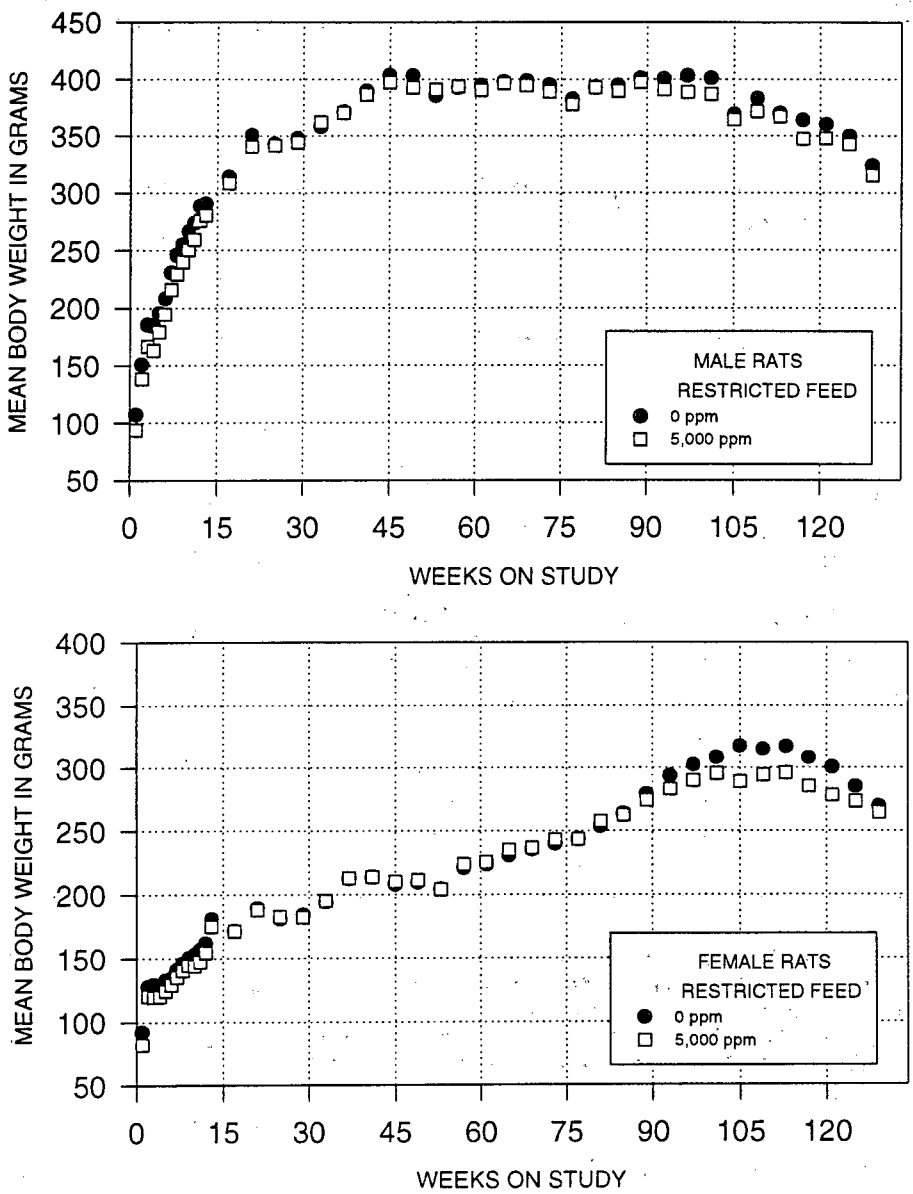


FIGURE 10
Growth Curves for Male and Female Rats Administered *t*-Butylhydroquinone in Feed for 30 Months: Restricted Feed Protocol

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms of the clitoral gland, mammary gland, and pituitary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix C for male rats and Appendix D for female rats.

Clitoral Gland: Exposed females had significantly greater incidences of clitoral gland adenoma and adenoma or carcinoma (combined) than those in the control females (Tables 13 and D2b).

TABLE 13
Incidences of Clitoral Gland Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: 30-Month Restricted Feed Protocol

	0 ppm	5,000 ppm
Adenoma		
Overall rate[a]	3/59 (5%)	10/59 (17%)
Adjusted rate[b]	13.4%	27.5%
Terminal rate[c]	1/18 (6%)	3/23 (13%)
First incidence (days)	866	673
Logistic regression test[d]		P=0.044
Carcinoma		
Overall rate	2/59 (3%)	5/59 (8%)
Adjusted rate	6.2%	21.7%
Terminal rate	0/18 (0%)	5/23 (22%)
First incidence (days)	788	911 (T)
Logistic regression test		P=0.279
Adenoma or Carcinoma		
Overall rate	5/59 (8%)	15/59 (25%)
Terminal rate	18.8%	45.6%
Adjusted rate	1/18 (6%)	8/23 (35%)
First incidence (days)	788	673
Logistic regression test		P=0.019

(T)Terminal sacrifice
[a] Number of animals with neoplasms per number of animals with clitoral gland examined microscopically
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence in animals surviving until the end of the study
[d] In the exposed group column are the P values corresponding to the pairwise comparisons between the controls and the exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.

Mammary Gland: Exposed females had significantly lower incidences of fibroadenoma and fibroadenoma or carcinoma (combined) than did the controls (Tables 14 and D2b).

Pituitary Gland: The incidence of adenoma of the pars distalis in exposed females was significantly less than in the controls (Tables 14 and D2b).

TABLE 14
Incidences of Selected Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: 30-Month Restricted Feed Protocol

	0 ppm	5,000 ppm
Mammary Gland		
Fibroadenoma		
Overall rate[a]	30/60 (50%)	17/60 (28%)
Adjusted rate[b]	86.8%	56.1%
Terminal rate[c]	14/18 (78%)	12/24 (50%)
First incidence (days)	688	780
Logistic regression test[d]		P=0.002N
Fibroadenoma or Carcinoma		
Overall rate	31/60 (52%)	17/60 (28%)
Adjusted rate	87.5%	56.1%
Terminal rate	14/18 (78%)	12/24 (50%)
First incidence (days)	688	780
Logistic regression test		P<0.001N
Pituitary Gland (Pars Distalis)		
Adenoma		
Overall rate	30/59 (51%)	18/60 (30%)
Adjusted rate	81.1%	50.8%
Terminal rate	11/17 (65%)	9/24 (38%)
First incidence (days)	638	649
Logistic regression test		P=0.007N

[a] Number of animals with neoplasms per number of animals examined. Denominator is number of animals examined microscopically for pituitary gland and number of animals necropsied for mammary gland.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence in animals surviving until the end of the study
[d] In the exposed group column are the P values corresponding to the pairwise comparisons between the controls and the exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in the exposed group is indicated by N.

SALICYLAZOSULFAPYRIDINE GAVAGE STUDIES
RATS
AD LIBITUM FEEDING AND WEIGHT-MATCHED CONTROLS PROTOCOLS

Survival

Estimates of 2-year survival probabilities for male rats fed *ad libitum* and the weight-matched control rats are shown in Table 15 and the Kaplan-Meier survival curves in Figure 11. The survival of dosed males was less than that of the controls fed *ad libitum* and slightly less than that of the weight-matched controls.

Body Weights

Mean body weights are given in Figure 12 and in Table J5. Because there was negligible body weight depression in the 337.5 mg/kg group throughout the study, no adjustments were made to the amount of feed presented to the weight-matched controls, thereby yielding a redundant control group. At 1 year, the mean body weight of dosed males was 96% that of the controls fed *ad libitum* and 98% that of the weight-matched controls. During the second year of the study, the mean body weight of dosed males remained within 5% of the mean body weights of both control groups.

Feed Consumption, Clinical Findings, and Organ Weights

Feed consumption by dosed males was similar to that by the control groups (Table K5). There were no clinical findings considered related to treatment with salicylazosulfapyridine. The absolute spleen weight of dosed males was significantly less than that of the controls fed *ad libitum*; there were no significant differences in organ weights between dosed males and the weight-matched controls (Table I3a).

TABLE 15
Survival of Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
Animals initially in study	70	60	60
6-Month interim evaluation[a]	10	0	0
15-Month interim evaluation[a]	10	10	10
Accidental deaths[a]	1	2	2
Moribund	13	16	15
Natural deaths	1	1	10
Animals surviving to study termination	35	31	23
Percent probability of survival at the end of study[b]	71	65	48
Mean survival (days)[c]	582	641	629
Survival analysis[d]			P=0.036
Survival analysis[e]			P=0.170

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table pairwise comparison (Cox, 1972) with the controls fed *ad libitum* is in the dosed group column.
[e] Result of life table pairwise comparison with the weight-matched controls

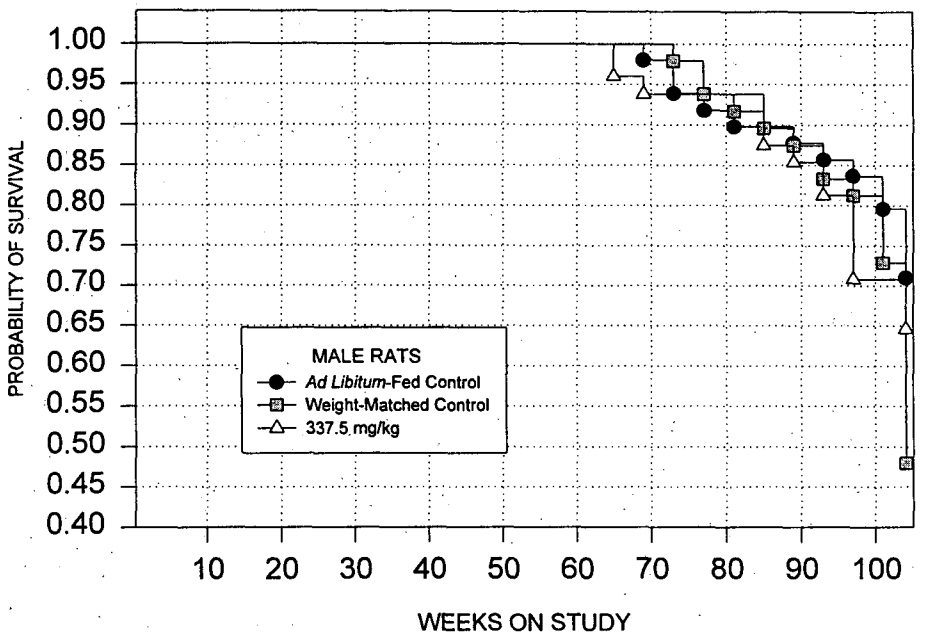


FIGURE 11
Kaplan-Meier Survival Curves for Male Rats Administered Salicylazosulfapyridine in Corn Oil by Gavage for 2 Years: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

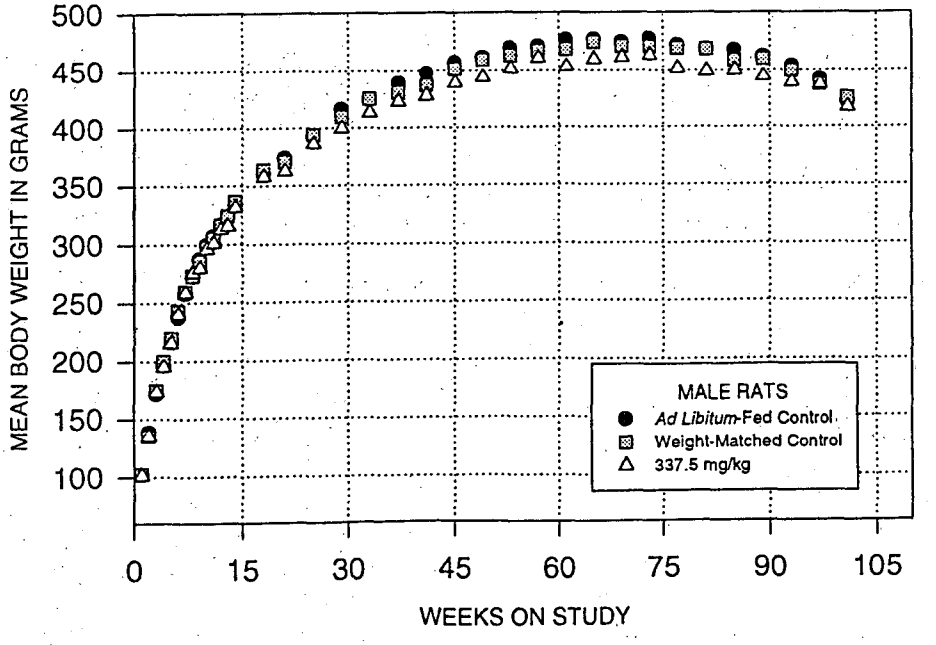


FIGURE 12
Growth Curves for Male Rats Administered Salicylazosulfapyridine in Corn Oil by Gavage for 2 Years: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and of neoplasms and/or nonneoplastic lesions of the urinary bladder, kidney, and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix E. Pathologic descriptions of neoplasms and nonneoplastic lesions occurring in rats in the salicylazosulfapyridine study are provided in NTP Technical Report 457 (NTP, 1997b).

Urinary Bladder: The incidence of urinary bladder papilloma was significantly greater in dosed males than in the controls fed *ad libitum* or the weight-matched controls (Tables 16 and E2a). Two dosed males had multiple papillomas; no papillomas occurred in either control group. Additionally, the incidences of hyperplasia of the urinary bladder mucosa, concretion, dilatation, and grossly diagnosed

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Urinary Bladder and Kidney in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
Urinary Bladder[a]	50	50	50
Concretion[b]	0	0	10**▲▲
Dilatation	0	1	7*▲
Mucosa, Hyperplasia	0	0	41**▲▲
Calculus (gross diagnosis)[c]	0	0	27**▲▲
Papilloma[d]			
Overall rate[e]	0/50 (0%)	0/50 (0%)	6/50 (12%)
Adjusted rate[f]	0.0%	0.0%	22.1%
Terminal rate[g]	0/35 (0%)	0/31 (0%)	3/23 (13%)
First incidence (days)	–[h]	–	653
Logistic regression test[i]			P=0.011
Logistic regression test[j]			P=0.013
Kidney	50	50	50
Concretion	0	0	33**▲▲
Hydronephrosis	0	0	28**▲▲
Mineralization	3	6	13**
Renal Tubule, Dilatation	0	1	11**▲▲
Transitional Epithelium, Hyperplasia	10	5	43**▲▲

* Significantly different (P≤0.05) from the *ad libitum*-fed controls by the logistic regression test
** P≤0.01
▲ Significantly different (P≤0.05) from the weight-matched controls by the logistic regression test
▲▲ P≤0.01
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Number of animals with grossly observed urinary bladder concretions (diagnosed as calculi at necropsy)
[d] Historical incidence for 2-year NTP gavage studies with control groups receiving corn oil by gavage and fed *ad libitum* (mean ± standard deviation): 1/904 (0.1% ± 0.5%); range, 0%-2%.
[e] Number of animals with neoplasms per number of animals with tissue examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence in animals surviving until the end of the study
[h] Not applicable; no neoplasms in animal group
[i] In the dosed group column is the P value corresponding to the pairwise comparison between the *ad libitum*-fed controls and the dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.
[j] Result of pairwise comparison between the weight-matched controls and the dosed group

calculi in dosed males were greater than those in either control group (Tables 16 and E3a).

Kidney: Dosed males had significantly greater incidences of concretions, transitional epithelial hyperplasia, hydronephrosis, mineralization, and renal tubule dilatation than the controls fed *ad libitum* or the weight-matched controls (Tables 16 and E3a).

Spleen: Dosed male rats had significantly greater incidences of hematopoietic cell proliferation (*ad libitum*-fed controls, 14/50; weight-matched controls, 9/50; 337.5 mg/kg, 23/50) and hemosiderin pigmentation (14/50, 20/50, 30/50) than the controls fed *ad libitum* or the weight-matched controls (Table E3a). The greater incidences of these lesions in dosed males are suggestive of erythrocyte toxicity and destruction (hemolysis).

Mononuclear Cell Leukemia: Dosed males had a significantly lower incidence of mononuclear cell leukemia than the controls fed *ad libitum* (Tables 17 and E2a). The incidence in dosed males was also lower than that in the weight-matched controls; however, the difference was not statistically significant.

TABLE 17
Incidences of Mononuclear Cell Leukemia in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
Mononuclear Cell Leukemia[a]			
Overall rate[b]	13/50 (26%)	10/50 (20%)	3/50 (6%)
Adjusted rate[c]	32.0%	26.2%	6.8%
Terminal rate[d]	8/35 (23%)	5/31 (16%)	0/23 (0%)
First incidence (days)	477	526	428
Life table test[e]			P=0.040N
Life table test[f]			P=0.076N

[a] Historical incidence for 2-year NTP gavage studies with control groups receiving corn oil by gavage and fed *ad libitum* (mean ± standard deviation): 224/922 (24.3% ± 10.2%); range, 10%-46%. Includes lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemias.
[b] Number of animals with neoplasms per number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the dosed group column is the P value corresponding to the pairwise comparison between the *ad libitum*-fed controls and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. A lower incidence in the dosed group is indicated by N.
[f] Result of pairwise comparison between the weight-matched controls and the dosed group

2-YEAR AND 30-MONTH RESTRICTED FEED PROTOCOLS

Survival

Estimates of 2-year and 30-month survival probabilities for male rats fed restricted diets are shown in Table 18 and the Kaplan-Meier survival curves in Figure 13. The survival of dosed rats was greater for the controls at 2 years and at 30 months. Survival in the control group was reduced to 20% at week 130.

Body Weights

Mean body weights are shown in Figure 14 and in Table J6. The mean body weights of dosed males were 94% those of the respective controls at 1 year. The mean body weights of dosed males ranged from 6% to 18% less than the mean body weights of the controls during the second year of the study. From 2 years to 30 months, the mean body weight of dosed males ranged from 16% to 20% less than that of the controls.

Feed Consumption, Clinical Findings, and Organ Weights

Feed consumption data are shown in Table K6. There were no clinical findings considered related to treatment with salicylazosulfapyridine. At the 15-month evaluation, there were no significant differences in organ weights between dosed and control males (Table I3b).

TABLE 18
Survival of Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Animals initially in study	61	60	49	50
15-Month interim evaluation[a]	10	10	0	0
Accidental deaths[a]	2	2	4	2
Moribund	13	6	28	14
Natural deaths	2	3	7	10
Animals surviving to study termination	34	39	10	24[b]
Percent probability of survival at the end of study[c]	70	82	22	50
Mean survival (days)[d]	658	642	765	798
Survival analysis[e]		P=0.313N		P=0.012N

[a] Censored from analyses
[b] Includes one animal that died during the last week of the study.
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[e] The result of the life table pairwise comparison (Cox, 1972) with the controls is in the dosed group column. A lower mortality in a dosed group is indicated by N.

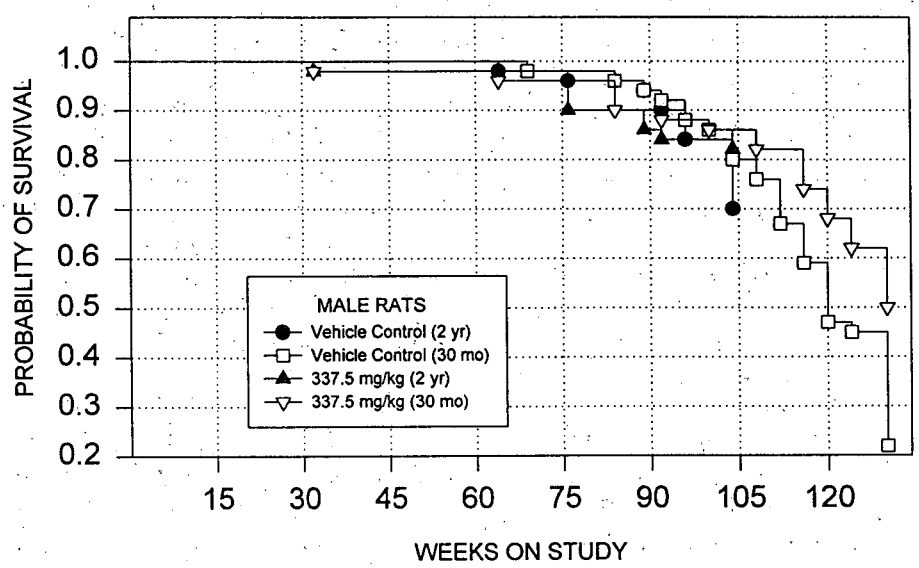


FIGURE 13
Kaplan-Meier Survival Curves for Male Rats Administered Salicylazosulfapyridine in Corn Oil by Gavage for up to 30 Months: 2-Year and 30-Month Restricted Feed Protocols

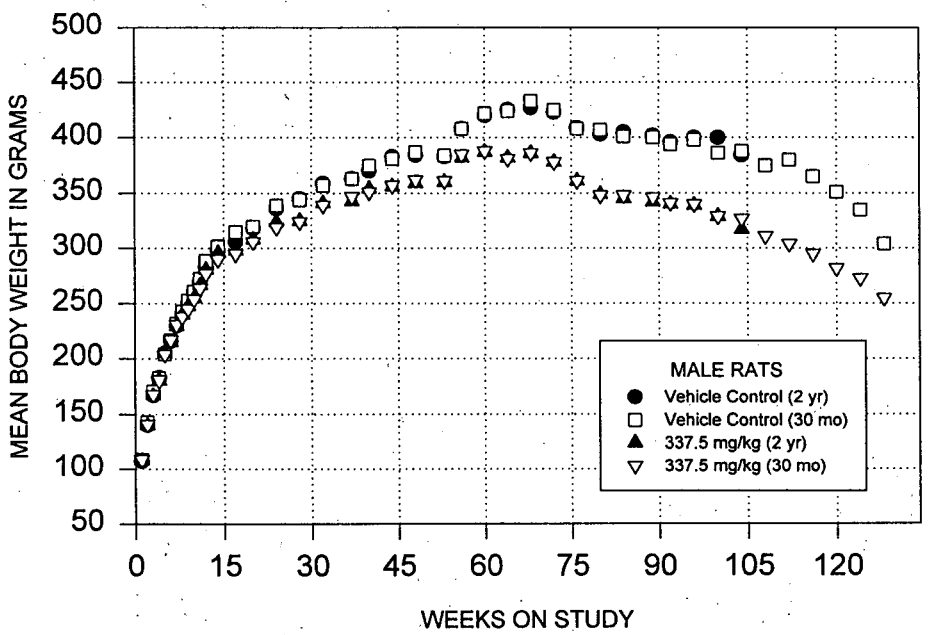


FIGURE 14
Growth Curves for Male Rats Administered Salicylazosulfapyridine in Corn Oil by Gavage for up to 30 Months: 2-Year and 30-Month Restricted Feed Protocols

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and of neoplasms and/or nonneoplastic lesions of the urinary bladder, kidney, spleen, and adrenal medulla. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix E.

Urinary Bladder: The urinary bladder effects observed in dosed male rats fed *ad libitum* did not occur in males fed a restricted diet for 2 years or 30 months. Hyperplasia of the mucosal transitional epithelium was the only urinary bladder lesion that occurred with a significantly greater incidence in dosed males fed restricted diets than in the controls at 2 years or at 30 months (Tables 19 and E3b). No papillomas of the urinary bladder occurred in dosed males at 2 years; at 30 months, one dosed male had a papilloma, and concretions (diagnosed as calculi) were observed grossly in four dosed males at necropsy.

Kidney: The incidences of concretion and transitional epithelial hyperplasia were significantly greater in dosed males at 2 years and at 30 months than in the controls (Tables 19 and E3b). Dosed males also had a significantly greater incidence of mineralization than the controls at 2 years. The incidence of nephropathy in dosed males was significantly greater than that in the controls at 30 months.

Spleen: Dosed males had significantly greater incidences of hemosiderin pigmentation than the controls at 2 years (vehicle control, 12/51; 337.5 mg/kg, 35/50) and at 30 months (15/49, 33/49) (Table E3b).

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions in the Urinary Bladder and Kidney in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Urinary Bladder[a]	51	50	49	49
Mucosa, Hyperplasia[b]	0	7**	0	8**
Calculus (gross diagnosis)[c]	0	0	0	4
Papilloma	0	0	0	1
Kidney	51	50	49	50
Concretion	0	22**	0	35**
Mineralization	2	11**	4	7
Nephropathy	44	46	39	48*
Transitional Epithelium, Hyperplasia	3	18**	1	37**

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Number of animals with grossly observed urinary bladder concretions (diagnosed as calculi at necropsy)

Mononuclear Cell Leukemia: At 2 years and at 30 months, the incidences of mononuclear cell leukemia in dosed males were significantly less than those in the controls (Tables 20 and E2b).

Adrenal Medulla: The incidences of benign pheochromocytoma and benign or malignant pheochromocytoma (combined) were significantly less in dosed rats than in the controls at 2 years and at 30 months (Tables 20 and E2b).

TABLE 20
Incidences of Selected Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Mononuclear Cell Leukemia				
Overall rate[a]	11/51 (22%)	2/50 (4%)	24/49 (49%)	8/50 (16%)
Adjusted rate[b]	43.4%	6.9%	71.3%	23.8%
Terminal rate[c]	3/34 (9%)	2/39 (5%)	3/10 (30%)	3/24 (13%)
First incidence (days)	520	731 (T)	556	430
Life table test[d]		P=0.009N		P<0.001N
Adrenal Medulla				
Benign Pheochromocytoma				
Overall rate	8/51 (16%)	1/50 (2%)	14/48 (29%)	8/50 (16%)
Adjusted rate	22.2%	3.4%	66.7%	31.1%
Terminal rate	6/34 (18%)	1/39 (3%)	4/10 (40%)	7/24 (29%)
First incidence (days)	700	731 (T)	752	812
Logistic regression test[d]		P=0.014N		P=0.011N
Malignant Pheochromocytoma				
Overall rate	2/51 (4%)	0/50 (0%)	1/48 (2%)	1/50 (2%)
Benign or Malignant Pheochromocytoma				
Overall rate	9/51 (18%)	1/50 (2%)	15/48 (31%)	8/50 (16%)
Adjusted rate	33.3%	3.4%	72.3%	31.1%
Terminal rate	7/34 (21%)	1/39 (3%)	5/10 (50%)	7/24 (29%)
First incidence (days)	700	731 (T)	752	812
Logistic regression test		P=0.007N		P=0.005N

(T)Terminal sacrifice

[a] Number of animals with neoplasms per number of animals examined. Denominator is number of animals examined microscopically for adrenal medulla and lung and number of animals necropsied for mononuclear cell leukemia.

[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence in animals surviving until the end of the study

[d] In the dosed group columns are the P values corresponding to the pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. For all tests, a lower incidence in a dosed group is indicated by N.

MICE
AD LIBITUM FEEDING AND WEIGHT-MATCHED CONTROLS PROTOCOLS

Survival
Estimates of 2-year survival probabilities for male mice fed *ad libitum* and the weight-matched controls are shown in Table 21 and the Kaplan-Meier survival curves in Figure 15. The survival rate of mice in the 2,700 mg/kg group was slightly greater than that of the controls fed *ad libitum* and was similar to that of the weight-matched controls.

Body Weights
Mean body weights are shown in Figure 16 and Table J7. The mean body weight of dosed males was 17% less than that of the controls fed *ad libitum* and 1% less than that of the weight-matched controls at 1 year. During the second year of the study, the mean body weight of dosed males ranged from 10% to 17% less than that of the controls fed *ad libitum* but remained within 10% that of the weight-matched controls.

Feed Consumption, Clinical Findings, and Organ Weights
Dosed males consumed more feed than the controls fed *ad libitum* (Table K7). There were no clinical findings considered related to salicylazosulfapyridine administration. The absolute and relative liver and spleen weights of dosed males were significantly greater than those of the weight-matched controls (Table I4a).

TABLE 21
Survival of Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
Animals initially in study	60	60	60
15-Month interim evaluation[a]	10	10	10
Accidental deaths[a]	2	1	0
Moribund	5	3	4
Natural deaths	3	1	0
Animals surviving to study termination	40	45	46
Percent probability of survival at the end of study[b]	84	92	93
Mean survival (days)[c]	649	665	653
Survival analysis[d]			P=0.350N
Survival analysis[e]			P=1.000

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table pairwise comparison (Cox, 1972) with the controls fed *ad libitum* is in the dosed group column. A lower mortality in the dosed group is indicated by N.
[e] Result of life table pairwise comparison with the weight-matched controls

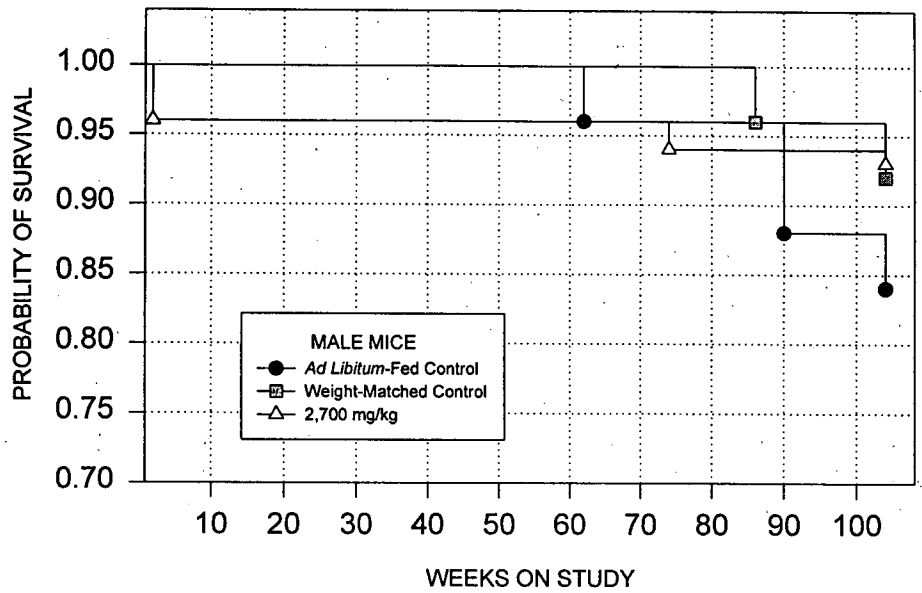


FIGURE 15
Kaplan-Meier Survival Curves for Male Mice Administered Salicylazosulfapyridine in Corn Oil by Gavage for 2 Years: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

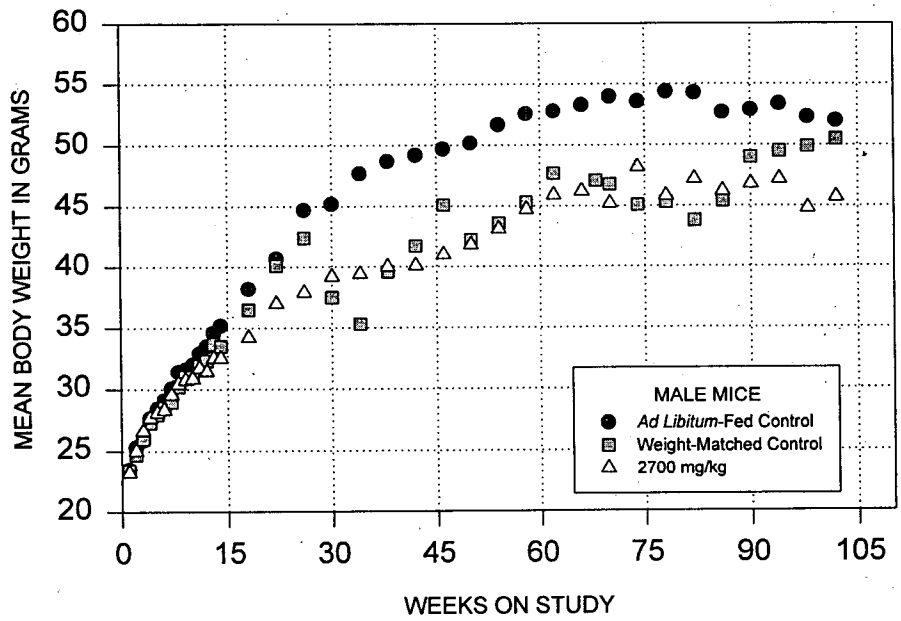


FIGURE 16
Growth Curves for Male Mice Administered Salicylazosulfapyridine in Corn Oil by Gavage for 2 Years: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the liver and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix F. Pathologic descriptions of neoplasms and nonneoplastic lesions occurring in mice in the salicylazosulfapyridine study are provided in NTP Technical Report 457 (NTP, 1997b).

Liver: Dosed mice had significantly greater incidences of hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) than the controls fed *ad libitum* or the weight-matched controls (Tables 22 and F2a). Additionally, the incidences of clear cell and eosinophilic foci were significantly greater in dosed males than in the *ad libitum*-fed and weight-matched control groups. However, the incidence of hepatocellular carcinomas in dosed males was slightly less than in the controls fed *ad libitum*.

Spleen: Dosed male mice had a significantly greater incidence of hemosiderin pigmentation than the *ad libitum*-fed or weight-matched controls (*ad libitum*-fed controls, 2/50; weight-matched controls, 1/50; 2,700 mg/kg, 47/50; Table F3a). The incidence of hematopoietic cell proliferation in dosed males was also significantly greater than that of the weight-matched controls (3/50, 13/50).

TABLE 22
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
Number Examined Microscopically	50	50	50
Clear Cell Focus[a]	2	2	11*▲▲
Eosinophilic Focus	6	1	22**▲▲
Hepatocellular Adenoma			
Overall rate[b]	13/50 (26%)	8/50 (16%)	42/50 (84%)
Adjusted rate[c]	32.5%	17.8%	87.5%
Terminal rate[d]	13/40 (33%)	8/45 (18%)	40/46 (87%)
First incidence (days)	728 (T)	728 (T)	497
Logistic regression test[e]			P<0.001
Logistic regression test[f]			P<0.001
Hepatocellular Adenoma, Multiple			
Overall rate	1/50 (2%)	0/50 (0%)	27/50 (54%)
Hepatocellular Carcinoma			
Overall rate	13/50 (26%)	6/50 (12%)	8/50 (16%)
Adjusted rate	29.2%	12.9%	17.4%
Terminal rate	9/40 (23%)	5/45 (11%)	8/46 (17%)
First incidence (days)	420	574	728 (T)
Logistic regression test			P=0.159N
Logistic regression test			P=0.378
Hepatocellular Adenoma or Carcinoma[g]			
Overall rate	24/50 (48%)	14/50 (28%)	44/50 (88%)
Adjusted rate	54.3%	30.3%	91.7%
Terminal rate	20/40 (50%)	13/45 (29%)	42/46 (91%)
First incidence (days)	420	574	497
Logistic regression test			P<0.001
Logistic regression test			P<0.001

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the *ad libitum*-fed controls by the logistic regression test
** P≤0.01
▲▲ Significantly different (P≤0.01) from the weight-matched controls by the logistic regression test
[a] Number of animals with lesion
[b] Number of animals with neoplasms per number of animals with liver examined microscopically
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the dosed group column are the P values corresponding to the pairwise comparisons between the *ad libitum*-fed controls and the dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in the dosed group is indicated by N.
[f] Result of pairwise comparison between the weight-matched controls and the dosed group
[g] Historical incidence for 2-year NTP gavage studies with control groups receiving corn oil by gavage and fed *ad libitum* (mean ± standard deviation): 340/763 (44.6% ± 14.6%); range, 25%-70%.

2-YEAR AND 3-YEAR RESTRICTED FEED PROTOCOLS

Survival

Estimates of 2-year and 3-year survival probabilities for male mice fed restricted diets are shown in Table 23 and the Kaplan-Meier survival curves in Figure 17. The survival of dosed mice was similar to that of the controls at 2 years but significantly greater than that of the controls at the end of the study.

Body Weights

Mean body weights are shown in Figure 18 and Table J8. The mean body weights of the two groups of dosed mice were about 80% those of the respective controls at 1 year. During the second year of the study, the mean body weights of the dosed males ranged from about 71% to 82% those of the controls; after 2 years, the mean body weight of dosed males recovered slightly, increasing to 89% that of the controls by the end of the study.

Feed Consumption, Clinical Findings, and Organ Weights

Feed consumption data are shown in Table K8. Dosed mice fed restricted diets had diarrhea; no other clinical findings were considered related to chemical administration. For dosed males, the absolute right kidney weight was significantly less than that of the controls, and the relative right kidney weight and absolute and relative spleen weights were significantly greater than those of the controls (Table I4b).

TABLE 23
Survival of Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
Animals initially in study	62	60	48	50
15-Month interim evaluation[a]	10	10	0	0
Moribund	6	5	21	9
Natural deaths	4	1	7	7
Animals surviving to study termination	42	44	20	34
Percent probability of survival at the end of study[b]	81	88	42	68
Mean survival (days)[c]	672	665	936	1,003
Survival analysis[d]		P=0.507N		P=0.010N

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table pairwise comparison (Cox, 1972) with the controls is in the dosed group column. A lower mortality in a dosed group is indicated by N.

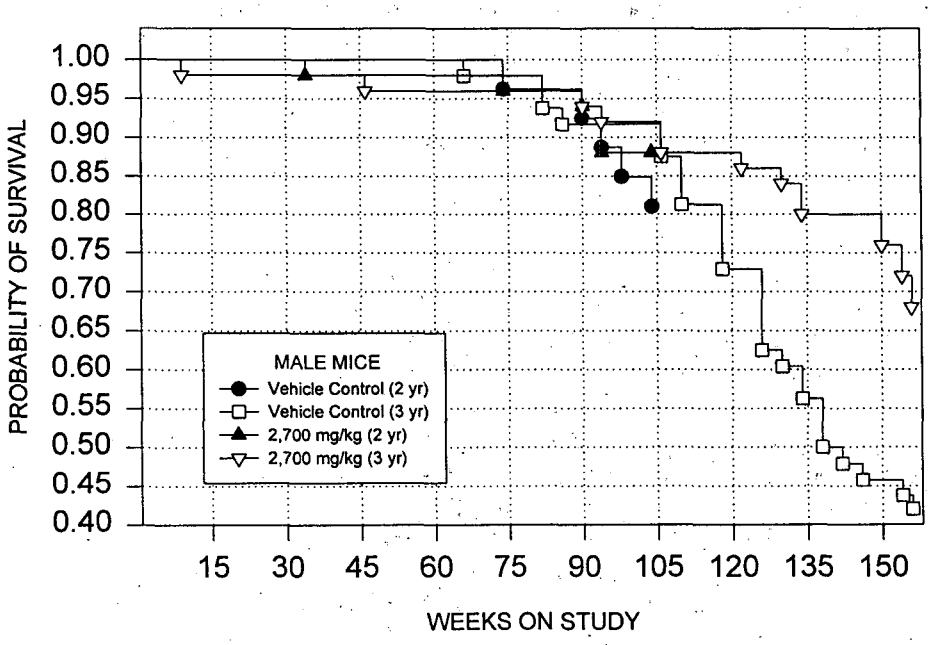


FIGURE 17
Kaplan-Meier Survival Curves for Male Mice Administered Salicylazosulfapyridine in Corn Oil by Gavage for 2 or 3 Years: 2-Year and 3-Year Restricted Feed Protocols

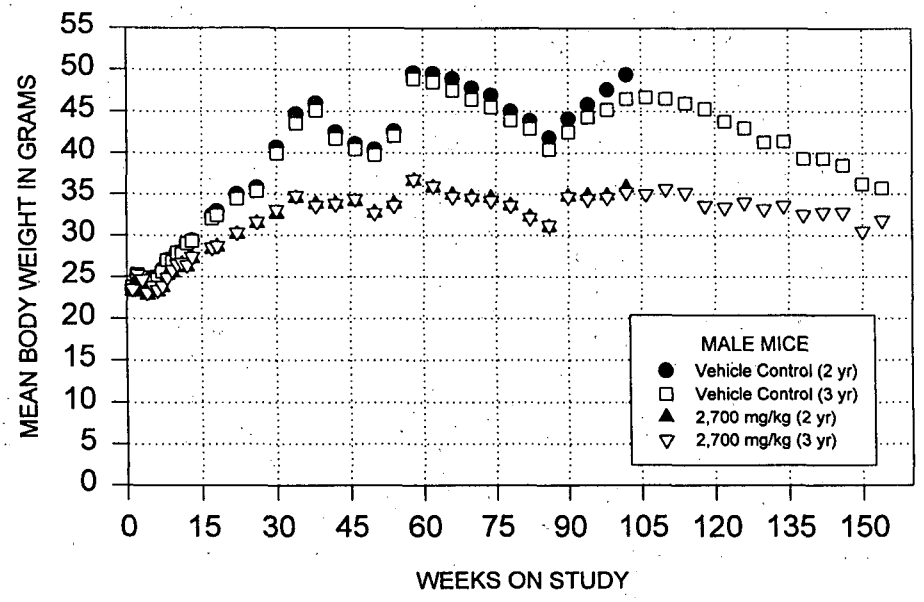


FIGURE 18
Growth Curves for Male Mice Administered Salicylazosulfapyridine in Corn Oil by Gavage for 2 or 3 Years: 2-Year and 3-Year Restricted Feed Protocols

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the harderian gland, liver, lung, and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix F.

Harderian Gland: At 3 years, the incidences of adenoma and adenoma or carcinoma (combined) were significantly less in dosed males than in the controls (Tables 24 and F2b). There were no significant differences in the incidence of harderian gland neoplasms between dosed and control males at 2 years.

Liver: In contrast to the results for mice in the *ad libitum* feeding and the weight-matched controls protocols, the incidences of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) in the 2,700 mg/kg group fed a restricted diet were significantly less than those in the controls after 2 years (Tables 24 and F2b). After 3 years, the incidence of hepatocellular carcinoma in dosed males was again significantly less than in the controls, but the combined incidences of hepatocellular adenoma or carcinoma in dosed and control males were similar.

Lung: The incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly less in dosed males than in the controls at 2 years, but not at 3 years (Tables 24 and F2b). However, at 3 years the incidence of alveolar/bronchiolar carcinoma in dosed males was significantly less than in the controls.

Spleen: The incidence of hemosiderin pigmentation in dosed males was significantly greater than in the controls at 2 years (0/52, 39/50) and at 3 years (0/48, 37/50) (Table F3b).

TABLE 24
Incidences of Selected Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
Harderian Gland				
Adenoma				
Overall rate[a]	2/52 (4%)	3/50 (6%)	6/48 (13%)	1/50 (2%)
Adjusted rate[b]	4.5%	8.6%	28.6%	2.8%
Terminal rate[c]	1/42 (2%)	3/44 (7%)	5/20 (25%)	0/34 (0%)
First incidence (days)	660	730 (T)	1,079	1,076
Logistic regression test[d]		P=0.479		P=0.008N
Carcinoma				
Overall rate	1/52 (2%)	0/50 (0%)	2/48 (4%)	0/50 (0%)
Adenoma or Carcinoma				
Overall rate	3/52 (6%)	3/50 (6%)	8/48 (17%)	1/50 (2%)
Adjusted rate	6.7%	8.6%	32.3%	2.8%
Terminal rate	1/42 (2%)	3/44 (7%)	5/20 (25%)	0/34 (0%)
First incidence (days)	660	730 (T)	750	1,076
Logistic regression test		P=0.641		P=0.007N

(continued)

TABLE 24
Incidences of Selected Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
Liver				
Hepatocellular Adenoma				
Overall rate	13/52 (25%)	9/50 (18%)	10/48 (21%)	14/50 (28%)
Adjusted rate	34.6%	22.7%	35.0%	38.6%
Terminal rate	10/42 (24%)	8/44 (18%)	5/20 (25%)	12/34 (35%)
First incidence (days)	616	648	555	933
Logistic regression test		P=0.274N		P=0.398
Hepatocellular Carcinoma				
Overall rate	7/52 (13%)	1/50 (2%)	16/48 (33%)	6/50 (12%)
Adjusted rate	14.9%	2.3%	42.2%	15.5%
Terminal rate	4/42 (10%)	1/44 (2%)	3/20 (15%)	3/34 (9%)
First incidence (days)	495	729 (T)	445	726
Logistic regression test		P=0.025N		P=0.020N
Hepatocellular Adenoma or Carcinoma				
Overall rate	18/52 (35%)	9/50 (18%)	21/48 (44%)	18/50 (36%)
Adjusted rate	42.2%	22.7%	55.5%	47.0%
Terminal rate	12/42 (29%)	8/44 (18%)	6/20 (30%)	14/34 (41%)
First incidence (days)	495	648	445	726
Logistic regression test		P=0.044N		P=0.292N
Lung				
Alveolar/bronchiolar Adenoma				
Overall rate	11/52 (21%)	3/50 (6%)	8/48 (17%)	7/50 (14%)
Adjusted rate	53.2%	7.9%	33.1%	18.6%
Terminal rate	9/42 (21%)	3/44 (7%)	5/20 (25%)	5/34 (15%)
First incidence (days)	717	729 (T)	862	719
Logistic regression test		P=0.023N		P=0.335N
Alveolar/bronchiolar Carcinoma				
Overall rate	2/52 (4%)	0/50 (0%)	13/48 (27%)	6/50 (12%)
Adjusted rate	13.0%	0.0%	38.4%	17.1%
Terminal rate	1/42 (2%)	0/44 (0%)	3/20 (15%)	5/34 (15%)
First incidence (days)	661	-[e]	718	1,076
Logistic regression test		P=0.237N		P=0.049N
Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/52 (25%)	3/50 (6%)	18/48 (38%)	12/50 (24%)
Adjusted rate	63.4%	7.9%	55.2%	31.8%
Terminal rate	10/42 (24%)	3/44 (7%)	7/20 (35%)	9/34 (26%)
First incidence (days)	661	729 (T)	718	719
Logistic regression test		P=0.009N		P=0.075N

(T)Terminal sacrifice
[a] Number of animals with neoplasms per number of animals examined. Denominator is number of animals examined microscopically for liver and lung and number of animals necropsied for harderian gland.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence in animals surviving until the end of the study
[d] In the dosed group columns are the P values corresponding to the pairwise comparisons between the controls and that dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in a dosed group is indicated by N.
[e] Not applicable; no neoplasms in animal group

SCOPOLAMINE HYDROBROMIDE TRIHYDRATE GAVAGE STUDY
ALL FEEDING PROTOCOLS

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Tables 25 and 26 and in the Kaplan-Meier survival curves (Figures 19 and 20). The survival rates of all groups of dosed mice were similar to those of the respective controls; the survival rates of mice fed under different protocols were also generally similar.

Body Weights

The mean body weights of dosed male and female mice fed *ad libitum* were lower than those of the controls (Figure 21); at 1 year, mean body weights in the 25 mg/kg groups were 20% (males) and 23% (females) less than those of the respective controls (Table J9). The mean body weight of the dosed males was 94% that of the weight-matched controls; the mean body weight of dosed females was 99% that of the weight-matched controls (Table J9). During the second year of the study, the mean body weight of dosed males remained approximately 20% less than that of controls fed *ad libitum* and remained within 10% that of the weight-matched controls; the mean body weight of females ranged from 16% to 25% less than that of the controls fed *ad libitum* and remained within 8% that of the weight-matched controls.

Among groups fed restricted diets, the mean body weights of males and females in the 25 mg/kg groups were slightly less than those of the respective controls at 1 year (Figure 22 and Table J10); dosed males continued to weigh slightly less than the controls through the end of the study, but the mean body weights of dosed and control females were similar at the end of the study.

Feed Consumption, Clinical Findings, and Organ Weights

Feed consumption by dosed and control mice fed *ad libitum* was similar (data not shown). Males and females administered scopolamine hydrobromide trihydrate had dilated pupils.

For dosed males fed *ad libitum*, the absolute right kidney weight was significantly less and the relative right kidney weight was significantly greater than those of the controls fed *ad libitum*; dosed females fed *ad libitum* had a greater relative liver weight than the controls fed *ad libitum* (Tables I5a). Dosed males and females fed *ad libitum* had greater absolute and relative liver weights than the weight-matched controls. For dosed males fed a restricted diet, the absolute right kidney weight was less than that of the diet-restricted controls (Table I5b); there were no significant differences in organ weights between dosed and control females fed a restricted diet.

TABLE 25
Survival of Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Male			
Animals initially in study	70	60	70
15-Month interim evaluation[a]	20	10	20
Accidental deaths[a]	0	1	2
Moribund	4	2	7
Natural deaths	6	6	2
Animals surviving to study termination	40	41	39
Percent probability of survival at the end of study[b]	81	85	83
Mean survival (days)[c]	632	605	622
Survival analysis[d]			P=1.000N
Survival analysis[e]			P=1.000
Female			
Animals initially in study	70	60	70
15-Month interim evaluation[a]	19	10	19
Accidental deaths[a]	2	1	0
Moribund	9	10	7
Natural deaths	7	3	6
Animals surviving to study termination	33	36	38
Percent probability of survival at the end of study	67	74	76
Mean survival (days)	617	654	624
Survival analysis			P=0.656N
Survival analysis			P=1.000

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The results of the life table pairwise comparisons (Cox, 1972) with the controls fed *ad libitum* are in the exposed group column. A lower mortality in the dosed group is indicated by N.
[e] Result of life table pairwise comparison with the weight-matched controls

TABLE 26
Survival of Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Male				
Animals initially in study	60	60	50	50
15-Month interim evaluation[a]	10	10	0	0
Moribund	0	0	11	5
Natural deaths	1	2	11	8
Animals surviving to study termination	49	48	28	37
Percent probability of survival at the end of study[b]	98	96	56	74
Mean survival (days)[c]	674	663	1,004	1,027
Survival analysis[d]		P=0.986		P=0.130N
Female				
Animals initially in study	60	60	50	50
15-Month interim evaluation[a]	10	10	0	0
Accidental deaths[a]	0	1	0	1
Moribund	2	2	18	16
Natural deaths	1	3	12	14
Animals surviving to study termination	47	44	20	19
Percent probability of survival at the end of study	94	90	40	39
Mean survival (days)	670	660	951	945
Survival analysis		P=0.691		P=1.000N

[a] Censored from analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table pairwise comparison (Cox, 1972) with the controls is in the exposed group column. A lower mortality in the dosed group is indicated by N.

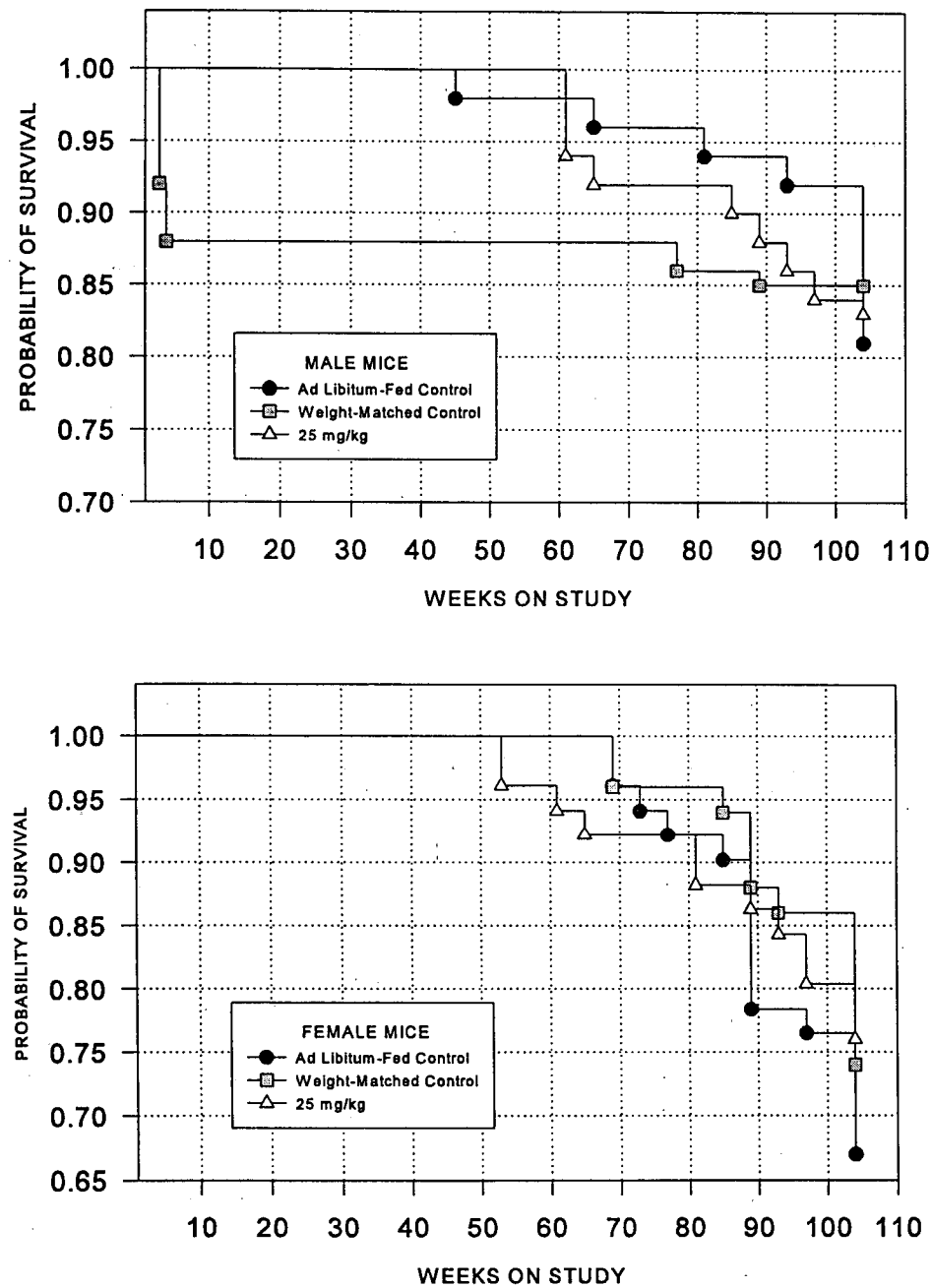


FIGURE 19
Kaplan-Meier Survival Curves for Male and Female Mice Administered Scopolamine Hydrobromide Trihydrate in Water by Gavage for 2 Years: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

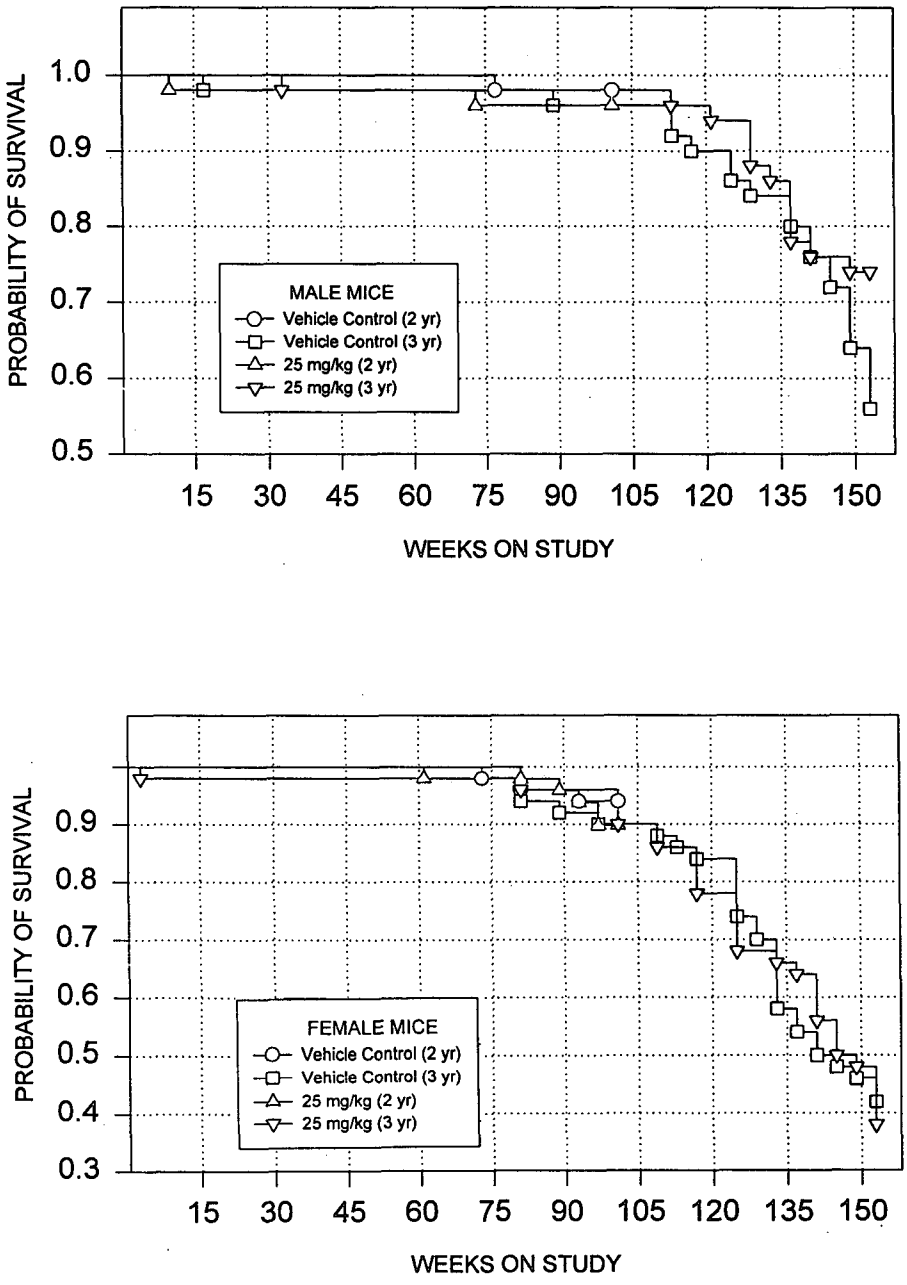


FIGURE 20
Kaplan-Meier Survival Curves for Male and Female Mice Administered Scopolamine Hydrobromide Trihydrate in Water by Gavage for 2 or 3 Years: 2-Year Restricted Feed and 3-Year Restricted Feed Protocols

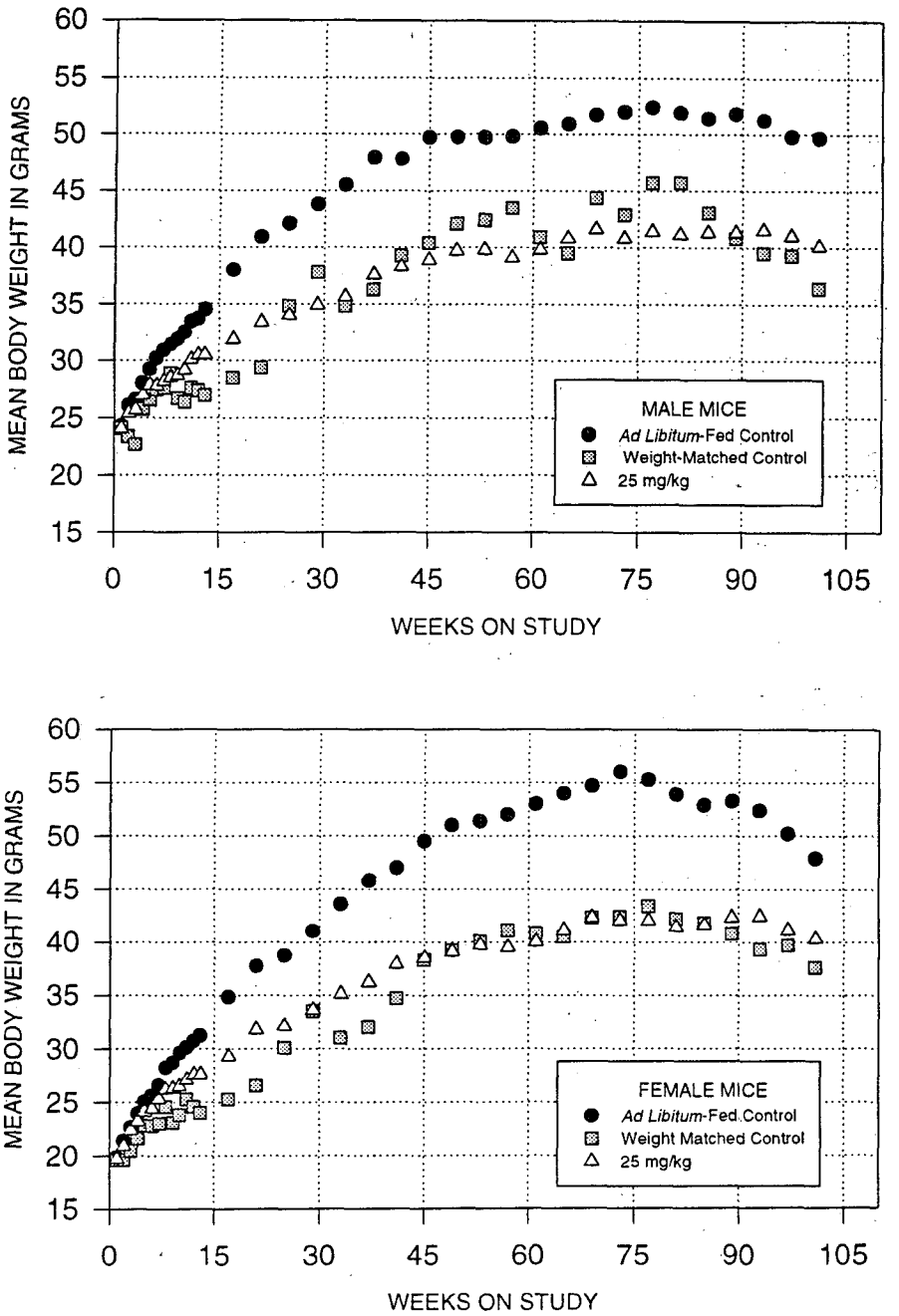


FIGURE 21
Growth Curves for Male and Female Mice Administered Scopolamine Hydrobromide Trihydrate in Water by Gavage for 2 Years: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

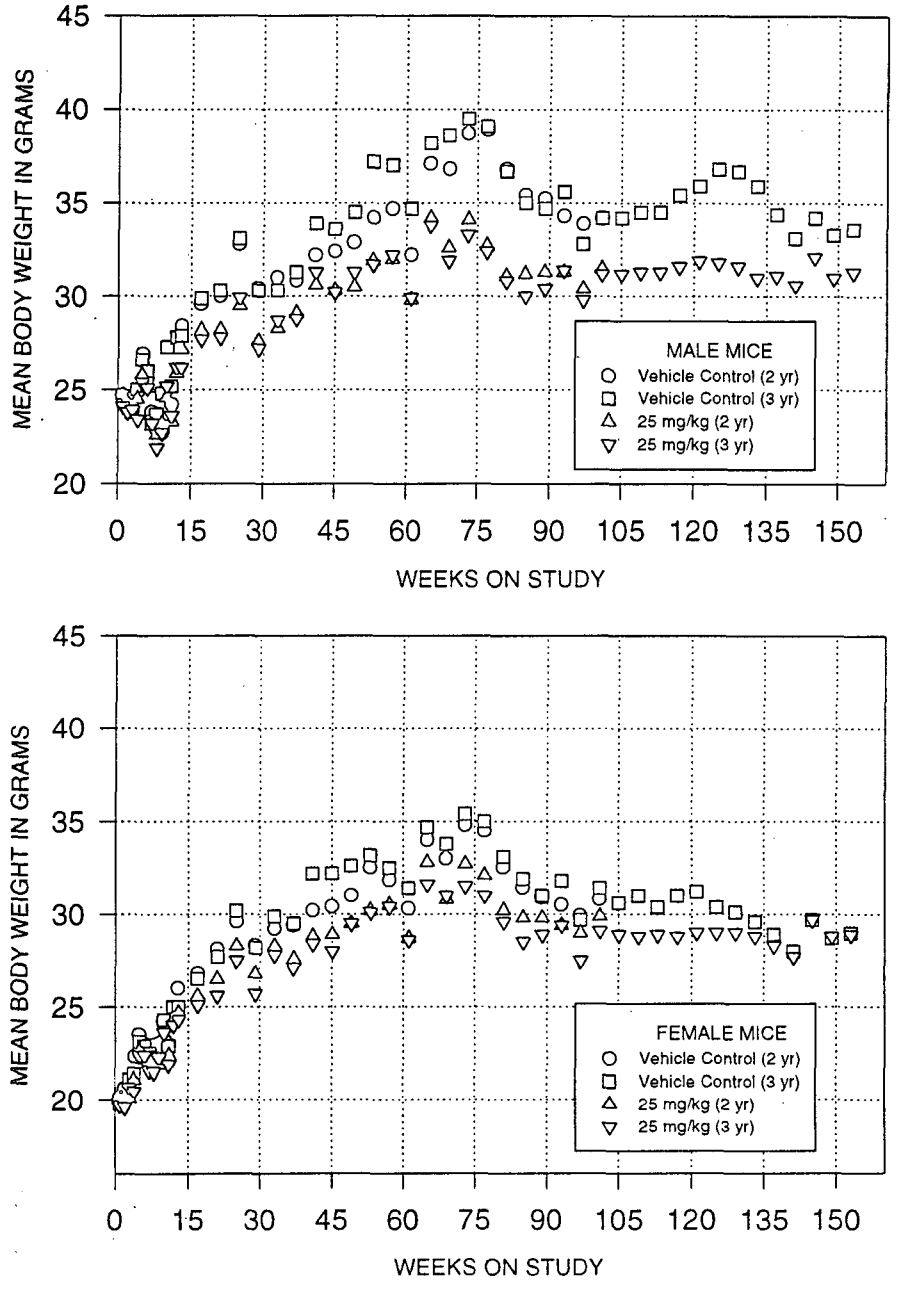


FIGURE 22
Growth Curves for Male and Female Mice Administered Scopolamine Hydrobromide Trihydrate in Water by Gavage for 2 or 3 Years: 2-Year Restricted Feed and 3-Year Restricted Feed Protocols

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the liver. Summaries of the incidences of neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix G for male mice and Appendix H for female mice. Pathologic descriptions of neoplasms and nonneoplastic lesions occurring in rats in the scopolamine hydrobromide trihydrate study are provided in NTP Technical Report 445 (NTP, 1997a).

No significantly increased neoplasm incidences were noted in dosed mice regardless of the method of feeding, suggesting that scopolamine hydrobromide trihydrate is not carcinogenic in mice. The incidences of liver neoplasms in dosed mice fed *ad libitum* (Table 27) and of a variety of nonneoplastic lesions in the weight-matched controls, diet-restricted controls, and mice in the 25 mg/kg groups fed *ad libitum* or receiving restricted diets were less than the incidences of these lesions in controls fed *ad libitum*, suggesting that the lower incidences were related to body weight depression.

TABLE 27
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Male			
15-Month Interim Evaluation			
Number Examined Microscopically	10	10	10
Hepatocellular Adenoma[a]	2	1	0
Hepatocellular Carcinoma	0	0	1
2-Year Study			
Number Examined Microscopically	50	50	50
Basophilic Focus	3	0	0
Clear Cell Focus	12	2	0**
Eosinophilic Focus	21	0	2**
Mixed Cell Focus	5	2	1
Hepatocellular Adenoma			
Overall rate[b]	26/50 (52%)	5/50 (10%)	8/50 (16%)
Adjusted rate[c]	59.0%	11.9%	19.1%
Terminal rate[d]	22/40 (55%)	4/41 (10%)	6/39 (15%)
First incidence (days)	680	721	587
Logistic regression test[e]			P<0.001N
Logistic regression test[f]			P=0.308
Hepatocellular Carcinoma			
Overall rate	6/50 (12%)	5/50 (10%)	7/50 (14%)
Adjusted rate	14.2%	11.8%	17.3%
Terminal rate	4/40 (10%)	4/41 (10%)	6/39 (15%)
First incidence (days)	700	532	622
Logistic regression test			P=0.468
Logistic regression test			P=0.413
Hepatocellular Adenoma or Carcinoma[g]			
Overall rate	30/50 (60%)	10/50 (20%)	15/50 (30%)
Adjusted rate	65.2%	23.2%	35.3%
Terminal rate	24/40 (60%)	8/41 (20%)	12/39 (31%)
First incidence (days)	680	532	587
Logistic regression test			P=0.004N
Logistic regression test			P=0.217

(continued)

TABLE 27
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Female			
15-Month Interim Evaluation			
Number Examined Microscopically	10	10	10
Hepatocellular Adenoma	1	0	0
2-Year Study			
Number Examined Microscopically	51	50	51
Clear Cell Focus	0	1	0
Eosinophilic Focus	17	4	9*
Mixed Cell Focus	6	1	3
Hepatocellular Adenoma			
Overall rate	15/51 (29%)	7/50 (14%)	6/51 (12%)
Adjusted rate	42.3%	18.9%	15.4%
Terminal rate	13/33 (39%)	6/36 (17%)	5/38 (13%)
First incidence (days)	604	721	694
Logistic regression test			P=0.017N
Logistic regression test			P=0.526N
Hepatocellular Carcinoma			
Overall rate	8/51 (16%)	2/50 (4%)	4/51 (8%)
Adjusted rate	21.1%	4.8%	10.3%
Terminal rate	5/33 (15%)	1/36 (3%)	3/38 (8%)
First incidence (days)	594	611	694
Logistic regression test			P=0.170N
Logistic regression test			P=0.339
Hepatocellular Adenoma or Carcinoma[h]			
Overall rate	22/51 (43%)	9/50 (18%)	9/51 (18%)
Adjusted rate	57.1%	23.2%	23.1%
Terminal rate	17/33 (52%)	7/36 (19%)	8/38 (21%)
First incidence (days)	594	611	694
Logistic regression test			P=0.003N
Logistic regression test			P=0.578

* Significantly different ($P \leq 0.05$) from the *ad libitum*-fed control group by the logistic regression test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Number of animals with neoplasms per number of animals with liver examined microscopically
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the dosed group column are the P values corresponding to the pairwise comparisons between the *ad libitum*-fed controls and the dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in the dosed group is indicated by N.
[f] Result of pairwise comparison between the weight-matched controls and the dosed group
[g] Historical incidence for 2-year NTP studies with control groups receiving water by gavage and fed *ad libitum* (mean ± standard deviation): 74/315 (23.5% ± 7.2%); range, 14%-36%
[h] Historical incidence: 21/315 (6.7% ± 4.2%); range, 2%-12%

DISCUSSION AND CONCLUSIONS

The studies presented here were undertaken to compare outcomes when four chemicals were evaluated under typical NTP bioassay conditions and by protocols employing dietary restriction. Specifically, experiments were designed to evaluate the effect of a 15% body weight reduction (attained through feed restriction) on the sensitivity of the bioassay to detect carcinogenicity compared with the results from concurrent evaluations with conventional *ad libitum*-fed animals. Because animals fed restricted diets live longer than those fed *ad libitum*, an arbitrary evaluation at 2 years results in comparisons at disproportionate times in the respective lifespans, thereby potentially masking age-dependent effects. Thus, an additional 3-year/20% survival study was conducted to determine whether an additional year of exposure to the chemicals would influence the neoplasm profile of animals fed restricted diets. Finally, because body weight changes alone, without chemical exposure, alter the expression of a variety of lesions, a comparison employing a weight-matched (pair-weighted) control group was included.

Overall, feed restriction increased the survival of rats and, to a lesser extent, mice, although not consistently in all studies. The enhanced longevity and decreased incidences of neoplasms and nonneoplastic lesions provide evidence that the restricted diets were nutritionally adequate for long-term health and survival. Thus, conditions of "undernutrition without malnutrition" (Weindruch, 1984) were achieved. The weight-matching procedure was generally effective in producing a control group with body weights similar to those of the dosed animals. Salicylazosulfapyridine had such a minor effect on the body weight of male rats that weight matching was not attempted, thereby resulting in a second *ad libitum*-fed control group. It was initially suspected that feed restriction of group-housed rats might result in a heterogenous population of animals with feed consumption ranging from minimally restricted to severely restricted. Because the group housing of rats precluded precise assessment of individual animal feed consumption, variability in body weights was employed as a surrogate indicator of variability in individual feed consumption. Examination of the standard deviations of the weekly body weights of *ad libitum*-fed versus feed-restricted control animals showed that this variability was not greater in feed-restricted animals (data not shown). In fact, the converse was observed; body weights of the feed-restricted animals were generally more homogenous.

The results presented in this report were consistent with observations by others that dietary restriction increases the survival rates and decreases the incidences of neoplasms and nonneoplastic lesions at a variety of sites in control and dosed animals. Table 28 provides a compilation of the increases and decreases in neoplasm responses to the four chemicals under the various protocols. The organ sites listed are those at which any protocol yielded a statistically significant increase or decrease. Following is a discussion of the differences in response between the *ad libitum* feeding, weight-matched, and restricted feed protocols for each chemical.

Butyl Benzyl Phthalate

The incidences of pancreatic acinar cell neoplasms were greater in male rats receiving butyl benzyl phthalate in feed than in the controls fed *ad libitum* or the weight-matched controls (Table 28). A concomitant increase in the incidence of pancreatic acinar cell hyperplasia (*ad libitum*-fed controls, 8%; weight-matched controls, 4%; 12,000 ppm, 24%) suggests that these lesions were related to chemical administration. This interpretation is supported by the observation that some other peroxisome proliferators also cause pancreatic acinar cell neoplasms (see NTP, 1997a). The incidences of these neoplasms were not increased in rats fed a restricted diet for 2 years. However, there was some suggestion of a treatment-related increase in the incidence of proliferative lesions of the pancreatic acinar cell after a longer period of chemical exposure: in the 30-month restricted feed protocol, three exposed male rats

TABLE 28
Summary of Neoplasm Incidences in Long-Term Bioassays by Various Feeding Protocols[a]

Chemical/ Route	Sex/ Species	Neoplasm Site	Control vs. Dosed Group			
			Protocol 1 *Ad Libitum* Feeding	Protocol 2 Weight-Matched Controls	Protocol 3 Restricted Feed (2 years)	Protocol 4 Restricted Feed (up to 3 years)
Increased Incidences						
Butyl benzyl phthalate (Feed)	Male rats	Leukemia	62% vs. 60%	30% vs. 60%**	42% vs. 54%	78% vs. 72%
		Adrenal medulla	20% vs. 20%	6% vs. 20%*	8% vs. 10%	18% vs. 12%
		Pancreas	6% vs. 22%*	2% vs. 22%**	0% vs. 0%	0% vs. 6%
	Female rats	Leukemia	42% vs. 38%	26% vs. 38%*	32% vs. 36%	58% vs. 78%
		Urinary bladder	2% vs. 4%	0% vs. 4%	0% vs. 4%	2% vs. 12%
t-Butylhydroquinone (Feed)	Male rats	Preputial gland	12% vs. 13%	0% vs. 13%**	NA	3% vs. 5%
	Female rats	Clitoral gland	21% vs. 23%	10% vs. 23%*	NA	8% vs. 25%*
Salicylazosulfapyridine (Corn oil gavage)	Male rats	Urinary bladder	0% vs. 12%*	0% vs. 12%*	0% vs. 0%	0% vs. 2%
	Male mice	Liver	48% vs. 88%**	28% vs. 88%**	35% vs. 18%*	44% vs. 36%
Scopolamine hydrobromide trihydrate (Water gavage)	Male and female mice		No carcinogenic effects under any protocol			
Decreased Incidences						
Butyl benzyl phthalate (Feed)	Male rats	Preputial gland	10% vs. 0%*	12% vs. 0%*	2% vs. 2%	2% vs. 4%
	Female rats	Clitoral gland	14% vs. 8%	6% vs. 8%	6% vs. 6%	20% vs. 4%*
		Mammary gland	58% vs. 22%**	14% vs. 22%	26% vs. 4%**	48% vs. 12%**
		Pituitary gland	45% vs. 26%	15% vs. 26%	30% vs. 12%*	52% vs. 32%*
		Skin (subcut.)	2% vs. 0%	2% vs. 0%	2% vs. 0%	8% vs. 0%*
t-Butylhydroquinone (Feed)	Male rats	Pancreas	5% vs. 0%*	0% vs. 0%	NA	0% vs. 0%
		Pituitary gland	32% vs. 10%**	32% vs. 10%**	NA	23% vs. 29%
	Female rats	Adrenal cortex	7% vs. 0%*	0% vs. 0%	NA	0% vs. 2%
		Mammary gland	80% vs. 50%**	43% vs. 50%	NA	52% vs. 28%**
		Pituitary gland	43% vs. 47%	53% vs. 47%	NA	51% vs. 30%**
Salicylazosulfapyridine (Corn oil gavage)	Male rats	Adrenal medulla	32% vs. 16%	20% vs. 16%	18% vs. 2%**	31% vs. 16%**
		Leukemia	26% vs. 6%*	20% vs. 6%	22% vs. 4%**	49% vs. 16%**
		Lung	4% vs. 0%	2% vs. 0%	4% vs. 0%	6% vs. 0%*
	Male mice	Liver	48% vs. 88%	28% vs. 88%	35% vs. 18%*	44% vs. 36%
		Forestomach	6% vs. 0%	10% vs. 0%*	4% vs. 4%	4% vs. 4%
		Harderian gland	6% vs. 4%	4% vs. 4%	6% vs. 6%	17% vs. 2%**
		Lung	28% vs. 22%	18% vs. 22%	25% vs. 6%**	38% vs. 24%
Scopolamine hydrobromide trihydrate (Water gavage)	Male mice	Liver	60% vs. 30%**	20% vs. 30%	10% vs. 2%	26% vs. 26%
	Female mice	Liver	43% vs. 18%**	18% vs. 18%	6% vs. 6%	30% vs. 22%

* Significantly different ($P \leq 0.05$) from the control group by life table analysis (leukemia only) or logistic regression analysis
** $P \leq 0.01$
[a] Rats in the *t*-butylhydroquinone study were fed *ad libitum* or received restricted diets for 30 months or until survival was reduced to 20% in the control or exposed group; males in the *ad libitum* feeding and weight-matched groups received 28 months of exposure, and all other groups received 30 months of exposure. In the other studies, animals in the first, second, and third protocols received 24 months of exposure; under the fourth protocol, animals received restricted diets for 36 months or until survival was reduced to 20%. In the butyl benzyl phthalate study, males received 30 months and females 32 months of exposure. In the salicylazosulfapyridine studies, male rats received 30 months and male mice 36 months of dosing. Mice in the scopolamine hydrobromide trihydrate study received 36 months of dosing.

developed pancreatic acinar cell adenomas. Three exposed male rats in the 2-year feed-restricted group and two in the 30-month feed-restricted group had acinar cell hyperplasia; no pancreatic hyperplasia or adenomas were observed in either control group.

There is evidence from the studies in this report and from the literature that lower body weights are associated with a decrease in the incidence of pancreatic acinar cell adenoma in rats. For example, the incidence of pancreatic acinar cell adenoma was lower in feed-restricted male control rats than in the *ad libitum*-fed controls in the three rat studies presented in this report: butyl benzyl phthalate study, 0% versus 6%; *t*-butylhydroquinone study, 0% versus 5%; salicylazosulfapyridine study, 10% versus 24% ($P<0.05$). The consistency of the results for these studies indicates that the stronger chemical-related proliferative response in the *ad libitum* feeding protocol compared to the restricted feed protocol is biologically significant. The low incidences of proliferative lesions in the dosed rats fed restricted diets for up to 30 months suggest that the effects of feed restriction may have delayed the development of spontaneous and treatment-related lesions of the pancreas.

Experimentally induced carcinogenesis of the exocrine pancreas is sensitive to dietary factors such as fat quantity and quality (Roebuck, 1986; NTP, 1994a) and can be inhibited by several different restriction regimens, including feed restriction (Roebuck *et al.*, 1981), caloric restriction, and meal feeding (Roebuck *et al.*, 1993). The reduction of feed intake by meal feeding for 5 hours per day for only the last 2 months of a 14-month study resulted in marked reduction of azaserine-induced pancreatic neoplasms without altering the mean body weights of these restricted animals relative to the *ad libitum*-fed controls (Roebuck *et al.*, 1993). Pancreatic acinar cells isolated from *ad libitum*-fed F334 rats exhibited faster growth rates *in vitro* and a greater proclivity for malignant transformation than those isolated from restricted rats (Hass *et al.*, 1992).

The incidence of adrenal gland pheochromocytoma was marginally greater in exposed male rats than in the weight-matched controls ($P=0.028$; Table A2a). However, the dosed group incidence was not significantly different from that in the *ad libitum*-fed controls, and the incidence of pheochromocytoma was not increased in exposed males in either of the restricted-feed protocols. Thus, this statistically significant difference reflects the decreased incidence of adrenal pheochromocytoma in the weight-matched controls relative to the *ad libitum*-fed controls.

The occurrence of adrenal gland pheochromocytoma is not strongly correlated with body weight in control animals (Seilkop, 1995), so the reduced neoplasm incidence in weight-matched controls (6%) relative to the *ad libitum*-fed controls (20%) was not expected. In the methylphenidate hydrochloride study (NTP, 1995), the maximum mean body weight of 430 g achieved by untreated male control rats approximates the mean body weight of 438 g observed for the weight-matched controls in the butyl benzyl phthalate study. The incidence of adrenal gland pheochromocytoma in untreated control male rats in that study (37%) was greater than the incidence of 20% observed in *ad libitum*-fed, exposed male rats in the butyl benzyl phthalate study and was much greater than the incidence of 6% in the equivalently weight-matched controls in the butyl benzyl phthalate study. The overall incidence of adrenal gland pheochromocytoma in untreated controls in the current NTP historical control database is 33.7% (398/1,182), considerably greater than the 20% observed in the exposed group. For these reasons, the greater incidence of adrenal medulla pheochromocytoma in exposed male rats relative to the weight-matched controls is considered unlikely to be a chemical-related effect.

Urinary bladder transitional cell neoplasms are rarely observed in untreated female F344/N rats and occurred in only 4 of 1,182 (0.3%) control female rats in the current NTP historical database. The four incidences in the historical control database were all papillomas; no carcinomas were observed. In the 32-month restricted feed protocol of the butyl benzyl phthalate study, urinary bladder transitional cell neoplasms occurred in six exposed female rats (two papillomas and four carcinomas); one papilloma occurred in the controls. In the 2-year restricted feed protocol, two exposed females and no control females had urinary bladder papillomas. Urinary bladder

papillomas also occurred in two exposed females fed *ad libitum* and in one *ad libitum*-fed control female; none occurred in the weight-matched controls.

The increased incidences of these urinary bladder neoplasms were accompanied by increased incidences of urinary bladder transitional epithelium hyperplasia in exposed females in the *ad libitum* feeding protocol (2% vs. 20%), the weight-matched controls protocol (0% vs. 20%), the 2-year restricted feed protocol (0% vs. 28%) and the 32-month restricted feed protocol (0% vs. 32%). The consistency of the urinary bladder neoplasm/hyperplasia response indicates that it is related to chemical administration. This effect was only observed in feed-restricted females, which had greater survival rates at 2 years and which were administered butyl benzyl phthalate for a longer period of time than *ad libitum*-fed rats. It is not certain if there was a sex difference in response to butyl benzyl phthalate. In the feed-restricted groups, one exposed male at 2 years and two at 30 months had urinary bladder neoplasms. However, exposed males received a concentration of butyl benzyl phthalate that was half that administered to females.

The incidence of mononuclear cell leukemia was greater in exposed male and female rats fed *ad libitum* than in the weight-matched controls (Table 28). However, these increases were not significantly different from those in the *ad libitum*-fed controls, and no treatment-related increases in the incidence of mononuclear cell leukemia occurred in either of the restricted feed protocols. Thus, these statistically significant differences were considered due to the decreased incidences of mononuclear cell leukemia in the weight-matched controls (males, 30%; females, 26%) relative to *ad libitum*-fed controls (males, 62%; females, 42%).

These increased incidences of mononuclear cell leukemia are considered an incidental finding for several reasons. First, these increases were only observed in the weight-matched controls protocol. Also, although the increased incidence in exposed male rats (30% vs. 60%) was highly significant, the increased incidence in females was not as great (26% vs. 38%) and was significant by the life table test (P=0.034) but not by logistic regression analysis (P=0.302).

The weight-matched controls in the butyl benzyl phthalate study were the only groups in the dietary restriction studies with both reduced mean body weights and decreased incidences of mononuclear cell leukemia. In the *t*-butylhydroquinone study, for example, the weight-matched and feed-restricted controls weighed much less than the *ad libitum*-fed controls and yet did not have lower incidences of mononuclear cell leukemia after 28 or 30 months (males: *ad libitum*-fed controls, 65%; weight-matched controls, 75%; feed-restricted controls, 77%; females: 45%, 42%, 62%). Similarly, in male rats in the salicylazosulfapyridine study, the *ad libitum*-fed and weight-matched controls weighed much more than the feed-restricted controls, and yet the mononuclear cell leukemia rates were similar among the three groups (26%, 20%, and 22%, respectively). Finally, even in the butyl benzyl phthalate study, the incidence of mononuclear cell leukemia in the feed-restricted control male rats (42%) was greater than that in the weight-matched controls (30%), even though the feed-restricted controls weighed much less than the weight-matched controls (368 g vs. 400 g at week 53).

The incidence of mononuclear cell leukemia is weakly and inconsistently correlated with body weight in control animals (Seilkop, 1995). In the previously mentioned methylphenidate hydrochloride study (NTP, 1995), in which the maximum mean body weight achieved by untreated male control rats approximates that observed in the weight-matched control males in the butyl benzyl phthalate study, the incidence of mononuclear cell leukemia in the untreated control group was 58%; this incidence is similar to that observed in the *ad libitum*-fed males administered butyl benzyl phthalate and much greater than the incidence in the weight-matched controls in the butyl benzyl phthalate study.

In contrast, other investigators have reported that feed restriction delays the occurrence (Yu *et al.*, 1982) and lessens the severity (Maeda *et al.*, 1985) of leukemia in F344 rats. Feed-restricted rats in lifetime studies have been shown to have greater incidences of mononuclear cell leukemia than rats fed *ad libitum*, probably because the feed-restricted rats lived longer (Shimokawa *et al.*, 1993; Thurman *et al.*, 1994). Feed restriction decreases the rate of transplanted mononuclear cell leukemia progression in Fischer 344

rats through its influence on cell proliferation via suppression of the GH:IGF-1 axis and its enhancement of host defenses against neoplastic cells (Hursting *et al.*, 1993). Finally, mononuclear cell leukemia is known to be sensitive to nutritional factors; the incidence of this neoplasm in male rats, but not in females, is decreased by gavage administration of corn oil (Haseman *et al.*, 1985; Hursting *et al.*, 1994).

In a previous NTP study of butyl benzyl phthalate (NTP, 1982a), female rats receiving the highest concentration (12,000 ppm) had a greater incidence of mononuclear cell leukemia than the controls. However, this concentration did not cause an increased incidence of mononuclear cell leukemia in the more recent NTP study (NTP, 1997c), and the increased incidence observed in the current study at an even higher concentration (24,000 ppm) was only marginally significant, as noted above. Thus, this effect is considered to be an uncertain finding.

t-Butylhydroquinone

The three protocols for the study of *t*-butylhydroquinone had disparate incidences of clitoral and preputial gland neoplasms in rats. No increases in the incidences of these neoplasms were observed in exposed rats in the *ad libitum* feeding protocol (Table 28). However, the incidences of these neoplasms in the weight-matched controls were markedly less than those in the *ad libitum*-fed controls; as a result, the incidences in exposed males (13%) and female rats (23%) were significantly greater ($P<0.01$) than those in the weight-matched controls (males, 0%; females, 10%). Exposed female rats fed a restricted diet also had a significantly greater incidence of clitoral gland neoplasms after 30 months than the feed-restricted controls (8% vs. 25%; $P<0.05$).

The increases in these neoplasm incidences are considered an uncertain finding for several reasons. First, the incidences of clitoral and preputial gland neoplasms are not strongly correlated with body weight in control animals (Seilkop, 1995), so the reduced neoplasm incidence in the weight-matched controls was not expected. Second, the clitoral and preputial gland neoplasm responses among the dietary restriction studies were inconsistent. For example, the weight-matched control male rats in the butyl benzyl phthalate study had approximately the same mean body weight as the weight-matched controls in the *t*-butylhydroquinone study and yet had a much greater incidence of preputial gland neoplasms at 2 years (12%) than the incidence in the controls in the *t*-butylhydroquinone study at 28 months (0%).

Similarly, the incidence of clitoral gland neoplasms in feed-restricted female control rats at 30 months in the *t*-butylhydroquinone study (8%) is much lower than the corresponding control incidence in the butyl benzyl phthalate study (20%; Table 28). These comparisons suggest that control incidences of clitoral and preputial gland neoplasms in the *t*-butylhydroquinone study may have been unusually low and that the greater neoplasm incidences in the exposed groups are therefore an incidental finding.

Salicylazosulfapyridine

Rats: Urinary bladder neoplasms were observed in six male rats receiving salicylazosulfapyridine by gavage but not in the *ad libitum*-fed or weight-matched controls (Table 28). The incidence of urinary bladder hyperplasia was concomitantly increased (*ad libitum*-fed controls, 0%; weight-matched controls, 0%; 337.5 mg/kg, 82%). The urinary bladder neoplasms all occurred in rats grossly observed at necropsy to have urinary bladder calculi; in addition, urinary bladder concretions were observed microscopically in 10 of 50 dosed rats fed *ad libitum* but in neither control group.

There was little evidence of urinary bladder concretion in feed-restricted rats, with only one dosed male affected after 30 months. The incidence of urinary bladder hyperplasia in dosed, feed-restricted rats was still greater than that in the controls at 2 years (0% vs. 14%) and at 30 months (0% vs. 16%), but the magnitude of the response was much less than that observed in the *ad libitum* feeding and weight-matched controls protocols. A single dosed rat in the 30-month feed restriction protocol had a urinary bladder neoplasm (one other rat had urinary bladder concretion). Thus, it appears that the absence of urinary bladder neoplasms in dosed rats in the restricted feed groups may have been related to the absence of urinary bladder calculi and concretions in these groups.

Feed restriction has been shown to delay the onset and slow the age-related severity of nephropathy in F344 rats (Yu *et al.*, 1982). The beneficial effects of both calorie and protein reduction on the severity of nephropathy has been observed in F344 rats and in other rat strains (Saxton and Kimball, 1941; Bras and Ross, 1964; Tucker *et al.*, 1976; Everitt *et al.*, 1982). The consumption of less food (and less protein) may have resulted in the decreased severity of nephropathy in diet-restricted rats, contributing to a more effective removal of precipitated salicylazosulfapyridine or its metabolites from the kidney and urinary bladder and decreasing the formation of crystals and subsequent urinary tract concretions.

The incidences of mononuclear cell leukemia in dosed male rats in the *ad libitum* feeding protocol and the 2-year and 30-month restricted feed protocols were significantly less than those in the respective controls. The incidences of hematopoietic cell proliferation and hemosiderin pigmentation in the spleen were concurrently increased in dosed males. The biological significance of these changes is uncertain; in a number of NTP studies, chemicals causing significantly decreased incidences of mononuclear cell leukemia have also caused changes suggestive of hematopoietic toxicity at 13 weeks, including increased incidences of splenic hematopoietic cell proliferation, hemosiderin pigmentation, and fibrosis (NTP, 1982b, 1989, 1994b, 1996). However, this association did not occur in all studies in which the incidence of mononuclear cell leukemia was decreased in treated groups (NTP, 1987, 1992). The consistency of the findings in the current studies suggest that salicylazosulfapyridine administration may indeed cause decreased incidences of mononuclear cell leukemia in rats.

Mice: Dosed mice fed *ad libitum* had increased incidences of hepatocellular adenoma relative to the *ad libitum*-fed and weight-matched controls (Table 28). Additionally, increased incidences of liver neoplasms also occurred in dosed female mice and in male mice receiving lower doses of salicylazosulfapyridine that caused no body weight changes (NTP, 1997b). No liver neoplasm response was observed in the restricted feed protocols, even after 3 years of dosing. In fact, a significantly lower incidence of liver neoplasms was observed in dosed mice fed a restricted diet (Table 28). The difference in liver neoplasm incidences between *ad libitum*-fed, dosed male mice (88%) and feed-restricted, dosed male mice (18%) was marked. Incidences of liver neoplasms in B6C3F$_1$ mice are strongly correlated with body weight (Turturro *et al.*, 1993; Seilkop, 1995).

Because the incidences of liver neoplasms were decreased in the control and dosed feed-restricted mice, it appears that the decreased incidences of these neoplasms were attributable in part to the lower mean body weights that resulted from feed restriction and from chemical treatment. In this case, factors associated with body weight, feed intake, or both were clearly stronger inhibitors of mouse liver carcinogenesis than the positive carcinogenic effects of salicylazosulfapyridine. It should be noted that the maximum tolerated dose of 2,700 mg/kg was used in these studies, and the lower mean body weight of dosed male mice fed a restricted diet (85% of the *ad libitum*-fed control mean body weight) may have contributed to the decreased incidence of liver neoplasms in this group.

Under conditions that significantly decreased the spontaneous formation of liver neoplasms in feed-restricted B6C3F$_1$ mice in comparison to *ad libitum*-fed mice, the apoptosis:proliferation ratio for hepatocytes was enhanced in the feed-restricted mice; this change is consistent with the observed protective effects of feed restriction against cancer (James and Muskhelishvili, 1994). Identical conclusions were reached in studies of chemical-induced hyperplasia and neoplasia in Wistar rats (Grasl-Kraupp *et al.*, 1994).

Scopolamine Hydrobromide Trihydrate

Scopolamine hydrobromide trihydrate dosing in mice did not result in significantly increased incidences of neoplasms at any site under any feeding protocol. The significantly lower incidences of liver neoplasms in dosed male and female mice fed *ad libitum*, which is interpretable as a chemical-related, protective effect against carcinogenesis, were not apparent when dosed mice were compared to the weight-matched controls.

Overall Considerations

Two of the four chemicals studied were convincingly found to cause neoplasms at three sites when evaluated under standard *ad libitum* feeding conditions. The affected organs were the urinary bladder and

pancreas in male rats and the liver in male mice. When dosed animals fed *ad libitum* were compared with weight-matched control animals, these three organs were again identified as sites of carcinogenicity. In contrast, none of these organs were sites of carcinogenesis after 2 or 3 years of dosing under the restricted feed protocols; an alternate site, the urinary bladder of female rats dosed for 32 months, was a target of carcinogenesis.

The increased survival of the feed-restricted animals allowed more opportunities for dosing and additional time for neoplasm development; however, this did not result in an enhanced ability to detect a carcinogenic response after 2 years. No neoplasm response associated with chemical exposure under *ad libitum* feeding protocols was identified under restricted feed protocols after 2 to 3 years of chemical treatment. As anticipated, the weight-matched control comparisons provided the largest number of statistically significant increases in neoplasm incidences. This clearly indicates a method to increase the sensitivity of the bioassay to detect potential carcinogenic responses.

The inclusion of concurrent weight-matched controls allows estimation of the effect of body weight changes on the "background" incidences of neoplasms in the dosed groups; three of the current studies demonstrate this. As discussed, the results for liver neoplasms in mice in the salicylazosulfapyridine study indicate that body weight has a greater influence on the neoplasm response than does exposure to the carcinogen. In this specific case, dosed mice fed *ad libitum* had an increased response; however, it is possible that the dose selected for a liver carcinogen could cause sufficient weight loss to mask the true carcinogenic potential of the chemical. Thus, a weight-matched control group can be employed to prevent false negatives for chemicals that suppress body weight.

The statistically significant decreases in the incidence of liver neoplasms in male and female mice in the scopolamine hydrobromide trihydrate study (Table 28), which might be interpreted as a chemical-related anticarcinogenic (protective) effect, were not apparent when the dosed mice were compared to the weight-matched controls. The previously discussed relationship between body weight and mouse liver neoplasms suggests this is an appropriate use of this control group. Because rodent carcinogenicity assays are used for identification of cancer prevention activity (Greenwald *et al.*, 1990; Kelloff *et al.*, 1993), recognition that chemical-related body weight decreases can cause decreased neoplasm incidences could preclude erroneous interpretations.

Finally, the alleviation of age-related nephropathy in feed-restricted male rats in the salicylazosulfapyridine study prevented the development of treatment-associated neoplasms of the urinary tract that occurred in similarly dosed rats fed *ad libitum*. This observation allowed a more definitive conclusion regarding the cause of these responses in the *ad libitum* feeding protocol.

The dose concentrations chosen for these comparisons were based upon the results of 13-week studies conducted under *ad libitum* feeding protocols. Because dietary restriction causes a variety of pleiotropic responses that affect the metabolism, distribution, and disposition of xenobiotics, it is probable that minimally toxic doses (maximum tolerated doses) under *ad libitum* feeding protocols will be altered under feed restriction conditions (Hart *et al.*, 1995). It remains to be seen what the results would be if the chemicals were evaluated at exposure concentrations that provide similar blood concentrations between *ad libitum* feeding and feed restriction regimens. It should be noted that in most cases, mean body weights of the dosed, feed-restricted animals were substantially less than those of the feed-restricted controls; this suggests that maximum tolerated doses were achieved in these restricted feed protocols. Whether a chemical evaluation is conducted under restricted feed or *ad libitum* feeding conditions, body weight changes should be expected in dosed animals, and consideration should be given to the inclusion of weight-matched controls to aid in the interpretation of these studies.

CONCLUSIONS

Butyl benzyl phthalate caused an increased incidence of pancreatic acinar cell neoplasms in *ad libitum*-fed male rats relative to *ad libitum*-fed and weight-matched controls. This change did not occur in rats in the restricted feed protocols after 2 years; however, acinar cell adenomas were observed in three exposed,

feed-restricted males at 30 months. Feed restriction is known to influence the incidence of pancreatic acinar cell neoplasms and may have prevented the full expression of this chemical-induced effect. Butyl benzyl phthalate also caused an increased incidence of urinary bladder neoplasms in female rats in the 32-month restricted feed protocol. The incidences of urinary bladder neoplasms were not significantly increased in female rats in any of the 2-year protocols, suggesting that the length of study, not body weight, was the primary factor in the detection of this carcinogenic response.

Salicylazosulfapyridine caused an increased incidence of urinary bladder papillomas in male rats fed *ad libitum* relative to *ad libitum*-fed and weight-matched controls. This increase was associated with an increased incidence of urinary bladder calculi; the incidences of urinary bladder concretions, dilatation, and hyperplasia were also increased in dosed males. The incidences of urinary bladder papillomas and calculi were not increased in male rats receiving salicylazosulfapyridine and which were fed restricted diets.

In male mice, salicylazosulfapyridine caused an increased incidence of liver neoplasms relative to the *ad libitum*-fed and weight-matched controls. This increased incidence did not occur in the restricted feed protocols. Liver neoplasms in mice are greatly influenced by body weight, and the marked mean body weight reduction observed in dosed male mice in the restricted feed protocols may have overridden the carcinogenic response.

Neither *t*-butylhydroquinone nor scopolamine hydrobromide trihydrate caused increased neoplasm incidences under any of the experimental protocols.

Regarding the future use of dietary restriction regimens in long-term studies, only limited conclusions can be drawn because only four chemicals were evaluated and none of these proved to be a strong carcinogen. However, the results of these studies are consistent with previous findings that dietary restriction increases survival rates and decreases the incidences of neoplasms and nonneoplastic lesions at a variety of sites in rats and mice. This association between reduced body weights and decreased neoplasm incidences underlines the necessity that the doses selected for chronic studies not exceed "minimally toxic doses" so that no marked weight reductions (or increases) will occur in the dosed groups. Such body weight changes complicate the detection of carcinogenic effects.

A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

REFERENCES

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

Bras, G., and Ross, M.H. (1964). Kidney disease and nutrition in the rat. *Toxicol. Appl. Pharmacol.* 6, 247-262.

Code of Federal Regulations (CFR) 21, Part 58.

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

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

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* 32, 236-248.

Everitt, A.V., Porter, B.D., and Wyndham, J.R. (1982). Effects of caloric intake and dietary composition on the development of proteinuria, age-associated renal disease and longevity in the male rat. *Gerontology* 28, 168-175.

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

Grasl-Kraupp, B., Bursch, W., Ruttkay-Nedecky, B., Wagner, A., Lauer, B., and Schulte-Hermann, R. (1994). Food restriction eliminates preneoplastic cells through apoptosis and antagonizes carcinogenesis in rat liver. *Proc. Natl. Acad. Sci. U.S.A.* 91, 9995-9999.

Greenwald, P., Nixon, D.W., Malone, W.F., Kelloff, G.J., Stern, H.R., and Witkin, K.M. (1990). Concepts in cancer chemoprevention research. *Cancer* 65, 1483-1490.

Gross, L., and Dreyfuss, Y. (1984). Reduction in the incidence of radiation-induced tumors in rats after restriction of food intake. *Proc. Natl. Acad. Sci. U.S.A.* 81, 7596-7598.

Hart, R.W., Keenan, K., Turturro, A., Abdo, K.M., Leakey, J., and Lyn-Cook, B. (1995). Caloric restriction and toxicity. *Fundam. Appl. Toxicol.* 25, 184-195.

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

Haseman, J.K. (1993). The value and limitations of a large source of control animal pathology data. In *Computerized Control Animal Pathology Databases: Will They Be Used?* (J.A.N. McAuslane, C. Parkinson, and C.E. Lumley, Eds.), pp. 11-16. Centre for Medicines Research, London.

Haseman, J.K., and Rao, G.N. (1992). Effects of corn oil, time-related changes, and inter-laboratory variability on tumor occurrence in control Fischer 344 (F344/N) rats. *Toxicol. Pathol.* 20, 52-60.

Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. *JNCI* 75, 975-984.

Hass, B.S., Hart, R.W., Gaylor, D.W., Poirier, L.A., and Lyn-Cook, B.D. (1992). An *in vitro* pancreas acinar cell model for testing the modulating effects of caloric restriction and ageing on cellular proliferation and transformation. *Carcinogenesis* 13, 2419-2425.

Hursting, S.D., Switzer, B.R., French, J.E., and Kari, F.W. (1993). The growth hormone: Insulin-like growth factor 1 axis is a mediator of diet restriction-induced inhibition of mononuclear cell leukemia in Fischer rats. *Cancer Res.* **53**, 2750-2757.

Hursting, S.D., Switzer, B.R., French, J.E., and Kari, F.W. (1994). Inhibition of rat mononuclear cell leukemia by corn oil gavage: *In vivo, in situ,* and immune competence studies. *Carcinogenesis* **15**, 193-199.

James, S.J., and Muskhelishvili, L. (1994). Rates of apoptosis and proliferation vary with caloric intake and may influence incidence of spontaneous hepatoma in C57BL/6 × C3H F_1 mice. *Cancer Res.* **54**, 5508-5510.

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

Kelloff, G., Boone, C., Malone, W., and Steele, V. (1993). Recent results in preclinical and clinical drug development of chemopreventive agents at the National Cancer Institute. *Basic Life Sci.* **61**, 373-386.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **80**, 639-648.

Maeda, H., Gleiser, C.A., Masoro, E.J., Murata, I., McMahan, C.A., and Yu, B.P. (1985). Nutritional influences on aging of Fischer 344 rats: II. Pathology. *J. Gerontol.* **40**, 671-688.

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

National Toxicology Program (NTP) (1982a). Carcinogenesis Bioassay of Butyl Benzyl Phthalate (CAS No. 85-68-7) in F344/N Rats and B6C3F_1 Mice (Feed Study). Technical Report Series No. 213. NIH Publication No. 82-1769. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1982b). Carcinogenesis Bioassay of C.I. Solvent Yellow 14 (CAS No. 842-07-9) in F344/N Rats and B6C3F_1 Mice (Feed Study). Technical Report Series No. 226. NIH Publication No. 82-1782. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1987). Toxicology and Carcinogenesis Studies of Phenylephrine Hydrochloride (CAS No. 61-76-7) in F344/N Rats and B6C3F_1 Mice (Feed Studies). Technical Report Series No. 322. NIH Publication No. 87-2578. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989). Toxicology and Carcinogenesis Studies of *para*-Chloroaniline Hydrochloride (CAS No. 20265-96-7) in F344/N Rats and B6C3F_1 Mice (Gavage Studies). Technical Report Series No. 351. NIH Publication No. 89-2806. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1992). Toxicology and Carcinogenesis Studies of C.I. Pigment Red 23 (CAS No. 6471-49-4) in F344/N Rats and B6C3F_1 Mice (Feed Studies). Technical Report Series No. 411. NIH Publication No. 93-3142. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1994a). Comparative Toxicology Studies of Corn Oil, Safflower Oil, and Tricaprylin (CAS Nos. 8001-30-7, 8001-23-8, and 538-23-8) in Male F344/N Rats as Vehicles for Gavage. Technical Report Series No. 426. NIH Publication No. 94-3157. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1994b). Toxicology and Carcinogenesis Studies of *p*-Nitrobenzoic Acid (CAS No. 62-23-7) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). Technical Report Series No. 442. NIH Publication No. 95-3358. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1995). Toxicology and Carcinogenesis Studies of Methylphenidate Hydrochloride (CAS No. 298-59-9) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). Technical Report Series No. 439. NIH Publication No. 95-3355. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1996). Toxicology and Carcinogenesis Studies of 1-Amino-2,4-dibromoanthraquinone (CAS No. 81-49-2) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). Technical Report Series No. 383. NIH Publication No. 96-2838. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1997a). Toxicology and Carcinogenesis Studies of Scopolamine Hydrobromide Trihydrate (CAS No. 6533-68-2) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 445. NIH Publication No. 97-3361. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1997b). Toxicology and Carcinogenesis Studies of Salicylazosulfapyridine (CAS No. 599-79-1) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 457. NIH Publication No. 97-3373. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1997c). Toxicology and Carcinogenesis Studies of Butyl Benzyl Phthalate (CAS No. 85-68-7) in F344/N Rats (Feed Studies). Technical Report Series No. 458. NIH Publication No. 97-3374. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

National Toxicology Program (NTP) (1997d). Toxicology and Carcinogenesis Studies of *t*-Butylhydroquinone (CAS No. 1948-33-0) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). Technical Report Series No. 459. NIH Publication No. 97-3375. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Pollard, M., Luckert, P.H., and Pan, G.-Y. (1984). Inhibition of intestinal tumorigenesis in methylazoxymethanol-treated rats by dietary restriction. *Cancer Treat. Rep.* 68, 405-408.

Roebuck, B.D. (1986). Effects of high levels of dietary fats on the growth of azaserine-induced foci in the rat pancreas. *Lipids* 21, 281-284.

Roebuck, B.D., Yager, J.D., Jr., Longnecker, D.S., and Wilpone, S.A. (1981). Promotion by unsaturated fat of azaserine-induced pancreatic carcinogenesis in the rat. *Cancer Res.* 41, 3961-3966.

Roebuck, B.D., Baumgartner, K.J., and MacMillan, D.L. (1993). Caloric restriction and intervention in pancreatic carcinogenesis in the rat. *Cancer Res.* 53, 46-52.

Ross, M.H., and Bras, G. (1973). Influence of protein under- and overnutrition on spontaneous tumor prevalence in the rat. *J. Nutr.* **103**, 944-963.

Saxton, J.A., Jr., and Kimball, J.C. (1941). Relation of nephrosis and other diseases of albino rats to age and to modifications of diet. *Arch. Pathol.* **32**, 951-965.

Seilkop, S.K. (1995). The effect of body weight on tumor incidence and carcinogenicity testing in B6C3F$_1$ mice and F344 rats. *Fundam. Appl. Toxicol.* **24**, 247-259.

Shimokawa, I., Higami, Y., Hubbard, G.B., McMahan, C.A., Masoro, E.J., and Yu, B.P. (1993). Diet and the suitability of the male Fischer 344 rat as a model for aging research. *J. Gerontol.: Biol. Sci.* **48**, B27-B32.

Tannenbaum, A. (1940). The initiation and growth of tumors. Introduction. I. Effects of underfeeding. *Am. J. Cancer* **38**, 335-350.

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

Thurman, J.D., Bucci, T.J., Hart, R.W., and Turturro, A. (1994). Survival, body weight, and spontaneous neoplasms in *ad libitum*-fed and food-restricted Fischer-344 rats. *Toxicol. Pathol.* **22**, 1-9.

Tucker, S.M., Mason, R.L., and Beauchene, R.E. (1976). Influence of diet and feed restriction on kidney function of aging male rats. *J. Gerontol.* **31**, 264-270.

Turturro, A., Duffy, P.H., and Hart, R.W. (1993). Modulation of toxicity by diet and dietary macronutrient restriction. *Mutat. Res.* **295**, 151-164.

Weindruch, R. (1984). Dietary restriction and the aging process. In *Free Radicals in Molecular Biology, Aging, and Disease* (D. Armstrong, R.S. Sohal, R.G. Cutler, and T.F. Slater, Eds.), pp. 181-202. Raven Press, New York.

Weindruch, R., and Walford, R.L. (1988). Dietary restriction: Effects on disease. In *The Retardation of Aging and Disease by Dietary Restriction*, pp. 73-116. Charles C Thomas, Springfield, IL.

Yu, B.P., Masoro, E.J., Murata, I., Bertrand, H.A., and Lynd, F.T. (1982). Life span study of SPF Fischer 344 male rats fed *ad libitum* or restricted diets: Longevity, growth, lean body mass and disease. *J. Gerontol.* **37**, 130-141.

Yu, B.P., Masoro, E.J., and McMahan, C.A. (1985). Nutritional influences on aging of Fischer 344 rats: I. Physical, metabolic, and longevity characteristics. *J. Gerontol.* **40**, 657-670.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE DIETARY RESTRICTION STUDY OF BUTYL BENZYL PHTHALATE

TABLE A1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Moribund	19	15	26
Natural deaths	3	1	2
Survivors			
Terminal sacrifice	28	33	22
Other		1	
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Endocrine System			
Adrenal medulla	(10)	(10)	(10)
Pheochromocytoma benign	1 (10%)		
Pituitary gland	(9)	(10)	(10)
Pars distalis, adenoma	2 (22%)	1 (10%)	1 (10%)
Thyroid gland	(10)	(10)	(10)
C-cell, adenoma			1 (10%)
Genital System			
Testes	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	3 (30%)	5 (50%)	5 (50%)
Interstitial cell, adenoma	4 (40%)	4 (40%)	4 (40%)
Hematopoietic System			
Spleen	(10)	(10)	(10)
Histiocytic sarcoma	1 (10%)		
Integumentary System			
Skin	(10)	(10)	(10)
Keratoacanthoma	1 (10%)		
Systemic Lesions			
Multiple organs[b]	(10)	(10)	(10)
Histiocytic sarcoma	1 (10%)		
Leukemia mononuclear			
Mesothelioma malignant			

TABLE A1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
15-Month Interim Evaluation (continued)			
Systems Examined With No Neoplasms Observed			
Alimentary System			
Cardiovascular System			
General Body System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			
2-Year Study			
Alimentary System			
Intestine large, colon	(44)	(49)	(48)
Carcinoid tumor malignant			1 (2%)
Intestine large, rectum	(49)	(48)	(50)
Leiomyosarcoma	1 (2%)		
Intestine small, duodenum	(50)	(50)	(50)
Intestine small, jejunum	(49)	(50)	(50)
Leiomyoma	1 (2%)		
Intestine small, ileum	(49)	(50)	(50)
Liver	(50)	(50)	(50)
Carcinoma, metastatic, pancreas			1 (2%)
Hepatocellular carcinoma		1 (2%)	
Hepatocellular adenoma	2 (4%)	1 (2%)	4 (8%)
Mesentery	(7)	(11)	(5)
Pancreas	(50)	(50)	(50)
Acinus, adenoma	3 (6%)		10 (20%)
Acinus, carcinoma		1 (2%)	1 (2%)
Salivary glands	(50)	(50)	(50)
Schwannoma malignant			1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)
Carcinoma			1 (2%)
Cardiovascular System			
Heart	(50)	(50)	(50)
Thymoma malignant, metastatic, thymus			1 (2%)

TABLE A1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
2-Year Study (continued)			
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Carcinoma		1 (2%)	
Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma malignant	2 (4%)	1 (2%)	2 (4%)
Pheochromocytoma benign	6 (12%)	3 (6%)	8 (16%)
Pheochromocytoma benign, multiple	3 (6%)		
Islets, pancreatic	(50)	(50)	(50)
Adenoma	5 (10%)	1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(49)
Pars distalis, adenoma	9 (18%)	9 (18%)	10 (20%)
Pars distalis, adenoma, multiple	1 (2%)	1 (2%)	
Pars intermedia, adenoma		1 (2%)	
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	5 (10%)	3 (6%)	1 (2%)
Follicular cell, adenoma			1 (2%)
Follicular cell, carcinoma			2 (4%)
General Body System			
None			
Genital System			
Preputial gland	(50)	(50)	(50)
Adenoma	4 (8%)	3 (6%)	
Carcinoma	1 (2%)	3 (6%)	
Prostate	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)
Testes	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	37 (74%)	40 (80%)	37 (74%)
Interstitial cell, adenoma	7 (14%)	5 (10%)	8 (16%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)	
Lymph node	(23)	(14)	(19)
Iliac, leiomyosarcoma, metastatic, intestine large, rectum	1 (4%)		
Mediastinal, schwannoma malignant, metastatic, skin		1 (7%)	
Lymph node, mandibular	(49)	(48)	(50)
Lymph node, mesenteric	(50)	(50)	(50)
Spleen	(50)	(50)	(50)
Thymus	(49)	(48)	(48)
Thymoma benign			1 (2%)
Thymoma malignant			1 (2%)

TABLE A1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
2-Year Study (continued)			
Integumentary System			
Mammary gland	(45)	(49)	(48)
Fibroadenoma	2 (4%)	3 (6%)	
Skin	(50)	(50)	(50)
Basal cell adenoma		2 (4%)	2 (4%)
Basal cell carcinoma	1 (2%)		1 (2%)
Keratoacanthoma	2 (4%)	1 (2%)	1 (2%)
Squamous cell papilloma	1 (2%)		1 (2%)
Subcutaneous tissue, fibroma	5 (10%)	1 (2%)	5 (10%)
Subcutaneous tissue, lipoma			1 (2%)
Subcutaneous tissue, melanoma malignant	1 (2%)		
Subcutaneous tissue, schwannoma malignant		1 (2%)	1 (2%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Chordoma	1 (2%)		
Osteoma		1 (2%)	
Osteosarcoma			1 (2%)
Skeletal muscle	(1)	(4)	
Carcinoma, metastatic, pancreas		1 (25%)	
Fibrosarcoma		1 (25%)	
Hemangiosarcoma	1 (100%)		
Squamous cell carcinoma, metastatic, lung		1 (25%)	
Nervous System			
Brain	(50)	(50)	(50)
Oligodendroglioma malignant	1 (2%)	2 (4%)	
Spinal cord	(2)		(2)
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma		2 (4%)	1 (2%)
Carcinoma, metastatic, pancreas *		1 (2%)	
Carcinoma, metastatic, adrenal cortex		1 (2%)	
Chordoma, metastatic, bone	1 (2%)		
Squamous cell carcinoma		1 (2%)	
Thymoma malignant, metastatic, thymus			1 (2%)

TABLE A1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
2-Year Study (continued)			
Special Senses System			
Zymbal's gland		(2)	
Carcinoma		2 (100%)	
Urinary System			
Kidney	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, lung		1 (2%)	
Renal tubule, adenoma	1 (2%)	1 (2%)	
Renal tubule, carcinoma			1 (2%)
Urinary bladder	(50)	(50)	(50)
Systemic Lesions			
Multiple organs	(50)	(50)	(50)
Leukemia mononuclear	31 (62%)	15 (30%)	30 (60%)
Mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)
Neoplasm Summary			
Total animals with primary neoplasms[c]			
15-Month interim evaluation	8	10	9
2-Year study	50	50	50
Total primary neoplasms			
15-Month interim evaluation	12	10	11
2-Year study	135	108	136
Total animals with benign neoplasms			
15-Month interim evaluation	8	10	9
2-Year study	46	47	47
Total benign neoplasms			
15-Month interim evaluation	11	10	11
2-Year study	94	76	91
Total animals with malignant neoplasms			
15-Month interim evaluation	1		
2-Year study	37	28	38
Total malignant neoplasms			
15-Month interim evaluation	1		
2-Year study	41	32	45
Total animals with metastatic neoplasms			
2-Year study	2	4	2
Total metastatic neoplasms			
2-Year study	2	7	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 A1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols[a]

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
Disposition Summary				
Animals initially in study	60	60	50	50
15-Month interim evaluation	10	10		
Early deaths				
Accidental death	1			
Moribund	14	17	37	29
Natural deaths	1	2	3	8
Survivors				
Terminal sacrifice	34	31	10	13
Animals examined microscopically	60	60	50	50
15-Month Interim Evaluation				
Genital System				
Testes	(10)	(10)		
Bilateral, interstitial cell, adenoma	1 (10%)	1 (10%)		
Interstitial cell, adenoma	6 (60%)	5 (50%)		
Respiratory System				
Lung	(10)	(10)		
Alveolar/bronchiolar adenoma	1 (10%)			
Systemic Lesions				
Multiple organs[b]	(10)	(10)		
Leukemia mononuclear		1 (10%)		
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				

TABLE A1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
2-Year and 30-Month Protocols				
Alimentary System				
Intestine large, colon	(49)	(48)	(49)	(48)
Intestine large, cecum	(49)	(50)	(49)	(49)
Intestine small, duodenum	(50)	(50)	(50)	(49)
Intestine small, jejunum	(49)	(50)	(50)	(48)
Carcinoma			2 (4%)	
Intestine small, ileum	(49)	(50)	(50)	(49)
Sarcoma				1 (2%)
Liver	(50)	(50)	(50)	(49)
Hepatocellular carcinoma			2 (4%)	
Hepatocellular adenoma	1 (2%)		1 (2%)	
Hepatocellular adenoma, multiple		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Mesentery	(7)	(9)	(12)	(9)
Fibrous histiocytoma		1 (11%)		
Sarcoma	1 (14%)			
Schwannoma malignant		1 (11%)		
Oral mucosa	(1)		(2)	(1)
Squamous cell carcinoma	1 (100%)		1 (50%)	
Squamous cell papilloma			1 (50%)	1 (100%)
Pancreas	(50)	(50)	(50)	(49)
Acinar cell, adenoma				1 (2%)
Acinus, adenoma				1 (2%)
Acinus, adenoma, multiple				1 (2%)
Sarcoma, metastatic, mesentery	1 (2%)			
Salivary glands	(50)	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Schwannoma malignant				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)			
Squamous cell papilloma	1 (2%)	1 (2%)	4 (8%)	
Stomach, glandular	(50)	(50)	(50)	(49)
Tongue	(1)	(1)	(1)	
Squamous cell carcinoma	1 (100%)			
Squamous cell papilloma		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)		1 (2%)
Pheochromocytoma benign	3 (6%)	4 (8%)	6 (12%)	6 (12%)
Pheochromocytoma benign, multiple			1 (2%)	
Bilateral, pheochromocytoma benign			2 (4%)	

TABLE A1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
2-Year and 30-Month Protocols (continued)				
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	4 (8%)	1 (2%)	3 (6%)	5 (10%)
Carcinoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Pituitary gland	(46)	(48)	(50)	(47)
Pars distalis, adenoma	4 (9%)	7 (15%)	7 (14%)	4 (9%)
Pars distalis, adenoma, multiple		1 (2%)		1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	4 (8%)	4 (8%)	4 (8%)	4 (8%)
General Body System				
Peritoneum	(2)	(1)	(2)	(2)
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		2 (4%)
Carcinoma			1 (2%)	
Prostate	(49)	(50)	(50)	(50)
Adenoma			1 (2%)	
Carcinoma		1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(48)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	42 (84%)	42 (84%)	37 (74%)	38 (76%)
Interstitial cell, adenoma	5 (10%)	6 (12%)	9 (18%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lymph node	(12)	(19)	(28)	(23)
Mediastinal, fibrous histiocytoma		1 (5%)		
Mediastinal, histiocytic sarcoma			1 (4%)	
Lymph node, mandibular	(48)	(47)	(49)	(49)
Histiocytic sarcoma			1 (2%)	
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Spleen	(50)	(50)	(50)	(49)
Fibroma		1 (2%)		
Sarcoma			1 (2%)	
Thymus	(46)	(48)	(46)	(45)
Thymoma benign		1 (2%)		1 (2%)

TABLE A1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
2-Year and 30-Month Protocols (continued)				
Integumentary System				
Mammary gland	(49)	(50)	(46)	(49)
Carcinoma				1 (2%)
Fibroadenoma	2 (4%)		3 (7%)	3 (6%)
Skin	(49)	(50)	(50)	(48)
Keratoacanthoma	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Trichoepithelioma			1 (2%)	
Subcutaneous tissue, fibroma		1 (2%)	5 (10%)	2 (4%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		
Subcutaneous tissue, lipoma				1 (2%)
Subcutaneous tissue, melanoma benign				2 (4%)
Subcutaneous tissue, melanoma malignant	1 (2%)			1 (2%)
Musculoskeletal System				
Skeletal muscle		(2)		
Fibrous histiocytoma		1 (50%)		
Fibrous histiocytoma, metastatic, skin		1 (50%)		
Nervous System				
Brain	(50)	(50)	(50)	(49)
Astrocytoma malignant		1 (2%)	2 (4%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma				2 (4%)
Alveolar/bronchiolar carcinoma			1 (2%)	1 (2%)
Sarcoma, metastatic, mesentery	1 (2%)			
Special Senses System				
Eye			(1)	(1)
Schwannoma malignant				1 (100%)
Zymbal's gland	(1)		(1)	(1)
Carcinoma	1 (100%)		1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Urinary bladder	(50)	(50)	(50)	(50)
Transitional epithelium, carcinoma				1 (2%)
Transitional epithelium, papilloma		1 (2%)		1 (2%)

TABLE A1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
2-Year and 30-Month Protocols (continued)				
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Leukemia mononuclear	21 (42%)	27 (54%)	39 (78%)	36 (72%)
Mesothelioma malignant	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	8	6		
2-Year and 30-month protocols	49	50	50	48
Total primary neoplasms				
15-Month interim evaluation	8	7		
2-Year and 30-month protocols	100	112	144	134
Total animals with benign neoplasms				
15-Month interim evaluation	8	6		
2-Year and 30-month protocols	48	50	47	46
Total benign neoplasms				
15-Month interim evaluation	8	6		
2-Year and 30-month protocols	69	75	88	85
Total animals with malignant neoplasms				
15-Month interim evaluation		1		
2-Year and 30-month protocols	29	32	46	42
Total malignant neoplasms				
15-Month interim evaluation		1		
2-Year and 30-month protocols	31	37	56	49
Total animals with metastatic neoplasms				
2-Year protocol	1	1		
Total metastatic neoplasms				
2-Year protocol	2	2		

[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 A2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	12,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm × Weight-Matched Control
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	9/50 (18%)	8/50 (16%)	3/50 (6%)	8/50 (16%)
Adjusted rate[b]	28.2%	25.4%	8.5%	25.4%
Terminal rate[c]	6/28 (21%)	3/22 (14%)	2/33 (6%)	3/22 (14%)
First incidence (days)	607	639	678	639
Life table test[d]		P=0.589N		P=0.049
Logistic regression test[d]		P=0.475N		P=0.086
Fisher exact test[d]		P=0.500N		P=0.100
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	10/50 (20%)	10/50 (20%)	3/50 (6%)	10/50 (20%)
Adjusted rate	30.1%	33.3%	8.5%	33.3%
Terminal rate	6/28 (21%)	5/22 (23%)	2/33 (6%)	5/22 (23%)
First incidence (days)	607	639	678	639
Life table test		P=0.496		P=0.012
Logistic regression test		P=0.573N		P=0.028
Fisher exact test		P=0.598N		P=0.036
Liver: Hepatocellular Adenoma				
Overall rate	2/50 (4%)	4/50 (8%)	1/50 (2%)	4/50 (8%)
Adjusted rate	6.5%	14.2%	3.0%	14.2%
Terminal rate	1/28 (4%)	2/22 (9%)	1/33 (3%)	2/22 (9%)
First incidence (days)	662	464	730 (T)	464
Life table test		P=0.291		P=0.107
Logistic regression test		P=0.339		P=0.180
Fisher exact test		P=0.339		P=0.181
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	2/50 (4%)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted rate	6.5%	14.2%	6.1%	14.2%
Terminal rate	1/28 (4%)	2/22 (9%)	2/33 (6%)	2/22 (9%)
First incidence (days)	662	464	730 (T)	464
Life table test		P=0.291		P=0.209
Logistic regression test		P=0.339		P=0.331
Fisher exact test		P=0.339		P=0.339
Mammary Gland: Fibroadenoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	7.1%	0.0%	9.1%	0.0%
Terminal rate	2/28 (7%)	0/22 (0%)	3/33 (9%)	0/22 (0%)
First incidence (days)	729 (T)	-[e]	730 (T)	-
Life table test		P=0.292N		P=0.200N
Logistic regression test		P=0.292N		P=0.200N
Fisher exact test		P=0.247N		P=0.121N

TABLE A2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	12,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm × Weight-Matched Control
Pancreas: Adenoma				
Overall rate	3/50 (6%)	10/50 (20%)	0/50 (0%)	10/50 (20%)
Adjusted rate	10.7%	41.0%	0.0%	41.0%
Terminal rate	3/28 (11%)	8/22 (36%)	0/33 (0%)	8/22 (36%)
First incidence (days)	729 (T)	709	–	709
Life table test		P=0.011		P<0.001
Logistic regression test		P=0.016		P<0.001
Fisher exact test		P=0.036		P<0.001
Pancreas: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	11/50 (22%)	1/50 (2%)	11/50 (22%)
Adjusted rate	10.7%	42.7%	3.0%	42.7%
Terminal rate	3/28 (11%)	8/22 (36%)	1/33 (3%)	8/22 (36%)
First incidence (days)	729 (T)	674	730 (T)	674
Life table test		P=0.007		P<0.001
Logistic regression test		P=0.014		P<0.001
Fisher exact test		P=0.020		P=0.002
Pancreatic Islets: Adenoma				
Overall rate	5/50 (10%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rate	17.9%	4.5%		
Terminal rate	5/28 (18%)	1/22 (5%)		
First incidence (days)	729 (T)	729 (T)		
Life table test		P=0.161N		
Logistic regression test		P=0.161N		
Fisher exact test		P=0.102N		
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	10/50 (20%)	10/49 (20%)	10/50 (20%)	10/49 (20%)
Adjusted rate	30.6%	35.1%	24.8%	35.1%
Terminal rate	7/28 (25%)	5/22 (23%)	5/33 (15%)	5/22 (23%)
First incidence (days)	438	684	479	684
Life table test		P=0.431		P=0.331
Logistic regression test		P=0.575N		P=0.565
Fisher exact test		P=0.579		P=0.579
Preputial Gland: Adenoma				
Overall rate	4/50 (8%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	12.8%	0.0%	8.5%	0.0%
Terminal rate	2/28 (7%)	0/22 (0%)	2/33 (6%)	0/22 (0%)
First incidence (days)	644	–	678	–
Life table test		P=0.087N		P=0.186N
Logistic regression test		P=0.059N		P=0.136N
Fisher exact test		P=0.059N		P=0.121N

TABLE A2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	12,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm × Weight-Matched Control
Preputial Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	0/50 (0%)	6/50 (12%)	0/50 (0%)
Adjusted rate	15.1%	0.0%	16.4%	0.0%
Terminal rate	2/28 (7%)	0/22 (0%)	4/33 (12%)	0/22 (0%)
First incidence (days)	614	-	607	-
Life table test		P=0.045N		P=0.042N
Logistic regression test		P=0.032N		P=0.020N
Fisher exact test		P=0.028N		P=0.013N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Adjusted rate	10.7%	9.1%	2.8%	9.1%
Terminal rate	3/28 (11%)	2/22 (9%)	0/33 (0%)	2/22 (9%)
First incidence (days)	729 (T)	729 (T)	719	730 (T)
Life table test		P=0.611N		P=0.351
Logistic regression test		P=0.611N		P=0.406
Fisher exact test		P=0.500N		P=0.500
Skin: Basal Cell Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted	2.5%	11.3%	6.1%	11.3%
Terminal rate	0/28 (0%)	2/22 (9%)	2/33 (6%)	2/22 (9%)
First incidence (days)	593	639	730 (T)	639
Life table test		P=0.289		P=0.351
Logistic regression test		P=0.307		P=0.458
Fisher exact test		P=0.309		P=0.500
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	4/50 (8%)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted	12.9%	20.2%	8.7%	20.2%
Terminal rate	3/28 (11%)	4/22 (18%)	2/33 (6%)	4/22 (18%)
First incidence (days)	593	639	719	639
Life table test		P=0.403		P=0.179
Logistic regression test		P=0.518		P=0.286
Fisher exact test		P=0.500		P=0.357
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	5/50 (10%)	5/50 (10%)	1/50 (2%)	5/50 (10%)
Adjusted rate	16.0%	17.3%	3.0%	17.3%
Terminal rate	3/28 (11%)	2/22 (9%)	1/33 (3%)	2/22 (9%)
First incidence (days)	614	668	730 (T)	668
Life table test		P=0.550		P=0.056
Logistic regression test		P=0.614N		P=0.086
Fisher exact test		P=0.630N		P=0.102

TABLE A2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	12,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm × Weight-Matched Control
Testes: Adenoma				
Overall rate	44/50 (88%)	45/50 (90%)	45/50 (90%)	45/50 (90%)
Adjusted rate	97.8%	100.0%	100.0%	100.0%
Terminal rate	27/28 (96%)	22/22 (100%)	33/33 (100%)	22/22 (100%)
First incidence (days)	477	464	422	464
Life table test		P=0.205		P=0.017
Logistic regression test		P=0.619		P=0.528
Fisher exact test		P=0.500		P=0.630N
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/50 (10%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	14.1%	3.6%	9.1%	3.6%
Terminal rate	2/28 (7%)	0/22 (0%)	3/33 (9%)	0/22 (0%)
First incidence (days)	438	709	730 (T)	709
Life table test		P=0.130N		P=0.444N
Logistic regression test		P=0.105N		P=0.387N
Fisher exact test		P=0.102N		P=0.309N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	11.6%	0.0%	11.6%
Terminal rate	0/28 (0%)	1/22 (5%)	0/33 (0%)	1/22 (5%)
First incidence (days)	–	698	–	698
Life table test		P=0.096		P=0.070
Logistic regression test		P=0.121		P=0.099
Fisher exact test		P=0.121		P=0.121
All Organs: Mononuclear Cell Leukemia				
Overall rate	31/50 (62%)	30/50 (60%)	15/50 (30%)	30/50 (60%)
Adjusted rate	71.8%	65.6%	34.9%	65.6%
Terminal rate	16/28 (57%)	7/22 (32%)	6/33 (18%)	7/22 (32%)
First incidence (days)	479	180	422	180
Life table test		P=0.478		P=0.002
Logistic regression test		P=0.492N		P=0.003
Fisher exact test		P=0.500N		P=0.002
All Organs: Benign Neoplasms				
Overall rate	46/50 (92%)	47/50 (94%)	47/50 (94%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	28/28 (100%)	22/22 (100%)	33/33 (100%)	22/22 (100%)
First incidence (days)	438	464	422	464
Life table test		P=0.199		P=0.020
Logistic regression test		P=0.601		P=0.631
Fisher exact test		P=0.500		P=0.661N

TABLE A2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	12,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm × Weight-Matched Control
All Organs: Malignant Neoplasms				
Overall rate	37/50 (74%)	38/50 (76%)	28/50 (56%)	38/50 (76%)
Adjusted rate	78.5%	77.5%	59.2%	77.5%
Terminal rate	18/28 (64%)	11/22 (50%)	14/33 (42%)	11/22 (50%)
First incidence (days)	255	180	339	180
Life table test		P=0.342		P=0.011
Logistic regression test		P=0.469		P=0.045
Fisher exact test		P=0.500		P=0.028
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	28/28 (100%)	22/22 (100%)	33/33 (100%)	22/22 (100%)
First incidence (days)	255	180	339	180
Life table test		P=0.260		P=0.027
Logistic regression test		-[f]		-
Fisher exact test		P=1.000N		P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the *ad libitum*-fed or weight-matched controls and the exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, 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 A2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/50 (6%)	4/50 (8%)	9/50 (18%)	6/50 (12%)
Adjusted rate[b]	7.3%	14.0%	47.6%	38.5%
Terminal rate[c]	1/34 (3%)	4/31 (13%)	3/10 (30%)	4/13 (31%)
First incidence (days)	467	729 (T)	730	807
Life table test[d]		P=0.458		P=0.165N
Logistic regression test[d]		P=0.502		P=0.239N
Fisher exact test[d]		P=0.500		P=0.288N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	4/50 (8%)	5/50 (10%)	9/50 (18%)	6/50 (12%)
Adjusted rate	9.9%	17.1%	47.6%	38.5%
Terminal rate	1/34 (3%)	5/31 (16%)	3/10 (30%)	4/13 (31%)
First incidence (days)	467	729 (T)	730	807
Life table test		P=0.447		P=0.165N
Logistic regression test		P=0.500		P=0.239N
Fisher exact test		P=0.500		P=0.288N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	0/49 (0%)
Adjusted rate			15.0%	0.0%
Terminal rate			1/10 (10%)	0/13 (0%)
First incidence (days)			710	-[e]
Life table test				P=0.117N
Logistic regression test				P=0.128N
Fisher exact test				P=0.125N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate			10.0%	17.4%
Terminal rate			1/10 (10%)	1/13 (8%)
First incidence (days)			897 (T)	827
Life table test				P=0.428
Logistic regression test				P=0.350
Fisher exact test				P=0.309
Mammary Gland: Fibroadenoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rate			14.6%	13.4%
Terminal rate			0/10 (0%)	1/13 (8%)
First incidence (days)			768	687
Life table test				P=0.619N
Logistic regression test				P=0.649
Fisher exact test				P=0.661N

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	4/50 (8%)
Adjusted rate	5.7%	0.0%	14.6%	18.0%
Terminal rate	2/34 (6%)	0/31 (0%)	0/10 (0%)	1/13 (8%)
First incidence (days)	729 (T)	-	768	687
Life table test				P=0.568
Logistic regression test				P=0.483
Fisher exact test				P=0.500
Pancreas: Adenoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/49 (6%)
Adjusted rate	0.0%	0.0%	0.0%	23.1%
Terminal rate	0/34 (0%)	0/31 (0%)	0/10 (0%)	3/13 (23%)
First incidence (days)	-	-	-	897 (T)
Life table test				P=0.163
Logistic regression test				P=0.163
Fisher exact test				P=0.117
Pancreatic Islets: Adenoma				
Overall rate	4/50 (8%)	1/50 (2%)	3/50 (6%)	5/49 (10%)
Adjusted rate	11.0%	4.8%	15.1%	32.9%
Terminal rate	2/34 (6%)	1/31 (3%)	0/10 (0%)	4/13 (31%)
First incidence (days)	719	730 (T)	755	723
Life table test		P=0.217N		P=0.465
Logistic regression test		P=0.206N		P=0.371
Fisher exact test		P=0.181N		P=0.346
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	5/50 (10%)	7/49 (14%)
Adjusted rate	13.8%	9.5%	28.1%	38.4%
Terminal rate	3/34 (9%)	2/31 (6%)	1/10 (10%)	4/13 (31%)
First incidence (days)	719	730 (T)	755	723
Life table test		P=0.263N		P=0.518
Logistic regression test		P=0.255N		P=0.385
Fisher exact test		P=0.218N		P=0.365
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/46 (9%)	8/48 (17%)	7/50 (14%)	5/47 (11%)
Adjusted rate	11.0%	25.5%	32.9%	35.4%
Terminal rate	3/33 (9%)	5/31 (16%)	2/10 (20%)	4/13 (31%)
First incidence (days)	681	350	597	869
Life table test		P=0.158		P=0.281N
Logistic regression test		P=0.227		P=0.407N
Fisher exact test		P=0.199		P=0.424N

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
Skin: Keratoacanthoma or Trichoepithelioma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate			23.3%	5.2%
Terminal rate			2/10 (20%)	0/13 (0%)
First incidence (days)			768	521
Life table test				P=0.453N
Logistic regression test				P=0.509N
Fisher exact test				P=0.500N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	0/50 (0%)	1/50 (2%)	5/50 (10%)	2/50 (4%)
Adjusted rate			26.4%	8.2%
Terminal rate			0/10 (0%)	0/13 (0%)
First incidence (days)			703	674
Life table test				P=0.180N
Logistic regression test				P=0.228N
Fisher exact test				P=0.218N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Fibrous Histiocytoma				
Overall rate	0/50 (0%)	2/50 (4%)	6/50 (12%)	2/50 (4%)
Adjusted rate			31.3%	8.2%
Terminal rate			0/10 (0%)	0/13 (0%)
First incidence (days)			703	674
Life table test				P=0.105N
Logistic regression test				P=0.142N
Fisher exact test				P=0.134N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted rate			19.1%	0.0%
Terminal rate			1/10 (10%)	0/13 (0%)
First incidence (days)			719	-
Life table test				P=0.060N
Logistic regression test				P=0.067N
Fisher exact test				P=0.059N
Testes: Adenoma				
Overall rate	47/50 (94%)	48/50 (96%)	46/50 (92%)	45/50 (90%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	34/34 (100%)	31/31 (100%)	10/10 (100%)	13/13 (100%)
First incidence (days)	549	530	516	498
Life table test		P=0.252		P=0.302N
Logistic regression test		P=0.775N		P=0.390
Fisher exact test		P=0.500		P=0.500N

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/50 (8%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted rate	9.9%	16.2%	14.3%	16.6%
Terminal rate	0/34 (0%)	3/31 (10%)	0/10 (0%)	1/13 (8%)
First incidence (days)	549	619	701	498
Life table test		P=0.598		P=0.605N
Logistic regression test		P=0.643N		P=0.639N
Fisher exact test		P=0.643N		P=0.643N
All Organs: Mononuclear Cell Leukemia				
Overall rate	21/50 (42%)	27/50 (54%)	39/50 (78%)	36/50 (72%)
Adjusted rate	47.4%	60.7%	91.1%	88.8%
Terminal rate	12/34 (35%)	12/31 (39%)	7/10 (70%)	9/13 (69%)
First incidence (days)	583	530	569	498
Life table test		P=0.145		P=0.276N
Logistic regression test		P=0.343		P=0.375N
Fisher exact test		P=0.158		P=0.322N
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	50/50 (100%)	47/50 (94%)	46/50 (92%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	34/34 (100%)	31/31 (100%)	10/10 (100%)	13/13 (100%)
First incidence (days)	467	350	516	498
Life table test		P=0.208		P=0.301N
Logistic regression test		P=0.162		P=0.224
Fisher exact test		P=0.247		P=0.500N
All Organs: Malignant Neoplasms				
Overall rate	29/50 (58%)	32/50 (64%)	46/50 (92%)	42/50 (84%)
Adjusted rate	59.1%	68.9%	95.8%	93.0%
Terminal rate	15/34 (44%)	15/31 (48%)	8/10 (80%)	10/13 (77%)
First incidence (days)	432	530	516	498
Life table test		P=0.281		P=0.228N
Logistic regression test		P=0.418		P=0.585N
Fisher exact test		P=0.341		P=0.178N

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	50/50 (100%)	50/50 (100%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	34/34 (100%)	31/31 (100%)	10/10 (100%)	13/13 (100%)
First incidence (days)	432	350	516	498
Life table test		P=0.264		P=0.280N
Logistic regression test		P=0.456		-[f]
Fisher exact test		P=0.500		P=0.247N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreas, pancreatic islets, pituitary gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, 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 A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Moribund	19	15	26
Natural deaths	3	1	2
Survivors			
Terminal sacrifice	28	33	22
Other		1	
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Intestine large, colon	(10)	(10)	(10)
Parasite metazoan	1 (10%)	1 (10%)	
Intestine large, rectum	(10)	(9)	(9)
Parasite metazoan	2 (20%)	2 (22%)	1 (11%)
Intestine large, cecum	(10)	(10)	(10)
Edema	1 (10%)		
Liver	(10)	(10)	(10)
Angiectasis	1 (10%)		
Basophilic focus	6 (60%)	2 (20%)	1 (10%)
Clear cell focus	2 (20%)	1 (10%)	1 (10%)
Eosinophilic focus	3 (30%)		2 (20%)
Granuloma			1 (10%)
Hemorrhage			1 (10%)
Hepatodiaphragmatic nodule	3 (30%)		1 (10%)
Inflammation, subacute		1 (10%)	1 (10%)
Mixed cell focus		1 (10%)	
Bile duct, hyperplasia	5 (50%)	5 (50%)	
Hepatocyte, vacuolization cytoplasmic	2 (20%)	3 (30%)	
Kupffer cell, pigmentation	1 (10%)		
Lobules, necrosis			2 (20%)
Mesentery	(4)	(4)	(1)
Accessory spleen		1 (25%)	1 (100%)
Fibrosis	1 (25%)		
Fat, necrosis	4 (100%)	3 (75%)	
Pancreas	(10)	(10)	(10)
Atrophy	3 (30%)	6 (60%)	4 (40%)
Cytoplasmic alteration			1 (10%)
Stomach, glandular	(10)	(10)	(10)
Mucosa, hyperplasia		1 (10%)	
Cardiovascular System			
Heart	(10)	(10)	(10)
Cardiomyopathy	8 (80%)	5 (50%)	6 (60%)

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

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
15-Month Interim Evaluation (continued)			
Endocrine System			
Adrenal cortex	(10)	(10)	(10)
Accessory adrenal cortical nodule	4 (40%)	3 (30%)	3 (30%)
Degeneration, fatty		1 (10%)	
Hyperplasia, focal	1 (10%)		
Hypertrophy, focal			1 (10%)
Pituitary gland	(9)	(10)	(10)
Pars distalis, angiectasis		1 (10%)	
Pars distalis, cyst	1 (11%)	1 (10%)	1 (10%)
Pars distalis, hemorrhage			1 (10%)
Pars distalis, hyperplasia, focal	3 (33%)	3 (30%)	2 (20%)
Thyroid gland	(10)	(10)	(10)
Ultimobranchial cyst		1 (10%)	2 (20%)
C-cell, hyperplasia			
Follicle, cyst			1 (10%)
Genital System			
Epididymis	(10)	(10)	(10)
Atypia cellular	1 (10%)	3 (30%)	2 (20%)
Hypospermia		1 (10%)	
Preputial gland	(10)	(10)	(10)
Inflammation, chronic	6 (60%)	7 (70%)	6 (60%)
Inflammation, suppurative	2 (20%)		1 (10%)
Prostate	(10)	(10)	(10)
Corpora amylacea	1 (10%)	2 (20%)	7 (70%)
Inflammation, suppurative	5 (50%)	7 (70%)	4 (40%)
Epithelium, hyperplasia	1 (10%)		
Testes	(10)	(10)	(10)
Interstitial cell, hyperplasia	5 (50%)	4 (40%)	4 (40%)
Hematopoietic System			
Lymph node	(2)		(1)
Deep cervical, hemorrhage	1 (50%)		
Deep cervical, pigmentation	1 (50%)		
Mediastinal, hemorrhage	2 (100%)		1 (100%)
Mediastinal, pigmentation	2 (100%)		1 (100%)
Lymph node, mandibular	(10)	(10)	(10)
Ectasia		1 (10%)	
Hemorrhage	2 (20%)	2 (20%)	
Hyperplasia, lymphoid	1 (10%)	1 (10%)	
Lymph node, mesenteric	(10)	(10)	(10)
Ectasia	1 (10%)		
Hemorrhage			
Hyperplasia, lymphoid			

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
15-Month Interim Evaluation (continued)			
Hematopoietic System (continued)			
Spleen	(10)	(10)	(10)
Hematopoietic cell proliferation	2 (20%)		1 (10%)
Pigmentation, hemosiderin	10 (100%)	9 (90%)	7 (70%)
Thymus	(10)	(10)	(9)
Cyst	1 (10%)		
Musculoskeletal System			
Bone	(10)	(10)	(10)
Femur, osteopetrosis	1 (10%)		
Respiratory System			
Lung	(10)	(10)	(10)
Hemorrhage	1 (10%)		
Infiltration cellular, histiocyte	2 (20%)	1 (10%)	2 (20%)
Alveolar epithelium, hyperplasia	1 (10%)		1 (10%)
Nose	(10)	(10)	(10)
Exudate		3 (30%)	
Foreign body		1 (10%)	
Fungus		2 (20%)	
Mucosa, hyperplasia		1 (10%)	
Mucosa, metaplasia, squamous		2 (20%)	
Special Senses System			
Eye			(1)
Cataract			1 (100%)
Hemorrhage			1 (100%)
Retina, degeneration			1 (100%)
Urinary System			
Kidney	(10)	(10)	(10)
Nephropathy	10 (100%)	9 (90%)	9 (90%)
Renal tubule, pigmentation	10 (100%)	10 (100%)	10 (100%)
Systems Examined With No Lesions Observed			
General Body System			
Integumentary System			
Nervous System			

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
2-Year Study			
Alimentary System			
Intestine large, colon	(44)	(49)	(48)
Dilatation	1 (2%)		
Parasite metazoan	5 (11%)	5 (10%)	4 (8%)
Intestine large, rectum	(49)	(48)	(50)
Parasite metazoan	10 (20%)	6 (13%)	8 (16%)
Intestine large, cecum	(47)	(50)	(50)
Edema	3 (6%)		
Parasite metazoan			1 (2%)
Ulcer	1 (2%)		1 (2%)
Intestine small, ileum	(49)	(50)	(50)
Parasite metazoan		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis		4 (8%)	2 (4%)
Basophilic focus	22 (44%)	20 (40%)	14 (28%)
Clear cell focus	15 (30%)	8 (16%)	8 (16%)
Cyst			2 (4%)
Degeneration, cystic	7 (14%)	7 (14%)	6 (12%)
Developmental malformation		1 (2%)	
Eosinophilic focus	3 (6%)	10 (20%)	4 (8%)
Granuloma			7 (14%)
Hematopoietic cell proliferation		1 (2%)	
Hemorrhage			1 (2%)
Hepatodiaphragmatic nodule	1 (2%)	4 (8%)	7 (14%)
Inflammation, subacute			4 (8%)
Mixed cell focus	6 (12%)	6 (12%)	7 (14%)
Bile duct, hyperplasia	39 (78%)	34 (68%)	27 (54%)
Centrilobular, necrosis	1 (2%)		2 (4%)
Hepatocyte, vacuolization cytoplasmic	6 (12%)	9 (18%)	4 (8%)
Kupffer cell, pigmentation	1 (2%)		6 (12%)
Lobules, necrosis	2 (4%)	2 (4%)	1 (2%)
Mesentery	(7)	(11)	(5)
Accessory spleen		1 (9%)	1 (20%)
Angiectasis	1 (14%)		
Fat, necrosis	5 (71%)	8 (73%)	3 (60%)
Pancreas	(50)	(50)	(50)
Atrophy	29 (58%)	31 (62%)	29 (58%)
Acinus, cytoplasmic alteration	1 (2%)	1 (2%)	
Acinus, hyperplasia, focal	4 (8%)	2 (4%)	12 (24%)
Stomach, forestomach	(50)	(50)	(50)
Edema	1 (2%)		3 (6%)
Ulcer	2 (4%)	1 (2%)	3 (6%)
Mucosa, hyperplasia	2 (4%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)
Edema	2 (4%)	1 (2%)	
Erosion	2 (4%)		1 (2%)
Ulcer	2 (4%)	1 (2%)	1 (2%)
Tongue			(1)
Epithelium, hyperplasia			1 (100%)

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
2-Year Study (continued)			
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Hypertrophy	2 (4%)	2 (4%)	
Inflammation, subacute	2 (4%)	2 (4%)	
Heart	(50)	(50)	(50)
Cardiomyopathy	32 (64%)	24 (48%)	34 (68%)
Inflammation, chronic		1 (2%)	
Thrombosis	2 (4%)		5 (10%)
Schwann cell, hyperplasia		1 (2%)	
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	11 (22%)	10 (20%)	6 (12%)
Angiectasis		8 (16%)	2 (4%)
Degeneration, fatty	3 (6%)	3 (6%)	8 (16%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	7 (14%)	9 (18%)	4 (8%)
Hypertrophy, focal	2 (4%)	3 (6%)	1 (2%)
Vacuolization cytoplasmic	1 (2%)		
Adrenal medulla	(50)	(50)	(50)
Hyperplasia	6 (12%)	6 (12%)	12 (24%)
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia	3 (6%)		2 (4%)
Parathyroid gland	(49)	(48)	(49)
Hyperplasia			1 (2%)
Pituitary gland	(50)	(50)	(49)
Pars distalis, angiectasis	3 (6%)	3 (6%)	
Pars distalis, cyst	3 (6%)	3 (6%)	2 (4%)
Pars distalis, hyperplasia	1 (2%)		2 (4%)
Pars distalis, hyperplasia, focal	7 (14%)	9 (18%)	5 (10%)
Pars distalis, necrosis			1 (2%)
Pars intermedia, angiectasis	3 (6%)	2 (4%)	
Pars intermedia, cyst	1 (2%)	1 (2%)	
Pars intermedia, hyperplasia		2 (4%)	
Thyroid gland	(50)	(50)	(50)
Hyperplasia		1 (2%)	
Ultimobranchial cyst	2 (4%)	1 (2%)	2 (4%)
C-cell, hyperplasia	4 (8%)	12 (24%)	7 (14%)
Follicle, cyst	2 (4%)		4 (8%)
Follicular cell, hyperplasia		1 (2%)	
General Body System			
None			

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
2-Year Study (continued)			
Genital System			
Epididymis	(50)	(50)	(50)
Atypia cellular	28 (56%)	30 (60%)	37 (74%)
Hypospermia	34 (68%)	40 (80%)	43 (86%)
Preputial gland	(50)	(50)	(50)
Ectasia	11 (22%)	9 (18%)	14 (28%)
Hyperplasia	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic	25 (50%)	21 (42%)	17 (34%)
Inflammation, suppurative	9 (18%)	5 (10%)	6 (12%)
Prostate	(50)	(50)	(50)
Corpora amylacea	17 (34%)	24 (48%)	30 (60%)
Fibrosis			1 (2%)
Inflammation, suppurative	29 (58%)	27 (54%)	19 (38%)
Epithelium, hyperplasia	4 (8%)	5 (10%)	3 (6%)
Seminal vesicle	(50)	(50)	(50)
Dilatation	4 (8%)		1 (2%)
Testes	(50)	(50)	(50)
Interstitial cell, hyperplasia	4 (8%)	5 (10%)	6 (12%)
Seminiferous tubule, atrophy	2 (4%)	2 (4%)	4 (8%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hypercellularity	1 (2%)	2 (4%)	
Myelofibrosis	2 (4%)	3 (6%)	5 (10%)
Lymph node	(23)	(14)	(19)
Iliac, hemorrhage	1 (4%)		
Iliac, hyperplasia, lymphoid	1 (4%)		
Iliac, pigmentation	1 (4%)		
Mediastinal, hemorrhage	5 (22%)	4 (29%)	
Mediastinal, hyperplasia, lymphoid		1 (7%)	
Mediastinal, pigmentation	5 (22%)	4 (29%)	5 (26%)
Pancreatic, hemorrhage			1 (5%)
Pancreatic, hyperplasia, lymphoid		1 (7%)	
Pancreatic, pigmentation		1 (7%)	2 (11%)
Renal, hyperplasia, lymphoid	1 (4%)		
Renal, pigmentation	2 (9%)		2 (11%)
Lymph node, mandibular	(49)	(48)	(50)
Congestion	1 (2%)		
Ectasia	6 (12%)	4 (8%)	4 (8%)
Hemorrhage	4 (8%)	8 (17%)	6 (12%)
Hyperplasia, lymphoid	3 (6%)	5 (10%)	5 (10%)
Pigmentation	2 (4%)	7 (15%)	
Lymph node, mesenteric	(50)	(50)	(50)
Ectasia	6 (12%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)	3 (6%)	4 (8%)
Hyperplasia, lymphoid	2 (4%)		

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
2-Year Study (continued)			
Hematopoietic System (continued)			
Spleen	(50)	(50)	(50)
Fibrosis	5 (10%)	7 (14%)	10 (20%)
Granuloma			1 (2%)
Hematopoietic cell proliferation	2 (4%)	6 (12%)	7 (14%)
Metaplasia, osseous	1 (2%)		
Necrosis	1 (2%)	1 (2%)	
Pigmentation, hemosiderin	14 (28%)	2 (4%)	6 (12%)
Thymus	(49)	(48)	(48)
Hemorrhage	1 (2%)		
Integumentary System			
Mammary gland	(45)	(49)	(48)
Hyperplasia	10 (22%)	8 (16%)	12 (25%)
Skin	(50)	(50)	(50)
Acanthosis		1 (2%)	10 (20%)
Cyst epithelial inclusion		1 (2%)	1 (2%)
Hemorrhage			1 (2%)
Hyperkeratosis		1 (2%)	13 (26%)
Inflammation, chronic		1 (2%)	2 (4%)
Inflammation, chronic, focal	1 (2%)		
Metaplasia, osseous	1 (2%)		
Ulcer		1 (2%)	3 (6%)
Subcutaneous tissue, inflammation, chronic		1 (2%)	
Musculoskeletal System			
Bone	(50)	(50)	(50)
Cranium, hyperostosis			1 (2%)
Cranium, osteopetrosis	1 (2%)		
Femur, osteopetrosis		2 (4%)	1 (2%)
Nervous System			
Brain	(50)	(50)	(50)
Compression	4 (8%)	4 (8%)	2 (4%)
Gliosis			1 (2%)
Hemorrhage			2 (4%)
Hydrocephalus	2 (4%)	2 (4%)	1 (2%)
Mineralization	1 (2%)		1 (2%)
Necrosis			2 (4%)
Cerebellum, necrosis			1 (2%)

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
2-Year Study (continued)			
Respiratory System			
Lung	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	13 (26%)	15 (30%)	6 (12%)
Inflammation, subacute	1 (2%)	1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	
Metaplasia, osseous	1 (2%)		
Alveolar epithelium, hyperplasia	7 (14%)	6 (12%)	2 (4%)
Nose	(50)	(50)	(50)
Exudate	17 (34%)	11 (22%)	17 (34%)
Foreign body	8 (16%)	3 (6%)	5 (10%)
Fungus	12 (24%)	10 (20%)	11 (22%)
Mucosa, hyperplasia	11 (22%)	8 (16%)	12 (24%)
Mucosa, metaplasia, squamous	9 (18%)	5 (10%)	2 (4%)
Special Senses System			
Eye	(1)		(1)
Atrophy	1 (100%)		
Urinary System			
Kidney	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	4 (8%)
Mineralization		1 (2%)	
Nephropathy	48 (96%)	48 (96%)	48 (96%)
Renal tubule, cytoplasmic alteration		2 (4%)	1 (2%)
Renal tubule, dilatation			1 (2%)
Renal tubule, hyaline droplet		1 (2%)	
Renal tubule, necrosis		1 (2%)	
Renal tubule, pigmentation	49 (98%)	49 (98%)	50 (100%)
Transitional epithelium, hyperplasia	6 (12%)		1 (2%)
Urinary bladder	(50)	(50)	(50)
Transitional epithelium, hyperplasia			2 (4%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols[a]

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
Disposition Summary				
Animals initially in study	60	60	50	50
15-Month interim evaluation	10	10		
Early deaths				
Accidental death	1			
Moribund	14	17	37	29
Natural deaths	1	2	3	8
Survivors				
Terminal sacrifice	34	31	10	13
Animals examined microscopically	60	60	50	50
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)		
Parasite metazoan	1 (10%)			
Intestine large, rectum	(10)	(10)		
Parasite metazoan	1 (10%)	2 (20%)		
Liver	(10)	(10)		
Basophilic focus	1 (10%)			
Clear cell focus	1 (10%)	3 (30%)		
Eosinophilic focus	1 (10%)	1 (10%)		
Granuloma		1 (10%)		
Bile duct, hyperplasia		1 (10%)		
Hepatocyte, vacuolization cytoplasmic	2 (20%)			
Kupffer cell, pigmentation		1 (10%)		
Mesentery	(3)	(1)		
Fat, necrosis	3 (100%)	1 (100%)		
Pancreas	(10)	(10)		
Atrophy	4 (40%)	5 (50%)		
Cardiovascular System				
Heart	(10)	(10)		
Cardiomyopathy	5 (50%)	4 (40%)		
Endocrine System				
Adrenal cortex	(10)	(10)		
Accessory adrenal cortical nodule	2 (20%)	3 (30%)		
Angiectasis	1 (10%)	1 (10%)		
Degeneration, fatty	2 (20%)			
Hyperplasia, focal	2 (20%)	1 (10%)		
Pituitary gland	(10)	(10)		
Pars distalis, cyst	2 (20%)	1 (10%)		
Pars distalis, hyperplasia, focal	2 (20%)			
Thyroid gland	(10)	(10)		
C-cell, hyperplasia	1 (10%)	1 (10%)		

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

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Epididymis	(10)	(10)		
Atypia cellular	1 (10%)	1 (10%)		
Preputial gland	(10)	(10)		
Inflammation, chronic	9 (90%)	10 (100%)		
Inflammation, suppurative		1 (10%)		
Prostate	(10)	(10)		
Corpora amylacea	2 (20%)	4 (40%)		
Inflammation, suppurative	7 (70%)	4 (40%)		
Epithelium, hyperplasia	1 (10%)	1 (10%)		
Testes	(10)	(10)		
Interstitial cell, hyperplasia	9 (90%)	9 (90%)		
Seminiferous tubule, atrophy	1 (10%)			
Hematopoietic System				
Bone marrow	(10)	(10)		
Hyperplasia, reticulum cell	1 (10%)			
Myelofibrosis		1 (10%)		
Lymph node	(2)			
Mediastinal, hemorrhage	2 (100%)			
Mediastinal, pigmentation	2 (100%)			
Lymph node, mandibular	(10)	(10)		
Hemorrhage	1 (10%)	1 (10%)		
Pigmentation	3 (30%)	1 (10%)		
Lymph node, mesenteric	(10)	(10)		
Hyperplasia, lymphoid	1 (10%)			
Spleen	(10)	(10)		
Pigmentation, hemosiderin		1 (10%)		
Thymus	(10)	(10)		
Hemorrhage	1 (10%)	1 (10%)		
Respiratory System				
Lung	(10)	(10)		
Alveolar epithelium, hyperplasia		1 (10%)		
Nose	(10)	(10)		
Exudate		2 (20%)		
Foreign body		1 (10%)		
Fungus		1 (10%)		
Mucosa, hyperplasia		1 (10%)		
Urinary System				
Kidney	(10)	(10)		
Mineralization		1 (10%)		
Nephropathy	8 (80%)	10 (100%)		
Renal tubule, pigmentation	8 (80%)	10 (100%)		

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year and 30-Month Protocols				
Alimentary System				
Intestine large, colon	(49)	(48)	(49)	(48)
Edema			1 (2%)	
Parasite metazoan	4 (8%)	5 (10%)	4 (8%)	4 (8%)
Intestine large, rectum	(50)	(50)	(50)	(48)
Parasite metazoan	5 (10%)	5 (10%)	5 (10%)	4 (8%)
Intestine large, cecum	(49)	(50)	(49)	(49)
Edema	1 (2%)	1 (2%)	3 (6%)	8 (16%)
Parasite metazoan	1 (2%)			
Ulcer	1 (2%)			1 (2%)
Liver	(50)	(50)	(50)	(49)
Angiectasis	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Basophilic focus	16 (32%)	15 (30%)	7 (14%)	12 (24%)
Clear cell focus	1 (2%)	5 (10%)		2 (4%)
Congestion		1 (2%)		1 (2%)
Cyst				1 (2%)
Degeneration, cystic		1 (2%)	5 (10%)	1 (2%)
Developmental malformation	2 (4%)		2 (4%)	
Eosinophilic focus	6 (12%)	4 (8%)	2 (4%)	8 (16%)
Granuloma	1 (2%)		1 (2%)	3 (6%)
Hematopoietic cell proliferation	2 (4%)		2 (4%)	
Hepatodiaphragmatic nodule	2 (4%)	7 (14%)	3 (6%)	2 (4%)
Inflammation, subacute	2 (4%)	2 (4%)		
Mixed cell focus	1 (2%)	1 (2%)		1 (2%)
Thrombosis			2 (4%)	1 (2%)
Bile duct, hyperplasia	32 (64%)	20 (40%)	36 (72%)	24 (49%)
Centrilobular, necrosis				1 (2%)
Hepatocyte, hyperplasia, focal			1 (2%)	1 (2%)
Hepatocyte, vacuolization cytoplasmic	4 (8%)		2 (4%)	4 (8%)
Kupffer cell, hyperplasia	1 (2%)			
Kupffer cell, pigmentation	3 (6%)	2 (4%)	5 (10%)	8 (16%)
Lobules, necrosis	1 (2%)	3 (6%)	5 (10%)	5 (10%)
Mesentery	(7)	(9)	(12)	(9)
Accessory spleen	2 (29%)	2 (22%)	1 (8%)	2 (22%)
Fat, necrosis	5 (71%)	5 (56%)	9 (75%)	6 (67%)
Pancreas	(50)	(50)	(50)	(49)
Atrophy	36 (72%)	31 (62%)	30 (60%)	27 (55%)
Edema			1 (2%)	
Inflammation, chronic				1 (2%)
Acinus, cytoplasmic alteration	2 (4%)		1 (2%)	3 (6%)
Acinus, hyperplasia, focal		3 (6%)		2 (4%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
2-Year and 30-Month Protocols (continued)				
Alimentary System (continued)				
Salivary glands	(50)	(49)	(50)	(50)
Atrophy				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, squamous		1 (2%)		
Mineralization		1 (2%)		
Ulcer		2 (4%)	2 (4%)	
Mucosa, hyperplasia	1 (2%)	3 (6%)	3 (6%)	
Stomach, glandular	(50)	(50)	(50)	(49)
Edema			2 (4%)	1 (2%)
Erosion	2 (4%)	2 (4%)	4 (8%)	6 (12%)
Mineralization				1 (2%)
Ulcer	1 (2%)	1 (2%)	3 (6%)	
Tongue	(1)	(1)	(1)	
Inflammation, suppurative			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	25 (50%)	29 (58%)	30 (60%)	32 (64%)
Inflammation, chronic	1 (2%)		1 (2%)	
Thrombosis	1 (2%)	1 (2%)	6 (12%)	4 (8%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	18 (36%)	15 (30%)	15 (30%)	18 (36%)
Angiectasis	26 (52%)	26 (52%)	21 (42%)	24 (48%)
Cyst		1 (2%)		1 (2%)
Degeneration, fatty	4 (8%)	3 (6%)	12 (24%)	4 (8%)
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia, focal	9 (18%)		7 (14%)	4 (8%)
Hypertrophy, focal	3 (6%)	2 (4%)	4 (8%)	3 (6%)
Metaplasia, osseous		1 (2%)		
Necrosis				1 (2%)
Thrombosis	1 (2%)		3 (6%)	1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	9 (18%)	8 (16%)	14 (28%)	4 (8%)
Necrosis			1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Pituitary gland	(46)	(48)	(50)	(47)
Pars distalis, angiectasis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Pars distalis, cyst	6 (13%)	6 (13%)	10 (20%)	7 (15%)
Pars distalis, hyperplasia, focal	13 (28%)	6 (13%)	9 (18%)	10 (12%)
Pars intermedia, angiectasis		1 (2%)		2 (4%)
Pars intermedia, cyst	1 (2%)	4 (8%)	6 (12%)	

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
2-Year and 30-Month Protocols (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	5 (10%)	4 (8%)	8 (16%)	4 (8%)
Follicle, cyst	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Follicular cell, hyperplasia				2 (4%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Atypia cellular	39 (78%)	35 (70%)	30 (60%)	23 (46%)
Hypospermia	38 (76%)	44 (88%)	39 (78%)	40 (80%)
Preputial gland	(50)	(50)	(50)	(50)
Ectasia	16 (32%)	16 (32%)	14 (28%)	9 (18%)
Hyperplasia	1 (2%)			1 (2%)
Inflammation, chronic	26 (52%)	15 (30%)	17 (34%)	13 (26%)
Inflammation, suppurative	9 (18%)	9 (18%)	12 (24%)	5 (10%)
Prostate	(49)	(50)	(50)	(50)
Corpora amylacea	22 (45%)	34 (68%)	22 (44%)	21 (42%)
Edema		1 (2%)		
Inflammation, suppurative	22 (45%)	21 (42%)	23 (46%)	15 (30%)
Epithelium, hyperplasia	5 (10%)	8 (16%)	11 (22%)	4 (8%)
Seminal vesicle	(50)	(50)		
Dilatation	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Interstitial cell, hyperplasia	4 (8%)	3 (6%)	9 (18%)	5 (10%)
Seminiferous tubule, atrophy	4 (8%)	5 (10%)	5 (10%)	4 (8%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hypercellularity	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Myelofibrosis	5 (10%)	1 (2%)	4 (8%)	5 (10%)
Lymph node	(12)	(19)	(28)	(23)
Deep cervical, hemorrhage			1 (4%)	
Iliac, hemorrhage				1 (4%)
Inguinal, pigmentation			1 (4%)	
Mediastinal, hemorrhage	1 (8%)	2 (11%)		2 (9%)
Mediastinal, pigmentation	7 (58%)	4 (21%)	10 (36%)	6 (26%)
Pancreatic, ectasia		1 (5%)		
Pancreatic, hemorrhage		1 (5%)	1 (4%)	
Pancreatic, necrosis				1 (4%)
Pancreatic, pigmentation	4 (33%)	4 (21%)	7 (25%)	5 (22%)
Renal, pigmentation	1 (8%)	1 (5%)	5 (18%)	2 (9%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
2-Year and 30-Month Protocols (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(47)	(49)	(49)
Ectasia	5 (10%)	2 (4%)	5 (10%)	2 (4%)
Hemorrhage	5 (10%)	7 (15%)	6 (12%)	5 (10%)
Hyperplasia, lymphoid	2 (4%)	3 (6%)	5 (10%)	1 (2%)
Pigmentation	10 (21%)	8 (17%)	8 (16%)	6 (12%)
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Ectasia	2 (4%)	1 (2%)		
Hemorrhage	2 (4%)	1 (2%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)		3 (6%)	1 (2%)
Pigmentation				1 (2%)
Spleen	(50)	(50)	(50)	(49)
Developmental malformation	1 (2%)			
Fibrosis	7 (14%)	8 (16%)	9 (18%)	15 (31%)
Hematopoietic cell proliferation	5 (10%)	4 (8%)	8 (16%)	4 (8%)
Infiltration cellular, histiocyte				1 (2%)
Inflammation, chronic				1 (2%)
Metaplasia, lipocyte			1 (2%)	
Necrosis		1 (2%)	1 (2%)	1 (2%)
Pigmentation, hemosiderin	6 (12%)	4 (8%)	8 (16%)	3 (6%)
Lymphoid follicle, hyperplasia	1 (2%)			
Thymus	(46)	(48)	(46)	(45)
Ectopic parathyroid gland				1 (2%)
Integumentary System				
Mammary gland	(49)	(50)	(46)	(49)
Hyperplasia	7 (14%)	10 (20%)	10 (22%)	8 (16%)
Skin	(49)	(50)	(50)	(48)
Acanthosis	2 (4%)		2 (4%)	7 (15%)
Cyst epithelial inclusion		1 (2%)	2 (4%)	1 (2%)
Hemorrhage	1 (2%)	1 (2%)		
Hyperkeratosis	2 (4%)		3 (6%)	7 (15%)
Inflammation, chronic active		1 (2%)	1 (2%)	3 (6%)
Ulcer	1 (2%)		2 (4%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, osteopetrosis	2 (4%)	2 (4%)	1 (2%)	
Femur, osteopetrosis	2 (4%)	2 (4%)		1 (2%)
Rib, osteopetrosis		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(49)
Compression	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Hydrocephalus	1 (2%)		3 (6%)	2 (4%)
Necrosis		1 (2%)		2 (4%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	0 ppm	12,000 ppm	0 ppm	12,000 ppm
2-Year and 30-Month Protocols (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Edema	1 (2%)		1 (2%)	1 (2%)
Hemorrhage		1 (2%)	1 (2%)	
Infiltration cellular, histiocyte	4 (8%)	12 (24%)	9 (18%)	12 (24%)
Inflammation, subacute	1 (2%)			2 (4%)
Inflammation, suppurative		1 (2%)		
Alveolar epithelium, hyperplasia	5 (10%)	2 (4%)	6 (12%)	3 (6%)
Nose	(50)	(50)	(50)	(50)
Exudate	5 (10%)	5 (10%)	16 (32%)	7 (14%)
Foreign body		1 (2%)	8 (16%)	1 (2%)
Fungus	4 (8%)	3 (6%)	11 (22%)	5 (10%)
Mucosa, hyperplasia	3 (6%)	1 (2%)	11 (22%)	6 (12%)
Mucosa, metaplasia, squamous	3 (6%)	2 (4%)	12 (24%)	4 (8%)
Special Senses System				
Eye			(1)	(1)
Hemorrhage			1 (100%)	
Inflammation, chronic			1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Calculus, microscopic observation only	1 (2%)	1 (2%)	1 (2%)	
Congestion		1 (2%)		
Cyst		3 (6%)	2 (4%)	
Hydronephrosis				1 (2%)
Mineralization	5 (10%)	4 (8%)	6 (12%)	5 (10%)
Nephropathy	43 (86%)	46 (92%)	49 (98%)	48 (98%)
Thrombosis			1 (2%)	2 (4%)
Renal tubule, atrophy		3 (6%)	1 (2%)	
Renal tubule, dilatation	2 (4%)	5 (10%)	2 (4%)	3 (6%)
Renal tubule, hyperplasia		1 (2%)		
Renal tubule, necrosis	1 (2%)	1 (2%)	4 (8%)	4 (8%)
Renal tubule, pigmentation	47 (94%)	47 (94%)	50 (100%)	47 (96%)
Transitional epithelium, hyperplasia	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage		2 (4%)		1 (2%)
Transitional epithelium, hyperplasia	1 (2%)	2 (4%)		1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE DIETARY RESTRICTION STUDY OF BUTYL BENZYL PHTHALATE

TABLE B1a
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Moribund	23	7	20
Natural deaths	2	2	1
Survivors			
Terminal sacrifice	25	41	29
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Endocrine System			
Pituitary gland	(10)	(10)	(10)
Pars distalis, adenoma		1 (10%)	
Thyroid gland	(10)	(10)	(10)
C-cell, adenoma, multiple	1 (10%)		
Follicular cell, adenoma	1 (10%)		
Genital System			
Uterus	(10)	(10)	(10)
Deciduoma benign	1 (10%)		
Polyp stromal	1 (10%)		
Systemic Lesions			
Multiple organs[b]	(10)	(10)	(10)
Leukemia mononuclear	1 (10%)		
Systems Examined With No Neoplasms Observed			
Alimentary System			
Cardiovascular System			
General Body System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			

TABLE B1a
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
2-Year Study			
Alimentary System			
Intestine large, colon	(50)	(49)	(50)
Intestine large, cecum	(50)	(50)	(49)
Intestine small, jejunum	(50)	(50)	(49)
Carcinoma		1 (2%)	
Intestine small, ileum	(49)	(49)	(50)
Liver	(50)	(50)	(50)
Carcinoma, metastatic, intestine small, jejunum		1 (2%)	
Hepatocellular adenoma			2 (4%)
Mesentery	(10)	(2)	(6)
Liposarcoma	1 (10%)		
Oral mucosa		(1)	(1)
Squamous cell papilloma		1 (100%)	
Pancreas	(50)	(49)	(50)
Acinus, adenoma			2 (4%)
Salivary glands	(49)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Stomach, glandular	(50)	(50)	(50)
Tongue	(3)	(1)	
Squamous cell papilloma	2 (67%)	1 (100%)	
Cardiovascular System			
Heart	(50)	(50)	(50)
Schwannoma malignant	1 (2%)	1 (2%)	1 (2%)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adenoma	1 (2%)		
Carcinoma		1 (2%)	
Adrenal medulla	(49)	(50)	(50)
Pheochromocytoma complex		1 (2%)	
Pheochromocytoma benign	1 (2%)		1 (2%)
Islets, pancreatic	(50)	(49)	(50)
Adenoma	1 (2%)		
Parathyroid gland	(47)	(46)	(48)
Adenoma		1 (2%)	
Pituitary gland	(49)	(47)	(50)
Pars distalis, adenoma	19 (39%)	7 (15%)	13 (26%)
Pars distalis, adenoma, multiple	1 (2%)		
Pars distalis, carcinoma	2 (4%)		
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(49)	(50)	(50)
C-cell, adenoma	4 (8%)	1 (2%)	2 (4%)
C-cell, carcinoma	1 (2%)		
C-cell, carcinoma, multiple			1 (2%)
Follicular cell, carcinoma		1 (2%)	

TABLE B1a
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
2-Year Study (continued)			
General Body System			
Tissue NOS	(1)		(1)
Genital System			
Clitoral gland	(50)	(50)	(50)
Adenoma	3 (6%)	2 (4%)	4 (8%)
Carcinoma	4 (8%)	1 (2%)	
Ovary	(50)	(50)	(50)
Granulosa cell tumor benign	2 (4%)		
Uterus	(50)	(50)	(50)
Deciduoma benign			1 (2%)
Leiomyoma	1 (2%)		
Leiomyosarcoma	1 (2%)		
Polyp stromal	6 (12%)	4 (8%)	7 (14%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Lymph node	(12)	(13)	(15)
Lymph node, mandibular	(49)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)
Spleen	(50)	(50)	(50)
Thymus	(49)	(49)	(48)
Carcinoma, metastatic, thyroid gland			1 (2%)
Integumentary System			
Mammary gland	(49)	(48)	(50)
Adenoma	2 (4%)		
Carcinoma	2 (4%)		
Fibroadenoma	28 (57%)	7 (15%)	11 (22%)
Skin	(50)	(50)	(50)
Basal cell adenoma		1 (2%)	1 (2%)
Keratoacanthoma	1 (2%)	1 (2%)	
Trichoepithelioma		1 (2%)	
Sebaceous gland, carcinoma		1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)
Carcinoma	1 (2%)		
Carcinoma, metastatic, pituitary gland	2 (4%)		

TABLE B1a
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
2-Year Study (continued)			
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)		
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Hemangioma			1 (2%)
Renal tubule, adenoma		1 (2%)	
Renal tubule, carcinoma	1 (2%)		
Urinary bladder	(50)	(50)	(50)
Transitional epithelium, papilloma	1 (2%)		2 (4%)
Systemic Lesions			
Multiple organs	(50)	(50)	(50)
Leukemia mononuclear	21 (42%)	13 (26%)	19 (38%)
Neoplasm Summary			
Total animals with primary neoplasms[c]			
15-Month interim evaluation	4	1	0
2-Year study	49	32	42
Total primary neoplasms			
15-Month interim evaluation	5	1	
2-Year study	112	49	70
Total animals with benign neoplasms			
15-Month interim evaluation	3	1	
2-Year study	40	19	31
Total benign neoplasms			
15-Month interim evaluation	4	1	
2-Year study	77	29	48
Total animals with malignant neoplasms			
15-Month interim evaluation	1		
2-Year study	30	20	22
Total malignant neoplasms			
15-Month interim evaluation	1		
2-Year study	35	20	22
Total animals with metastatic neoplasms			
2-Year study	2	1	1
Total metastatic neoplasms			
2-Year study	2	1	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 B1b
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols[a]

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Disposition Summary				
Animals initially in study	60	60	50	50
15-Month interim evaluation	10	10		
Early deaths				
Moribund	11	10	34	38
Natural deaths	4	1	6	1
Survivors				
Terminal sacrifice	35	39	10	11
Animals examined microscopically	60	60	50	50
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(10)	(10)		
Pars distalis, adenoma	1 (10%)			
Genital System				
Clitoral gland	(10)	(10)		
Adenoma	1 (10%)			
Systemic Lesions				
Multiple organs[b]	(10)	(10)		
Leukemia mononuclear		1 (10%)		
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year and 32-Month Protocols				
Alimentary System				
Intestine large, colon	(50)	(49)	(49)	(50)
Intestine large, cecum	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(49)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)	1 (2%)		

TABLE B1b
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
2-Year and 32-Month Protocols (continued)				
Alimentary System (continued)				
Intestine small, ileum	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma		1 (2%)		2 (4%)
Hepatocellular adenoma	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Mesentery	(1)		(5)	(4)
Lipoma				1 (25%)
Pancreas	(47)	(50)	(50)	(50)
Acinus, adenoma				1 (2%)
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(48)	(50)
Stomach, glandular	(50)	(50)	(48)	(50)
Tongue			(1)	
Squamous cell papilloma			1 (100%)	
Tooth		(1)		(3)
Odontoma				1 (33%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma malignant		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)			
Adrenal medulla	(49)	(50)	(49)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma complex	1 (2%)			
Pheochromocytoma benign	1 (2%)		2 (4%)	5 (10%)
Islets, pancreatic	(47)	(50)	(50)	(50)
Adenoma			1 (2%)	1 (2%)
Carcinoma	1 (2%)			
Pituitary gland	(50)	(49)	(50)	(50)
Pars distalis, adenoma	15 (30%)	6 (12%)	23 (46%)	16 (32%)
Pars distalis, adenoma, multiple			2 (4%)	
Pars distalis, carcinoma			1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
C-cell, adenoma	2 (4%)	2 (4%)	4 (8%)	5 (10%)
C-cell, carcinoma			1 (2%)	
Follicular cell, adenoma	1 (2%)			
Follicular cell, carcinoma				1 (2%)
General Body System				
Tissue NOS	(1)			
Sarcoma	1 (100%)			

TABLE B1b
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
2-Year and 32-Month Protocols (continued)				
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Adenoma	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Carcinoma			5 (10%)	
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor benign	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Polyp stromal		2 (4%)	3 (6%)	7 (14%)
Polyp stromal, multiple			1 (2%)	
Sarcoma stromal			1 (2%)	
Vagina	(1)	(1)	(1)	(1)
Squamous cell papilloma			1 (100%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(10)	(8)	(21)	(18)
Lymph node, mandibular	(49)	(50)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Thymus	(50)	(50)	(49)	(46)
Thymoma benign	1 (2%)			
Integumentary System				
Mammary gland	(50)	(49)	(49)	(50)
Carcinoma	1 (2%)		4 (8%)	1 (2%)
Fibroadenoma	10 (20%)	2 (4%)	18 (37%)	5 (10%)
Fibroadenoma, multiple	2 (4%)		3 (6%)	
Skin	(50)	(50)	(50)	(50)
Keratoacanthoma	1 (2%)		2 (4%)	1 (2%)
Squamous cell papilloma	1 (2%)		1 (2%)	
Sebaceous gland, basal cell adenoma			1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)		3 (6%)	
Subcutaneous tissue, fibroma, multiple			1 (2%)	
Subcutaneous tissue, melanoma malignant			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma			1 (2%)	
Skeletal muscle				(1)
Rhabdomyosarcoma				1 (100%)

TABLE B1b
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
2-Year and 32-Month Protocols (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(49)
Astrocytoma malignant	1 (2%)			1 (2%)
Carcinoma, metastatic, pituitary gland			1 (2%)	
Carcinoma, metastatic, Zymbal's gland				1 (2%)
Ependymoma malignant			1 (2%)	
Glioma malignant			1 (2%)	
Oligodendroglioma malignant	1 (2%)	1 (2%)		
Spinal cord	(1)		(2)	(1)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, Zymbal's gland				1 (2%)
Sarcoma, metastatic, tissue NOS	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland	(1)	(1)	(1)	(1)
Carcinoma	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(49)	(50)
Mast cell tumor benign	1 (2%)			
Transitional epithelium, carcinoma				4 (8%)
Transitional epithelium, papilloma		2 (4%)	1 (2%)	2 (4%)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Leukemia mononuclear	16 (32%)	18 (36%)	29 (58%)	39 (78%)
Mesothelioma NOS				1 (2%)

TABLE B1b
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2	1		
2-Year and 32-month protocols	42	28	50	49
Total primary neoplasms				
15-Month interim evaluation	2	1		
2-Year and 32-month protocols	69	41	121	102
Total animals with benign neoplasms				
15-Month interim evaluation	2			
2-Year and 32-month protocols	29	15	43	34
Total benign neoplasms				
15-Month interim evaluation	2			
2-Year and 32-month protocols	43	18	74	51
Total animals with malignant neoplasms				
15-Month interim evaluation		1		
2-Year and 32-month protocols	24	20	39	41
Total malignant neoplasms				
15-Month interim evaluation		1		
2-Year and 32-month protocols	26	23	47	50
Total animals with metastatic neoplasms				
2-Year and 32-month protocols	1		1	1
Total metastatic neoplasms				
2-Year and 32-month protocols	1		1	2
Total animals with uncertain neoplasms–benign or malignant				
32-Month protocol				1
Total uncertain neoplasms				
32-Month protocol				2

[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 B2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	24,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	24,000 ppm × Weight-Matched Control
Clitoral Gland: Adenoma				
Overall rate[a]	3/50 (6%)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted rate[b]	11.2%	13.8%	4.9%	13.8%
Terminal rate[c]	2/25 (8%)	4/29 (14%)	2/41 (5%)	4/29 (14%)
First incidence (days)	725	736 (T)	737 (T)	737 (T)
Life table test[d]		P=0.572		P=0.191
Logistic regression test[d]		P=0.530		P=0.191
Fisher exact test[d]		P=0.500		P=0.339
Clitoral Gland: Carcinoma				
Overall rate	4/50 (8%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate	14.3%	0.0%		
Terminal rate	3/25 (12%)	0/29 (0%)		
First incidence (days)	702	-[e]		
Life table test		P=0.054N		
Logistic regression test		P=0.069N		
Fisher exact test		P=0.059N		
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	4/50 (8%)	3/50 (6%)	4/50 (8%)
Adjusted rate	24.7%	13.8%	7.3%	13.8%
Terminal rate	5/25 (20%)	4/29 (14%)	3/41 (7%)	4/29 (14%)
First incidence (days)	702	736 (T)	737 (T)	737 (T)
Life table test		P=0.198N		P=0.315
Logistic regression test		P=0.265N		P=0.315
Fisher exact test		P=0.262N		P=0.500
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	28/50 (56%)	11/50 (22%)	7/50 (14%)	11/50 (22%)
Adjusted rate	71.0%	28.9%	16.5%	28.9%
Terminal rate	14/25 (56%)	5/29 (17%)	6/41 (15%)	5/29 (17%)
First incidence (days)	587	487	722	487
Life table test		P=0.001N		P=0.084
Logistic regression test		P<0.001N		P=0.225
Fisher exact test		P<0.001N		P=0.218
Mammary Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	14.6%	0.0%		
Terminal rate	3/25 (12%)	0/29 (0%)		
First incidence (days)	716	-		
Life table test		P=0.052N		
Logistic regression test		P=0.064N		
Fisher exact test		P=0.059N		

TABLE B2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	24,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	24,000 ppm × Weight-Matched Control
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	29/50 (58%)	11/50 (22%)	7/50 (14%)	11/50 (22%)
Adjusted rate	71.8%	28.9%	16.5%	28.9%
Terminal rate	14/25 (56%)	5/29 (17%)	6/41 (15%)	5/29 (17%)
First incidence (days)	587	487	722	487
Life table test		P<0.001N		P=0.084
Logistic regression test		P<0.001N		P=0.225
Fisher exact test		P<0.001N		P=0.218
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	20/49 (41%)	13/50 (26%)	7/47 (15%)	13/50 (26%)
Adjusted rate	57.0%	36.1%	17.1%	36.1%
Terminal rate	11/25 (44%)	7/29 (24%)	5/38 (13%)	7/29 (24%)
First incidence (days)	598	592	722	592
Life table test		P=0.086N		P=0.033
Logistic regression test		P=0.121N		P=0.077
Fisher exact test		P=0.088N		P=0.135
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	22/49 (45%)	13/50 (26%)	7/47 (15%)	13/50 (26%)
Adjusted rate	61.3%	36.1%	17.1%	36.1%
Terminal rate	12/25 (48%)	7/29 (24%)	5/38 (13%)	7/29 (24%)
First incidence (days)	598	592	722	592
Life table test		P=0.042N		P=0.033
Logistic regression test		P=0.058N		P=0.077
Fisher exact test		P=0.039N		P=0.135
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/49 (8%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Adjusted rate	11.4%	6.9%		
Terminal rate	1/25 (4%)	2/29 (7%)		
First incidence (days)	702	736 (T)		
Life table test		P=0.326N		
Logistic regression test		P=0.359N		
Fisher exact test		P=0.329N		
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/49 (10%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	15.1%	8.8%	2.4%	8.8%
Terminal rate	2/25 (8%)	2/29 (7%)	1/41 (2%)	2/29 (7%)
First incidence (days)	702	452	737 (T)	452
Life table test		P=0.337N		P=0.219
Logistic regression test		P=0.346N		P=0.336
Fisher exact test		P=0.346N		P=0.309

TABLE B2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	24,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	24,000 ppm × Weight-Matched Control
Uterus: Stromal Polyp				
Overall rate	6/50 (12%)	7/50 (14%)	4/50 (8%)	7/50 (14%)
Adjusted rate	19.6%	22.4%	9.8%	22.4%
Terminal rate	3/25 (12%)	6/29 (21%)	4/41 (10%)	6/29 (21%)
First incidence (days)	681	487	737 (T)	487
Life table test		P=0.571		P=0.111
Logistic regression test		P=0.470		P=0.214
Fisher exact test		P=0.500		P=0.262
All Organs: Mononuclear Cell Leukemia				
Overall rate	21/50 (42%)	19/50 (38%)	13/50 (26%)	19/50 (38%)
Adjusted rate	51.7%	46.1%	28.6%	46.1%
Terminal rate	7/25 (28%)	8/29 (28%)	9/41 (22%)	8/29 (28%)
First incidence (days)	368	452	551	452
Life table test		P=0.398N		P=0.034
Logistic regression test		P=0.422N		P=0.302
Fisher exact test		P=0.419N		P=0.142
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	31/50 (62%)	19/50 (38%)	31/50 (62%)
Adjusted rate	88.7%	74.9%	43.2%	74.9%
Terminal rate	20/25 (80%)	19/29 (66%)	16/41 (39%)	19/29 (66%)
First incidence (days)	512	452	722	452
Life table test		P=0.060N		P<0.001
Logistic regression test		P=0.047N		P=0.006
Fisher exact test		P=0.038N		P=0.014
All Organs: Malignant Neoplasms				
Overall rate	30/50 (60%)	22/50 (44%)	20/50 (40%)	22/50 (44%)
Adjusted rate	70.1%	50.7%	42.3%	50.7%
Terminal rate	13/25 (52%)	9/29 (31%)	14/41 (34%)	9/29 (31%)
First incidence (days)	39	404	225	404
Life table test		P=0.110N		P=0.128
Logistic regression test		P=0.067N		P=0.582
Fisher exact test		P=0.080N		P=0.420

TABLE B2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	24,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	24,000 ppm × Weight-Matched Control
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	42/50 (84%)	32/50 (64%)	42/50 (84%)
Adjusted rate	98.0%	84.0%	65.3%	84.0%
Terminal rate	24/25 (96%)	21/29 (72%)	24/41 (59%)	21/29 (72%)
First incidence (days)	39	404	225	404
Life table test		P=0.123N		P=0.002
Logistic regression test		P=0.027N		P=0.054
Fisher exact test		P=0.015N		P=0.020

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the *ad libitum*-fed or weight-matched controls and the exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	1/49 (2%)	0/50 (0%)	2/49 (4%)	5/50 (10%)
Adjusted rate[b]			15.6%	18.8%
Terminal rate[c]			1/10 (10%)	1/11 (9%)
First incidence (days)			922	716
Life table test[d]				P=0.296
Logistic regression test[d]				P=0.244
Fisher exact test[d]				P=0.226
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	3/49 (6%)	0/50 (0%)	2/49 (4%)	5/50 (10%)
Adjusted rate	7.9%	0.0%	15.6%	18.8%
Terminal rate	2/35 (6%)	0/39 (0%)	1/10 (10%)	1/11 (9%)
First incidence (days)	624	-	922	716
Life table test		P=0.108N		P=0.296
Logistic regression test		P=0.118N		P=0.244
Fisher exact test		P=0.117N		P=0.226
Clitoral Gland: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	5/50 (10%)	2/49 (4%)
Adjusted rate	16.4%	8.8%	16.2%	11.7%
Terminal rate	2/35 (6%)	3/39 (8%)	0/10 (0%)	1/11 (9%)
First incidence (days)	677	731 (T)	649	779
Life table test		P=0.616N		P=0.176N
Logistic regression test		P=0.636N		P=0.253N
Fisher exact test		P=0.661N		P=0.226N
Clitoral Gland: Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	0/49 (0%)
Adjusted rate			38.5%	0.0%
Terminal rate			3/10 (30%)	0/11 (0%)
First incidence (days)			829	-
Life table test				P=0.023N
Logistic regression test				P=0.021N
Fisher exact test				P=0.030N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	10/50 (20%)	2/49 (4%)
Adjusted rate	16.4%	8.8%	48.5%	11.7%
Terminal rate	2/35 (6%)	3/39 (8%)	3/10 (30%)	1/11 (9%)
First incidence (days)	677	731 (T)	649	779
Life table test		P=0.616N		P=0.010N
Logistic regression test		P=0.636N		P=0.012N
Fisher exact test		P=0.661N		P=0.015N

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Liver: Hepatocellular Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate			10.0%	20.0%
Terminal rate			1/10 (10%)	2/11 (18%)
First incidence (days)			977 (T)	696
Life table test				P=0.344
Logistic regression test				P=0.348
Fisher exact test				P=0.309
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/50 (2%)	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted rate			10.0%	29.5%
Terminal rate			1/10 (10%)	2/11 (18%)
First incidence (days)			977 (T)	696
Life table test				P=0.136
Logistic regression test				P=0.131
Fisher exact test				P=0.102
Mammary Gland: Fibroadenoma				
Overall rate	12/50 (24%)	2/50 (4%)	21/50 (42%)	5/50 (10%)
Adjusted rate	44.9%	5.0%	78.9%	26.1%
Terminal rate	12/35 (34%)	1/39 (3%)	5/10 (50%)	2/11 (18%)
First incidence (days)	730 (T)	600	687	796
Life table test		P=0.002N		P<0.001N
Logistic regression test		P=0.003N		P<0.001N
Fisher exact test		P=0.004N		P<0.001N
Mammary Gland: Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate			14.8%	9.1%
Terminal rate			0/10 (0%)	1/11 (9%)
First incidence (days)			694	977 (T)
Life table test				P=0.150N
Logistic regression test				P=0.173N
Fisher exact test				P=0.181N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	13/50 (26%)	2/50 (4%)	24/50 (48%)	6/50 (12%)
Adjusted rate	46.4%	5.0%	81.5%	34.4%
Terminal rate	12/35 (34%)	1/39 (3%)	5/10 (50%)	3/11 (27%)
First incidence (days)	712	600	687	796
Life table test		P=0.001N		P<0.001N
Logistic regression test		P=0.002N		P<0.001N
Fisher exact test		P=0.002N		P<0.001N

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	15/50 (30%)	6/49 (12%)	25/50 (50%)	16/50 (32%)
Adjusted rate	45.8%	14.9%	85.4%	81.8%
Terminal rate	12/35 (34%)	4/39 (10%)	7/10 (70%)	8/11 (73%)
First incidence (days)	564	600	478	731
Life table test		P=0.016N		P=0.028N
Logistic regression test		P=0.023N		P=0.018N
Fisher exact test		P=0.027N		P=0.052N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	15/50 (30%)	6/49 (12%)	26/50 (52%)	16/50 (32%)
Adjusted rate	45.8%	14.9%	86.0%	81.8%
Terminal rate	12/35 (34%)	4/39 (10%)	7/10 (70%)	8/11 (73%)
First incidence (days)	564	600	478	731
Life table test		P=0.016N		P=0.019N
Logistic regression test		P=0.023N		P=0.011N
Fisher exact test		P=0.027N		P=0.034N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate			23.1%	9.1%
Terminal rate			2/10 (20%)	1/11 (9%)
First incidence (days)			816	977 (T)
Life table test				P=0.261N
Logistic regression test				P=0.256N
Fisher exact test				P=0.309N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate			28.0%	0.0%
Terminal rate			2/10 (20%)	0/11 (0%)
First incidence (days)			687	-
Life table test				P=0.054N
Logistic regression test				P=0.048N
Fisher exact test				P=0.059N
Thyroid Gland (C-cell): Adenoma				
Overall rate	2/49 (4%)	2/50 (4%)	4/50 (8%)	5/50 (10%)
Adjusted rate			18.4%	20.4%
Terminal rate			1/10 (10%)	0/11 (0%)
First incidence (days)			722	634
Life table test				P=0.591
Logistic regression test				P=0.491
Fisher exact test				P=0.500

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	2/49 (4%)	2/50 (4%)	5/50 (10%)	5/50 (10%)
Adjusted rate			24.7%	20.4%
Terminal rate			1/10 (10%)	0/11 (0%)
First incidence (days)			722	634
Life table test				P=0.535N
Logistic regression test				P=0.620N
Fisher exact test				P=0.630N
Urinary Bladder: Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	4/50 (8%)
Adjusted rate			0.0%	29.0%
Terminal rate			0/10 (0%)	3/11 (27%)
First incidence (days)			-	719
Life table test				P=0.075
Logistic regression test				P=0.079
Fisher exact test				P=0.061
Urinary Bladder: Papilloma or Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	1/49 (2%)	6/50 (12%)
Adjusted rate			2.6%	41.0%
Terminal rate			0/10 (0%)	4/11 (36%)
First incidence (days)			694	719
Life table test				P=0.077
Logistic regression test				P=0.077
Fisher exact test				P=0.059
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	0/50 (0%)	2/50 (4%)	4/50 (8%)	7/50 (14%)
Adjusted rate	0.0%		24.0%	32.6%
Terminal rate	0/35 (0%)		2/10 (20%)	2/11 (18%)
First incidence (days)	-		649	684
Life table test				P=0.345
Logistic regression test				P=0.289
Fisher exact test				P=0.262
All Organs: Mononuclear Cell Leukemia				
Overall rate	16/50 (32%)	18/50 (36%)	29/50 (58%)	39/50 (78%)
Adjusted rate	43.9%	40.8%	84.6%	91.7%
Terminal rate	7/35 (20%)	11/39 (28%)	6/10 (60%)	8/11 (73%)
First incidence (days)	359	592	358	530
Life table test		P=0.530		P=0.288
Logistic regression test		P=0.375		P=0.027
Fisher exact test		P=0.417		P=0.026

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
All Organs: Benign Neoplasms				
Overall rate	29/50 (58%)	15/50 (30%)	43/50 (86%)	34/50 (68%)
Adjusted rate	84.9%	38.4%	100.0%	96.8%
Terminal rate	24/35 (69%)	12/39 (31%)	10/10 (100%)	10/11 (91%)
First incidence (days)	564	600	478	634
Life table test		P=0.002N		P=0.043N
Logistic regression test		P=0.002N		P=0.002N
Fisher exact test		P=0.004N		P=0.028N
All Organs: Malignant Neoplasms				
Overall rate	24/50 (48%)	20/50 (40%)	39/50 (78%)	41/50 (82%)
Adjusted rate	58.2%	44.3%	97.0%	94.7%
Terminal rate	11/35 (31%)	12/39 (31%)	9/10 (90%)	9/11 (82%)
First incidence (days)	359	498	358	530
Life table test		P=0.215N		P=0.382N
Logistic regression test		P=0.304N		P=0.426
Fisher exact test		P=0.273N		P=0.402
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	28/50 (56%)	50/50 (100%)	49/50 (98%)
Adjusted rate	92.1%	58.9%	100.0%	100.0%
Terminal rate	28/35 (80%)	18/39 (46%)	10/10 (100%)	11/11 (100%)
First incidence (days)	359	498	358	530
Life table test		P=0.006N		P=0.226N
Logistic regression test		P=0.001N		P=0.404N
Fisher exact test		P=0.002N		P=0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, liver, pituitary gland, thyroid gland, urinary bladder, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Moribund	23	7	20
Natural deaths	2	2	1
Survivors			
Terminal sacrifice	25	41	29
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Intestine large, colon	(10)	(10)	(10)
Parasite metazoan		1 (10%)	1 (10%)
Intestine large, rectum	(10)	(8)	(10)
Parasite metazoan		2 (25%)	
Liver	(10)	(10)	(10)
Basophilic focus	10 (100%)	7 (70%)	9 (90%)
Eosinophilic focus		1 (10%)	
Granuloma	1 (10%)	2 (20%)	
Hepatodiaphragmatic nodule	1 (10%)	3 (30%)	
Bile duct, hyperplasia	1 (10%)		
Mesentery	(1)		
Fat, necrosis	1 (100%)		
Pancreas	(10)	(10)	(10)
Atrophy	1 (10%)	1 (10%)	
Tongue			(1)
Epithelium, hyperplasia			1 (100%)
Cardiovascular System			
Heart	(10)	(10)	(10)
Cardiomyopathy	1 (10%)		
Endocrine System			
Adrenal cortex	(10)	(10)	(10)
Accessory adrenal cortical nodule	2 (20%)	4 (40%)	4 (40%)
Angiectasis	5 (50%)	1 (10%)	3 (30%)
Cyst			1 (10%)
Degeneration, fatty	1 (10%)		
Hyperplasia, focal		1 (10%)	1 (10%)
Hypertrophy, focal	1 (10%)		

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

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
15-Month Interim Evaluation (continued)			
Endocrine System (continued)			
Pituitary gland	(10)	(10)	(10)
Pars distalis, angiectasis	1 (10%)	1 (10%)	
Pars distalis, cyst	6 (60%)	2 (20%)	1 (10%)
Pars distalis, hyperplasia, focal	1 (10%)	1 (10%)	1 (10%)
Thyroid gland	(10)	(10)	(10)
Ultimobranchial cyst	1 (10%)		
Genital System			
Clitoral gland	(10)	(10)	(10)
Ectasia			1 (10%)
Inflammation, chronic	2 (20%)		
Ovary	(10)	(10)	(10)
Cyst			1 (10%)
Uterus	(10)	(10)	(10)
Hydrometra	2 (20%)	1 (10%)	2 (20%)
Hyperplasia, cystic			1 (10%)
Inflammation, suppurative	1 (10%)		
Hematopoietic System			
Bone marrow	(10)	(10)	(10)
Myelofibrosis		1 (10%)	
Lymph node			(1)
Mediastinal, hemorrhage			1 (100%)
Mediastinal, pigmentation			1 (100%)
Lymph node, mandibular	(10)	(10)	(10)
Ectasia	1 (10%)		2 (20%)
Hemorrhage			1 (10%)
Hyperplasia, lymphoid	2 (20%)		
Pigmentation	3 (30%)	2 (20%)	4 (40%)
Spleen	(10)	(10)	(10)
Hematopoietic cell proliferation	1 (10%)	1 (10%)	3 (30%)
Pigmentation, hemosiderin	10 (100%)	10 (100%)	10 (100%)
Integumentary System			
Mammary gland	(10)	(10)	(10)
Hyperplasia	3 (30%)		1 (10%)
Musculoskeletal System			
Bone	(10)	(10)	(10)
Cranium, osteopetrosis			1 (10%)
Femur, osteopetrosis			2 (20%)

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
15-Month Interim Evaluation (continued)			
Respiratory System			
Lung	(10)	(10)	(10)
Infiltration cellular, histiocyte	2 (20%)	3 (30%)	2 (20%)
Nose	(10)	(10)	(10)
Exudate	1 (10%)		
Fungus	1 (10%)		
Mucosa, metaplasia, squamous	1 (10%)		
Urinary System			
Kidney	(10)	(10)	(10)
Cyst	1 (10%)		
Mineralization	10 (100%)	9 (90%)	8 (80%)
Nephropathy	7 (70%)	2 (20%)	10 (100%)
Renal tubule, atrophy	1 (10%)		
Renal tubule, pigmentation	10 (100%)	9 (90%)	10 (100%)
Systems Examined With No Lesions Observed			
General Body System			
Nervous System			
Special Senses System			
2-Year Study			
Alimentary System			
Intestine large, colon	(50)	(49)	(50)
Parasite metazoan	3 (6%)	1 (2%)	3 (6%)
Intestine large, rectum	(50)	(50)	(50)
Parasite metazoan	3 (6%)	4 (8%)	4 (8%)
Intestine large, cecum	(50)	(50)	(49)
Edema	2 (4%)		1 (2%)
Parasite metazoan	2 (4%)	1 (2%)	1 (2%)
Intestine small, ileum	(49)	(49)	(50)
Ulcer	1 (2%)		
Liver	(50)	(50)	(50)
Basophilic focus	37 (74%)	40 (80%)	39 (78%)
Clear cell focus	3 (6%)	2 (4%)	9 (18%)
Cyst			2 (4%)
Developmental malformation	1 (2%)		
Eosinophilic focus	19 (38%)	16 (32%)	20 (40%)
Granuloma	6 (12%)	4 (8%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	1 (2%)
Hepatodiaphragmatic nodule	9 (18%)	4 (8%)	12 (24%)
Inflammation, subacute	3 (6%)	1 (2%)	
Mixed cell focus	10 (20%)	4 (8%)	6 (12%)
Bile duct, hyperplasia	10 (20%)	10 (20%)	9 (18%)

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
2-Year Study (continued)			
Alimentary System (continued)			
Liver (continued)	(50)	(50)	(50)
Centrilobular, necrosis	1 (2%)	2 (4%)	
Hepatocyte, vacuolization cytoplasmic	7 (14%)	1 (2%)	
Kupffer cell, hyperplasia	1 (2%)		
Kupffer cell, pigmentation	4 (8%)	4 (8%)	10 (20%)
Lobules, necrosis	6 (12%)	1 (2%)	6 (12%)
Mesentery	(10)	(2)	(6)
Accessory spleen	1 (10%)		1 (17%)
Fat, necrosis	9 (90%)	2 (100%)	6 (100%)
Oral mucosa		(1)	(1)
Hyperplasia			1 (100%)
Pancreas	(50)	(49)	(50)
Atrophy	18 (36%)	17 (35%)	12 (24%)
Cyst		1 (2%)	
Acinus, cytoplasmic alteration	1 (2%)	2 (4%)	
Acinus, hyperplasia, focal	1 (2%)		
Salivary glands	(49)	(50)	(50)
Atrophy	1 (2%)		
Hyperplasia	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Edema	2 (4%)		
Ulcer		1 (2%)	1 (2%)
Mucosa, hyperplasia	1 (2%)		1 (2%)
Stomach, glandular	(50)	(50)	(50)
Erosion	1 (2%)		
Inflammation, chronic	1 (2%)		
Mineralization	1 (2%)		
Ulcer	3 (6%)		
Tongue	(3)	(1)	
Epithelium, hyperplasia	1 (33%)		
Cardiovascular System			
Heart	(50)	(50)	(50)
Cardiomyopathy	16 (32%)	14 (28%)	13 (26%)
Mineralization			1 (2%)
Thrombosis	1 (2%)		1 (2%)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	5 (10%)	6 (12%)	6 (12%)
Angiectasis	22 (44%)	15 (30%)	29 (58%)
Cyst			1 (2%)
Degeneration, fatty	10 (20%)	4 (8%)	4 (8%)
Hemorrhage			1 (2%)
Hyperplasia, focal	9 (18%)	9 (18%)	2 (4%)
Hypertrophy, focal	9 (18%)	3 (6%)	
Metaplasia, osseous		1 (2%)	

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
2-Year Study (continued)			
Endocrine System (continued)			
Adrenal medulla	(49)	(50)	(50)
Hyperplasia	1 (2%)	3 (6%)	1 (2%)
Islets, pancreatic	(50)	(49)	(50)
Metaplasia, hepatocyte			1 (2%)
Pituitary gland	(49)	(47)	(50)
Pars distalis, angiectasis	7 (14%)	7 (15%)	7 (14%)
Pars distalis, cyst	24 (49%)	8 (17%)	19 (38%)
Pars distalis, hyperplasia			1 (2%)
Pars distalis, hyperplasia, focal	12 (24%)	13 (28%)	11 (22%)
Pars intermedia, cyst		2 (4%)	
Pars intermedia, hyperplasia	1 (2%)		
Thyroid gland	(49)	(50)	(50)
Ultimobranchial cyst	2 (4%)		
C-cell, hyperplasia	6 (12%)	4 (8%)	3 (6%)
Follicular cell, hyperplasia			1 (2%)
General Body System			
Tissue NOS	(1)		(1)
Hemorrhage	1 (100%)		
Genital System			
Clitoral gland	(50)	(50)	(50)
Ectasia	12 (24%)	4 (8%)	10 (20%)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	4 (8%)	3 (6%)	1 (2%)
Inflammation, suppurative	3 (6%)	4 (8%)	3 (6%)
Ovary	(50)	(50)	(50)
Cyst	3 (6%)		5 (10%)
Inflammation, chronic	1 (2%)		
Uterus	(50)	(50)	(50)
Hydrometra	2 (4%)	4 (8%)	3 (6%)
Hyperplasia, cystic	4 (8%)	4 (8%)	11 (22%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hypercellularity	1 (2%)	2 (4%)	1 (2%)
Myelofibrosis	4 (8%)	2 (4%)	6 (12%)
Lymph node	(12)	(13)	(15)
Mediastinal, hemorrhage	1 (8%)	3 (23%)	1 (7%)
Mediastinal, pigmentation	2 (17%)	6 (46%)	9 (60%)
Pancreatic, pigmentation	1 (8%)		3 (20%)
Renal, hemorrhage		1 (8%)	
Renal, pigmentation	1 (8%)	4 (31%)	4 (27%)

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
2-Year Study (continued)			
Hematopoietic System (continued)			
Lymph node, mandibular	(49)	(50)	(50)
Ectasia	1 (2%)	2 (4%)	3 (6%)
Hemorrhage	5 (10%)	8 (16%)	5 (10%)
Hyperplasia, lymphoid	6 (12%)	3 (6%)	
Pigmentation	12 (24%)	19 (38%)	16 (32%)
Lymph node, mesenteric	(50)	(50)	(50)
Ectasia	1 (2%)		
Hemorrhage	3 (6%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
Spleen	(50)	(50)	(50)
Developmental malformation			1 (2%)
Fibrosis	1 (2%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation	10 (20%)	4 (8%)	14 (28%)
Hemorrhage		1 (2%)	
Necrosis	1 (2%)		
Pigmentation, hemosiderin	19 (38%)	13 (26%)	29 (58%)
Thymus	(49)	(49)	(48)
Hemorrhage	1 (2%)		1 (2%)
Integumentary System			
Mammary gland	(49)	(48)	(50)
Ectasia	12 (24%)	5 (10%)	11 (22%)
Hyperplasia	30 (61%)	9 (19%)	17 (34%)
Skin	(50)	(50)	(50)
Acanthosis	1 (2%)		1 (2%)
Cyst epithelial inclusion	1 (2%)	1 (2%)	
Hyperkeratosis	3 (6%)	4 (8%)	
Inflammation, chronic	1 (2%)		
Ulcer	2 (4%)	1 (2%)	2 (4%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Cranium, osteopetrosis	7 (14%)	3 (6%)	6 (12%)
Femur, osteopetrosis	5 (10%)	4 (8%)	3 (6%)
Rib, osteopetrosis		1 (2%)	1 (2%)
Skeletal muscle	(1)		(1)
Hemorrhage	1 (100%)		1 (100%)
Nervous System			
Brain	(50)	(50)	(50)
Compression	9 (18%)	1 (2%)	8 (16%)
Gliosis	1 (2%)		
Hemorrhage		1 (2%)	
Hydrocephalus	2 (4%)	1 (2%)	1 (2%)
Necrosis		1 (2%)	

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
2-Year Study (continued)			
Respiratory System			
Lung	(50)	(50)	(50)
Congestion			1 (2%)
Edema		1 (2%)	
Hemorrhage		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	21 (42%)	17 (34%)	19 (38%)
Inflammation, subacute	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	1 (2%)	2 (4%)
Nose	(50)	(50)	(50)
Exudate	6 (12%)	3 (6%)	4 (8%)
Foreign body	5 (10%)	1 (2%)	
Fungus	3 (6%)	2 (4%)	
Mucosa, hyperplasia	3 (6%)	3 (6%)	1 (2%)
Mucosa, metaplasia, squamous	3 (6%)		1 (2%)
Special Senses System			
Eye	(2)	(2)	(3)
Atrophy	1 (50%)		
Cataract		2 (100%)	2 (67%)
Hemorrhage	1 (50%)		1 (33%)
Retina, degeneration		2 (100%)	2 (67%)
Urinary System			
Kidney	(50)	(50)	(50)
Calculus, microscopic observation only			1 (2%)
Cyst		1 (2%)	2 (4%)
Hydronephrosis		2 (4%)	1 (2%)
Mineralization	43 (86%)	49 (98%)	35 (70%)
Nephropathy	34 (68%)	32 (64%)	45 (90%)
Renal tubule, atrophy			2 (4%)
Renal tubule, cytoplasmic alteration	1 (2%)		
Renal tubule, dilatation	1 (2%)		1 (2%)
Renal tubule, necrosis	1 (2%)		1 (2%)
Renal tubule, pigmentation	49 (98%)	48 (96%)	47 (94%)
Transitional epithelium, hyperplasia		4 (8%)	4 (8%)
Ureter			(1)
Dilatation			1 (100%)
Transitional epithelium, hyperplasia			1 (100%)
Urinary bladder	(50)	(50)	(50)
Edema	1 (2%)		
Transitional epithelium, hyperplasia	4 (8%)		10 (20%)

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols[a]

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
Disposition Summary				
Animals initially in study	60	60	50	50
15-Month interim evaluation	10	10		
Early deaths				
Moribund	11	10	34	38
Natural deaths	4	1	6	1
Survivors				
Terminal sacrifice	35	39	10	11
Animals examined microscopically	60	60	50	50
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)		
Basophilic focus	10 (100%)	3 (30%)		
Clear cell focus	1 (10%)	1 (10%)		
Granuloma	1 (10%)			
Hepatodiaphragmatic nodule	2 (20%)	1 (10%)		
Inflammation, subacute	1 (10%)			
Mixed cell focus	1 (10%)			
Mesentery		(1)		
Hemorrhage		1 (100%)		
Fat, necrosis		1 (100%)		
Pancreas	(10)	(10)		
Atrophy	1 (10%)	1 (10%)		
Stomach, glandular	(10)	(10)		
Mineralization	1 (10%)			
Cardiovascular System				
Heart	(10)	(10)		
Cardiomyopathy	2 (20%)			
Endocrine System				
Adrenal cortex	(10)	(10)		
Accessory adrenal cortical nodule	3 (30%)	3 (30%)		
Angiectasis	1 (10%)			
Pituitary gland	(10)	(10)		
Pars distalis, angiectasis		1 (10%)		
Pars distalis, cyst	3 (30%)			
Pars distalis, hyperplasia, focal	3 (30%)			
Pars intermedia, cyst		1 (10%)		
Pars intermedia, hemorrhage	1 (10%)			

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

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(10)	(10)		
Ectasia		1 (10%)		
Inflammation, chronic	2 (20%)	1 (10%)		
Uterus	(10)	(10)		
Hydrometra	2 (20%)	1 (10%)		
Hyperplasia, cystic	1 (10%)	1 (10%)		
Metaplasia, squamous	1 (10%)			
Hematopoietic System				
Bone marrow	(10)	(10)		
Myelofibrosis	1 (10%)	2 (20%)		
Lymph node	(1)	(1)		
Mediastinal, hemorrhage	1 (100%)			
Mediastinal, pigmentation	1 (100%)			
Lymph node, mandibular	(10)	(10)		
Hemorrhage		3 (30%)		
Pigmentation		2 (20%)		
Lymph node, mesenteric	(10)	(10)		
Hemorrhage		1 (10%)		
Spleen	(10)	(10)		
Hematopoietic cell proliferation	3 (30%)	1 (10%)		
Pigmentation, hemosiderin	9 (90%)	9 (90%)		
Thymus	(10)	(10)		
Cyst	1 (10%)			
Integumentary System				
Mammary gland	(10)	(10)		
Hyperplasia	2 (20%)			
Skin	(10)	(9)		
Ulcer		1 (11%)		
Musculoskeletal System				
Bone	(10)	(10)		
Femur, osteopetrosis		1 (10%)		
Respiratory System				
Lung	(10)	(10)		
Infiltration cellular, histiocyte	2 (20%)	5 (50%)		
Nose	(10)	(10)		
Mucosa, hyperplasia	1 (10%)			

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
15-Month Interim Evaluation (continued)				
Special Senses System				
Eye	(1)			
Cataract	1 (100%)			
Retina, degeneration	1 (100%)			
Urinary System				
Kidney	(10)	(10)		
Cyst		1 (10%)		
Mineralization	10 (100%)	8 (80%)		
Nephropathy	10 (100%)	9 (90%)		
Renal tubule, atrophy		2 (20%)		
Renal tubule, dilatation		1 (10%)		
Renal tubule, pigmentation	10 (100%)	10 (100%)		
Systems Examined With No Lesions Observed				
General Body System				
Nervous System				
2-Year and 32-Month Protocols				
Alimentary System				
Intestine large, colon	(50)	(49)	(49)	(50)
Edema			1 (2%)	
Parasite metazoan	6 (12%)	2 (4%)	5 (10%)	2 (4%)
Intestine large, rectum	(50)	(50)	(48)	(50)
Parasite metazoan	3 (6%)	3 (6%)	3 (6%)	6 (12%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Edema			1 (2%)	1 (2%)
Parasite metazoan				1 (2%)
Intestine small, duodenum	(50)	(50)	(49)	(50)
Erosion		1 (2%)	1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Fibrosis		1 (2%)		
Perforation		1 (2%)		
Muscularis, hyperplasia				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)		4 (8%)	1 (2%)
Basophilic focus	40 (80%)	41 (82%)	32 (64%)	38 (76%)
Clear cell focus	3 (6%)	2 (4%)	2 (4%)	
Developmental malformation	1 (2%)		1 (2%)	
Eosinophilic focus	13 (26%)	21 (42%)	8 (16%)	13 (26%)
Granuloma	8 (16%)	8 (16%)	11 (22%)	5 (10%)
Hematopoietic cell proliferation			3 (6%)	1 (2%)
Hemorrhage			1 (2%)	
Hepatodiaphragmatic nodule	3 (6%)	3 (6%)	2 (4%)	10 (20%)
Inflammation, subacute	3 (6%)	3 (6%)	1 (2%)	

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
2-Year and 32-Month Protocols (continued)				
Alimentary System (continued)				
Liver (continued)	(50)	(50)	(50)	(50)
Mixed cell focus	5 (10%)		11 (22%)	1 (2%)
Thrombosis				2 (4%)
Bile duct, hyperplasia	4 (8%)	5 (10%)	13 (26%)	11 (22%)
Centrilobular, necrosis			1 (2%)	
Hepatocyte, hyperplasia, focal		1 (2%)		
Hepatocyte, vacuolization cytoplasmic		1 (2%)	6 (12%)	
Kupffer cell, pigmentation	1 (2%)	5 (10%)	9 (18%)	21 (42%)
Lobules, necrosis	6 (12%)	2 (4%)	4 (8%)	4 (8%)
Mesentery	(1)		(5)	(4)
Accessory spleen	1 (100%)		3 (60%)	1 (25%)
Fat, necrosis			2 (40%)	
Pancreas	(47)	(50)	(50)	(50)
Atrophy	27 (57%)	16 (32%)	25 (50%)	22 (44%)
Acinar cell, hyperplasia, focal				1 (2%)
Acinus, metaplasia, goblet cell				1 (2%)
Acinus, cytoplasmic alteration		1 (2%)		
Salivary glands	(49)	(50)	(50)	(50)
Duct, cyst				1 (2%)
Stomach, forestomach	(49)	(50)	(48)	(50)
Edema			2 (4%)	1 (2%)
Ulcer	1 (2%)			1 (2%)
Mucosa, hyperplasia	1 (2%)		4 (8%)	4 (8%)
Stomach, glandular	(50)	(50)	(48)	(50)
Erosion	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Ulcer		1 (2%)		
Cardiovascular System				
Blood vessel	(49)	(50)	(50)	(50)
Hypertrophy		1 (2%)		
Thrombosis		1 (2%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	15 (30%)	13 (26%)	23 (46%)	26 (52%)
Thrombosis			1 (2%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	12 (24%)	15 (30%)	8 (16%)	17 (34%)
Angiectasis	27 (54%)	33 (66%)	27 (54%)	37 (74%)
Degeneration, fatty	11 (22%)	7 (14%)	16 (32%)	13 (26%)
Hematopoietic cell proliferation				1 (2%)
Hemorrhage		4 (8%)		4 (8%)
Hyperplasia, diffuse		1 (2%)		
Hyperplasia, focal	4 (8%)	5 (10%)	6 (12%)	3 (6%)
Hypertrophy, focal	8 (16%)	3 (6%)	7 (14%)	2 (4%)
Necrosis			1 (2%)	

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
2-Year and 32-Month Protocols (continued)				
Endocrine System (continued)				
Adrenal medulla	(49)	(50)	(49)	(50)
Hyperplasia	3 (6%)	1 (2%)	10 (20%)	9 (18%)
Islets, pancreatic	(47)	(50)	(50)	(50)
Hyperplasia		1 (2%)		1 (2%)
Metaplasia, hepatocyte		1 (2%)		1 (2%)
Parathyroid gland	(49)	(46)	(48)	(49)
Angiectasis				1 (2%)
Cyst		1 (2%)		
Pituitary gland	(50)	(49)	(50)	(50)
Pars distalis, angiectasis	8 (16%)	4 (8%)	8 (16%)	6 (12%)
Pars distalis, cyst	14 (28%)	10 (20%)	10 (20%)	11 (22%)
Pars distalis, hyperplasia, focal	11 (22%)	6 (12%)	9 (18%)	16 (32%)
Pars intermedia, angiectasis	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Pars intermedia, cyst	4 (8%)	2 (4%)	3 (6%)	6 (12%)
Thyroid gland	(49)	(50)	(50)	(50)
Ultimobranchial cyst			1 (2%)	
C-cell, hyperplasia	1 (2%)	5 (10%)	9 (18%)	6 (12%)
Follicle, cyst	2 (4%)		4 (8%)	2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Ectasia	11 (22%)	6 (12%)	15 (30%)	12 (24%)
Hyperplasia	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Inflammation, chronic		3 (6%)	4 (8%)	1 (2%)
Inflammation, suppurative	5 (10%)	3 (6%)	7 (14%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Cyst	3 (6%)	6 (12%)	6 (12%)	6 (12%)
Uterus	(50)	(50)	(50)	(50)
Hydrometra	3 (6%)	7 (14%)	2 (4%)	2 (4%)
Hyperplasia, cystic	7 (14%)	16 (32%)	7 (14%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hypercellularity		1 (2%)	2 (4%)	1 (2%)
Hyperplasia, reticulum cell				1 (2%)
Myelofibrosis	2 (4%)		3 (6%)	5 (10%)
Necrosis				1 (2%)

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
2-Year and 32-Month Protocols (continued)				
Hematopoietic System (continued)				
Lymph node	(10)	(8)	(21)	(18)
Iliac, ectasia			2 (10%)	
Iliac, hyperplasia, lymphoid			2 (10%)	
Inguinal, hyperplasia, lymphoid			1 (5%)	
Mediastinal, hemorrhage	1 (10%)	1 (13%)	1 (5%)	1 (6%)
Mediastinal, hyperplasia, lymphoid		1 (13%)		
Mediastinal, pigmentation	3 (30%)		7 (33%)	3 (17%)
Pancreatic, pigmentation	1 (10%)	3 (38%)	2 (10%)	4 (22%)
Renal, hemorrhage	1 (10%)	1 (13%)		
Renal, pigmentation		2 (25%)	2 (10%)	4 (22%)
Lymph node, mandibular	(49)	(50)	(50)	(50)
Ectasia	3 (6%)	2 (4%)	3 (60%)	7 (14%)
Hemorrhage	5 (10%)	7 (14%)	6 (12%)	7 (14%)
Hyperplasia, lymphoid			1 (2%)	6 (12%)
Pigmentation	15 (31%)	10 (20%)	19 (38%)	17 (34%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Hemorrhage	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Spleen	(50)	(50)	(50)	(50)
Fibrosis	3 (6%)	2 (4%)	6 (12%)	7 (14%)
Hematopoietic cell proliferation	13 (26%)	8 (16%)	13 (26%)	8 (16%)
Hemorrhage	2 (4%)			1 (2%)
Necrosis		1 (2%)		
Pigmentation, hemosiderin	21 (42%)	18 (36%)	18 (36%)	24 (48%)
Thymus	(50)	(50)	(49)	(46)
Atrophy		1 (2%)		
Hemorrhage			1 (2%)	
Integumentary System				
Mammary gland	(50)	(49)	(49)	(50)
Ectasia	16 (32%)	5 (10%)	22 (45%)	12 (24%)
Galactocele	1 (2%)		2 (4%)	
Hyperplasia	18 (36%)	18 (37%)	20 (41%)	32 (64%)
Skin	(50)	(50)	(50)	(50)
Acanthosis	3 (6%)	5 (10%)	2 (4%)	6 (12%)
Cyst epithelial inclusion				1 (2%)
Edema				2 (4%)
Hyperkeratosis	1 (2%)		2 (4%)	2 (4%)
Inflammation, chronic			1 (2%)	1 (2%)
Ulcer	3 (6%)	3 (6%)		4 (8%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, osteopetrosis	12 (24%)	2 (4%)	6 (12%)	9 (18%)
Femur, osteopetrosis	7 (14%)	4 (8%)	7 (14%)	8 (16%)
Rib, osteopetrosis	1 (2%)			1 (2%)

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 32-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		32-Month Restricted Feed	
	0 ppm	24,000 ppm	0 ppm	24,000 ppm
2-Year and 32-Month Protocols (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(49)
Compression	5 (10%)	5 (10%)	14 (28%)	7 (14%)
Hemorrhage		1 (2%)	1 (2%)	2 (4%)
Hydrocephalus	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Inflammation, chronic		1 (2%)		
Necrosis			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	2 (4%)		1 (2%)	
Edema	1 (2%)			1 (2%)
Hemorrhage			3 (6%)	1 (2%)
Infiltration cellular, histiocyte	18 (36%)	18 (36%)	14 (28%)	21 (42%)
Inflammation, subacute	1 (2%)	1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia	5 (10%)	1 (2%)	4 (8%)	1 (2%)
Nose	(50)	(50)	(50)	(50)
Exudate		3 (6%)	6 (12%)	6 (12%)
Foreign body	1 (2%)	1 (2%)	1 (2%)	
Fungus		1 (2%)	2 (4%)	1 (2%)
Mucosa, hyperplasia	1 (2%)	3 (6%)	3 (6%)	3 (6%)
Mucosa, metaplasia, squamous			3 (6%)	1 (2%)
Special Senses System				
Eye	(3)	(2)	(1)	(2)
Atrophy			1 (100%)	
Cataract	2 (67%)	2 (100%)		2 (100%)
Retina, degeneration	2 (67%)	2 (100%)		2 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Calculus, microscopic observation only		8 (16%)	1 (2%)	9 (18%)
Cyst		1 (2%)		
Hydronephrosis		1 (2%)		
Inflammation, suppurative				2 (4%)
Mineralization	46 (92%)	34 (68%)	45 (90%)	31 (62%)
Nephropathy	40 (80%)	47 (94%)	40 (80%)	49 (98%)
Papilla, necrosis				3 (6%)
Renal tubule, atrophy		3 (6%)		4 (8%)
Renal tubule, dilatation		5 (10%)		12 (24%)
Renal tubule, hyperplasia			1 (2%)	1 (2%)
Renal tubule, necrosis				1 (2%)
Renal tubule, pigmentation	48 (96%)	50 (100%)	48 (96%)	48 (96%)
Transitional epithelium, hyperplasia	1 (2%)	20 (40%)	2 (4%)	29 (58%)
Urinary bladder	(50)	(50)	(49)	(50)
Calculus, microscopic observation only				1 (2%)
Transitional epithelium, hyperplasia		14 (28%)		16 (32%)

APPENDIX C
SUMMARY OF LESIONS IN MALE RATS IN THE DIETARY RESTRICTION STUDY OF *t*-BUTYLHYDROQUINONE

TABLE C1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Disposition Summary			
Animals initially in study	70	70	70
3-Month interim evaluation	10	10	10
Early deaths			
Moribund	48	41	42
Natural deaths	4	7	4
Survivors			
Terminal sacrifice	8	12	14
Animals examined microscopically	70	70	70
Systems Examined At 3 Months With No Neoplasms Observed			
Alimentary System			
Cardiovascular System			
Endocrine System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			
30-Month Study			
Alimentary System			
Intestine large, colon	(58)	(60)	(60)
Intestine large, rectum	(59)	(58)	(59)
Intestine large, cecum	(60)	(60)	(60)
Intestine small, duodenum	(60)	(60)	(60)
Intestine small, jejunum	(60)	(59)	(60)
Intestine small, ileum	(60)	(59)	(59)
Liver	(60)	(60)	(60)
Hemangiosarcoma		1 (2%)	
Hepatocellular carcinoma			2 (3%)
Hepatocellular adenoma	4 (7%)	1 (2%)	3 (5%)
Histiocytic sarcoma	1 (2%)		
Mesentery	(20)	(15)	(16)
Histiocytic sarcoma	1 (5%)		
Schwannoma malignant	1 (5%)		
Oral mucosa	(1)		
Squamous cell carcinoma	1 (100%)		
Pancreas	(60)	(60)	(60)
Acinus, adenoma	3 (5%)		
Mixed tumor benign		1 (2%)	
Salivary glands	(60)	(60)	(60)

TABLE C1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Alimentary System (continued)			
Stomach, forestomach	(60)	(60)	(59)
Squamous cell papilloma		2 (3%)	1 (2%)
Stomach, glandular	(60)	(60)	(60)
Tongue	(1)	(2)	(4)
Squamous cell carcinoma	1 (100%)	1 (50%)	
Squamous cell papilloma			2 (50%)
Cardiovascular System			
Heart	(60)	(60)	(60)
Schwannoma malignant	1 (2%)		
Endocrine System			
Adrenal cortex	(60)	(60)	(60)
Adenoma	1 (2%)	1 (2%)	1 (2%)
Adrenal medulla	(60)	(60)	(60)
Pheochromocytoma malignant	1 (2%)	1 (2%)	3 (5%)
Pheochromocytoma complex		1 (2%)	
Pheochromocytoma benign	13 (22%)	11 (18%)	11 (18%)
Pheochromocytoma benign, multiple	1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(60)	(60)	(60)
Adenoma	5 (8%)	2 (3%)	3 (5%)
Carcinoma	1 (2%)		
Pituitary gland	(60)	(59)	(60)
Pars distalis, adenoma	19 (32%)	19 (32%)	6 (10%)
Pars distalis, carcinoma		1 (2%)	1 (2%)
Thyroid gland	(60)	(60)	(60)
C-cell, adenoma	5 (8%)	5 (8%)	4 (7%)
C-cell, carcinoma		1 (2%)	2 (3%)
Follicular cell, carcinoma			3 (5%)
General Body System			
Peritoneum	(1)		(3)
Genital System			
Epididymis	(60)	(60)	(60)
Preputial gland	(60)	(60)	(60)
Adenoma	5 (8%)		3 (5%)
Carcinoma	2 (3%)		5 (8%)
Prostate	(60)	(60)	(60)
Adenoma	2 (3%)	3 (5%)	1 (2%)
Seminal vesicle	(60)	(60)	(60)
Testes	(60)	(60)	(60)
Bilateral, interstitial cell, adenoma	42 (70%)	53 (88%)	50 (83%)
Interstitial cell, adenoma	13 (22%)	5 (8%)	9 (15%)

TABLE C1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Hematopoietic System			
Bone marrow	(60)	(60)	(60)
Lymph node	(33)	(33)	(35)
Lymph node, mandibular	(60)	(59)	(60)
Carcinoma, metastatic, Zymbal's gland			1 (2%)
Lymph node, mesenteric	(60)	(58)	(60)
Hemangioma			1 (2%)
Spleen	(60)	(60)	(60)
Fibroma	2 (3%)	1 (2%)	
Histiocytic sarcoma	1 (2%)		
Hemangiosarcoma		1 (2%)	
Sarcoma	1 (2%)		1 (2%)
Thymus	(58)	(55)	(56)
Thymoma malignant			1 (2%)
Integumentary System			
Mammary gland	(57)	(58)	(58)
Adenoma	1 (2%)	1 (2%)	
Fibroadenoma	9 (16%)	6 (10%)	6 (10%)
Fibroadenoma, multiple	1 (2%)		1 (2%)
Skin	(60)	(60)	(60)
Basal cell carcinoma	1 (2%)		
Hemangioma		1 (2%)	
Keratoacanthoma	3 (5%)	2 (3%)	4 (7%)
Keratoacanthoma, multiple	1 (2%)		
Squamous cell carcinoma, metastatic, tongue		1 (2%)	
Squamous cell papilloma	2 (3%)	1 (2%)	2 (3%)
Trichoepithelioma	2 (3%)	1 (2%)	1 (2%)
Sebaceous gland, adenoma	1 (2%)		
Subcutaneous tissue, fibroma	3 (5%)	7 (12%)	6 (10%)
Subcutaneous tissue, fibroma, multiple	1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)	3 (5%)	1 (2%)
Subcutaneous tissue, hemangioma	1 (2%)		
Subcutaneous tissue, hemangiosarcoma	1 (2%)		
Subcutaneous tissue, schwannoma benign	1 (2%)		
Subcutaneous tissue, schwannoma malignant			1 (2%)
Musculoskeletal System			
None			
Nervous System			
Brain	(60)	(60)	(60)
Astrocytoma malignant	1 (2%)		
Carcinoma, metastatic, pituitary gland		1 (2%)	
Oligodendroglioma malignant	1 (2%)		
Spinal cord	(2)		(1)

TABLE C1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Respiratory System			
Lung	(60)	(60)	(60)
Alveolar/bronchiolar adenoma	3 (5%)	2 (3%)	1 (2%)
Alveolar/bronchiolar carcinoma		3 (5%)	1 (2%)
Histiocytic sarcoma	1 (2%)		
Nose	(60)	(60)	(60)
Squamous cell papilloma	1 (2%)		
Special Senses System			
Eye	(4)	(4)	(2)
Schwannoma malignant		1 (25%)	
Zymbal's gland	(2)	(1)	(4)
Adenoma			1 (25%)
Carcinoma	2 (100%)	1 (100%)	3 (75%)
Urinary System			
Kidney	(60)	(60)	(60)
Lipoma	1 (2%)		
Renal tubule, adenoma	2 (3%)		1 (2%)
Transitional epithelium, carcinoma	1 (2%)		
Urinary bladder	(60)	(60)	(60)
Papilloma			1 (2%)
Systemic Lesions			
Multiple organs[b]	(60)	(60)	(60)
Histiocytic sarcoma	1 (2%)		
Leukemia mononuclear	39 (65%)	45 (75%)	32 (53%)
Lymphoma malignant	1 (2%)		
Mesothelioma malignant	1 (2%)		3 (5%)

TABLE C1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Neoplasm Summary			
Total animals with primary neoplasms[c]			
28-Month study	60	60	60
Total primary neoplasms			
28-Month study	207	186	179
Total animals with benign neoplasms			
28-Month study	60	59	59
Total benign neoplasms			
28-Month study	148	126	120
Total animals with malignant neoplasms			
28-Month study	51	51	47
Total malignant neoplasms			
28-Month study	59	60	59
Total animals with metastatic neoplasms			
28-Month study		2	2
Total metastatic neoplasms			
28-Month study		2	2

[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 C1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol[a]

	0 ppm	5,000 ppm
Disposition Summary		
Animals initially in s	70	70
3-Month interim evaluation	10	10
Early deaths		
Moribund	43	33
Natural deaths	7	5
Survivors		
Terminal sacrifice	10	22
Animals examined microscopically	70	70
Systems Examined At 3 Months With No Neoplasms Observed		
Alimentary System		
Cardiovascular System		
Endocrine System		
General Body System		
Genital System		
Hematopoietic System		
Integumentary System		
Musculoskeletal System		
Nervous System		
Respiratory System		
Special Senses System		
Urinary System		
30-Month Study		
Alimentary System		
Intestine large, colon	(60)	(60)
Intestine large, cecum	(60)	(60)
Intestine small, duodenum	(60)	(60)
Intestine small, jejunum	(60)	(60)
Leiomyosarcoma	1 (2%)	
Intestine small, ileum	(60)	(59)
Liver	(60)	(60)
Carcinoma, metastatic, thyroid gland	1 (2%)	
Mesentery	(8)	(5)
Hemangiosarcoma		1 (20%)
Oral mucosa		(2)
Carcinoma		1 (50%)
Squamous cell papilloma		1 (50%)
Pancreas	(58)	(60)
Acinus, leiomyosarcoma, metastatic, stomach, forestomach		1 (2%)
Salivary glands	(60)	(60)
Stomach, forestomach	(60)	(60)
Leiomyosarcoma		1 (2%)
Squamous cell papilloma		3 (5%)

TABLE C1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Alimentary System (continued)		
Stomach, glandular	(60)	(60)
Tongue	(1)	(2)
Squamous cell carcinoma	1 (100%)	
Squamous cell papilloma		1 (50%)
Cardiovascular System		
Blood vessel	(60)	(60)
Heart	(60)	(60)
Endocrine System		
Adrenal cortex	(60)	(60)
Carcinoma, metastatic, thyroid gland	1 (2%)	
Osteosarcoma, metastatic, bone		1 (2%)
Adrenal medulla	(59)	(60)
Pheochromocytoma malignant	2 (3%)	2 (3%)
Pheochromocytoma complex	1 (2%)	
Pheochromocytoma benign	7 (12%)	11 (18%)
Pheochromocytoma benign, multiple	5 (8%)	1 (2%)
Islets, pancreatic	(58)	(60)
Adenoma	2 (3%)	5 (8%)
Adenoma, multiple		1 (2%)
Pituitary gland	(57)	(56)
Pars distalis, adenoma	13 (23%)	16 (29%)
Thyroid gland	(60)	(59)
C-cell, adenoma	7 (12%)	5 (8%)
C-cell, adenoma, multiple		1 (2%)
C-cell, carcinoma		5 (8%)
Follicular cell, carcinoma	2 (3%)	
General Body System		
Peritoneum	(3)	(3)
Genital System		
Preputial gland	(60)	(59)
Adenoma	1 (2%)	1 (2%)
Carcinoma	1 (2%)	2 (3%)
Prostate	(60)	(60)
Seminal vesicle	(60)	(60)
Testes	(60)	(60)
Bilateral, interstitial cell, adenoma	52 (87%)	56 (93%)
Interstitial cell, adenoma	7 (12%)	4 (7%)

TABLE C1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Hematopoietic System		
Bone marrow	(60)	(60)
Lymph node	(36)	(23)
Deep cervical, carcinoma, metastatic, thyroid gland	1 (3%)	1 (4%)
Lymph node, mandibular	(60)	(60)
Carcinoma, metastatic, thyroid gland	1 (2%)	
Lymph node, mesenteric	(60)	(60)
Spleen	(60)	(60)
Thymus	(54)	(58)
Integumentary System		
Mammary gland	(58)	(58)
Carcinoma	1 (2%)	1 (2%)
Fibroadenoma	4 (7%)	6 (10%)
Skin	(60)	(60)
Basal cell adenoma		1 (2%)
Basal cell carcinoma	1 (2%)	
Keratoacanthoma	1 (2%)	1 (2%)
Sebaceous gland, adenoma	1 (2%)	
Subcutaneous tissue, fibroma	6 (10%)	3 (5%)
Subcutaneous tissue, fibrosarcoma		1 (2%)
Subcutaneous tissue, schwannoma malignant		1 (2%)
Musculoskeletal System		
Bone	(60)	(60)
Osteosarcoma		2 (3%)
Nervous System		
Brain	(60)	(60)
Astrocytoma malignant		1 (2%)
Spinal cord	(2)	
Respiratory System		
Lung	(60)	(60)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)
Carcinoma, metastatic, thyroid gland	1 (2%)	1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)
Leiomyosarcoma, metastatic, stomach, forestomach		1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)
Nose	(60)	(60)
Squamous cell carcinoma		1 (2%)
Vomeronasal organ, adenoma		1 (2%)

TABLE C1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Special Senses System		
Zymbal's gland		(1)
Carcinoma		1 (100%)
Urinary System		
Kidney	(60)	(60)
Renal tubule, adenoma		1 (2%)
Transitional epithelium, carcinoma		1 (2%)
Urinary bladder	(60)	(60)
Papilloma		1 (2%)
Systemic Lesions		
Multiple organs[b]	(60)	(60)
Leukemia mononuclear	46 (77%)	39 (65%)
Mesothelioma malignant	3 (5%)	4 (7%)
Neoplasm Summary		
Total animals with primary neoplasms[c]		
2-Year study	59	60
Total primary neoplasms		
2-Year study	166	187
Total animals with benign neoplasms		
2-Year study	59	60
Total benign neoplasms		
2-Year study	107	122
Total animals with malignant neoplasms		
2-Year study	52	49
Total malignant neoplasms		
2-Year study	59	65
Total animals with metastatic neoplasms		
2-Year study	1	4
Total metastatic neoplasms		
2-Year study	5	7

[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 C2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	14/60 (23%)	12/60 (20%)	12/60 (20%)	12/60 (20%)
Adjusted rate[b]	59.8%	49.8%	45.3%	49.8%
Terminal rate[c]	2/8 (25%)	5/14 (36%)	2/12 (17%)	5/14 (36%)
First incidence (days)	667	487	617	487
Life table test[d]		P=0.193N		P=0.481
Logistic regression test[d]		P=0.351N		P=0.482
Fisher exact test[d]		P=0.412N		P=0.590N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	1/60 (2%)	3/60 (5%)	1/60 (2%)	3/60 (5%)
Adjusted rate	3.1%	21.4%	8.3%	21.4%
Terminal rate	0/8 (0%)	3/14 (21%)	1/12 (8%)	3/14 (21%)
First incidence (days)	710	857 (T)	857 (T)	857 (T)
Life table test		P=0.465		P=0.356
Logistic regression test		P=0.394		P=0.356
Fisher exact test		P=0.309		P=0.309
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	14/60 (23%)	13/60 (22%)	13/60 (22%)	13/60 (22%)
Adjusted rate	59.8%	55.4%	50.8%	55.4%
Terminal rate	2/8 (25%)	6/14 (43%)	3/12 (25%)	6/14 (43%)
First incidence (days)	667	487	617	487
Life table test		P=0.239N		P=0.494
Logistic regression test		P=0.431N		P=0.455
Fisher exact test		P=0.500N		P=0.588N
Liver: Hepatocellular Adenoma				
Overall rate	4/60 (7%)	3/60 (5%)	1/60 (2%)	3/60 (5%)
Adjusted rate	25.1%	12.7%	2.2%	12.7%
Terminal rate	1/8 (13%)	1/14 (7%)	0/12 (0%)	1/14 (7%)
First incidence (days)	642	708	673	708
Life table test		P=0.370N		P=0.285
Logistic regression test		P=0.463N		P=0.297
Fisher exact test		P=0.500N		P=0.309
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	4/60 (7%)	5/60 (8%)	1/60 (2%)	5/60 (8%)
Adjusted rate	25.1%	21.0%	2.2%	21.0%
Terminal rate	1/8 (13%)	1/14 (7%)	0/12 (0%)	1/14 (7%)
First incidence (days)	642	708	673	708
Life table test		P=0.611N		P=0.081
Logistic regression test		P=0.548		P=0.090
Fisher exact test		P=0.500		P=0.103

TABLE C2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/60 (5%)	1/60 (2%)	2/60 (3%)	1/60 (2%)
Adjusted rate	10.2%	4.3%		
Terminal rate	0/8 (0%)	0/14 (0%)		
First incidence (days)	618	773		
Life table test		P=0.276N		
Logistic regression test		P=0.306N		
Fisher exact test		P=0.309N		
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/60 (0%)	1/60 (2%)	3/60 (5%)	1/60 (2%)
Adjusted rate			20.1%	7.1%
Terminal rate			2/12 (17%)	1/14 (7%)
First incidence (days)			814	857 (T)
Life table test				P=0.301N
Logistic regression test				P=0.373N
Fisher exact test				P=0.309N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/60 (5%)	2/60 (3%)	5/60 (8%)	2/60 (3%)
Adjusted rate	10.2%	11.2%	30.1%	11.2%
Terminal rate	0/8 (0%)	1/14 (7%)	3/12 (25%)	1/14 (7%)
First incidence (days)	618	773	722	773
Life table test		P=0.418N		P=0.226N
Logistic regression test		P=0.488N		P=0.297N
Fisher exact test		P=0.500N		P=0.219N
Mammary Gland: Fibroadenoma				
Overall rate	10/60 (17%)	7/60 (12%)	6/60 (10%)	7/60 (12%)
Adjusted rate	72.0%	40.2%	37.9%	40.2%
Terminal rate	5/8 (63%)	5/14 (36%)	3/12 (25%)	5/14 (36%)
First incidence (days)	381	708	810	708
Life table test		P=0.059N		P=0.527
Logistic regression test		P=0.107N		P=0.330
Fisher exact test		P=0.301N		P=0.500
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	11/60 (18%)	7/60 (12%)	7/60 (12%)	7/60 (12%)
Adjusted rate	72.6%	40.2%	40.8%	40.2%
Terminal rate	5/8 (63%)	5/14 (36%)	3/12 (25%)	5/14 (36%)
First incidence (days)	381	708	810	708
Life table test		P=0.039N		P=0.609N
Logistic regression test		P=0.076N		P=0.439
Fisher exact test		P=0.222N		P=0.611N

TABLE C2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Pancreas: Adenoma				
Overall rate	3/60 (5%)	0/60 (0%)	0/60 (0%)	0/60 (0%)
Adjusted rate	37.5%	0.0%		
Terminal rate	3/8 (38%)	0/14 (0%)		
First incidence (days)	857 (T)	–		
Life table test		P=0.038N		
Logistic regression test		P=0.038N		
Fisher exact test		P=0.122N		
Pancreatic Islets: Adenoma				
Overall rate	5/60 (8%)	3/60 (5%)	2/60 (3%)	3/60 (5%)
Adjusted rate	32.5%	15.9%	10.7%	15.9%
Terminal rate	1/8 (13%)	1/14 (7%)	1/12 (8%)	1/14 (7%)
First incidence (days)	667	708	715	708
Life table test		P=0.208N		P=0.492
Logistic regression test		P=0.287N		P=0.432
Fisher exact test		P=0.359N		P=0.500
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	6/60 (10%)	3/60 (5%)	2/60 (3%)	3/60 (5%)
Adjusted rate	42.1%	15.9%	10.7%	15.9%
Terminal rate	2/8 (25%)	1/14 (7%)	1/12 (8%)	1/14 (7%)
First incidence (days)	667	708	715	708
Life table test		P=0.112N		P=0.492
Logistic regression test		P=0.170N		P=0.432
Fisher exact test		P=0.245N		P=0.500
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	19/60 (32%)	6/60 (10%)	19/59 (32%)	6/60 (10%)
Adjusted rate	63.8%	30.2%	72.4%	30.2%
Terminal rate	2/8 (25%)	3/14 (21%)	7/12 (58%)	3/14 (21%)
First incidence (days)	528	668	638	668
Life table test		P=0.002N		P=0.008N
Logistic regression test		P=0.002N		P=0.007N
Fisher exact test		P=0.003N		P=0.003N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	19/60 (32%)	7/60 (12%)	20/59 (34%)	7/60 (12%)
Adjusted rate	63.8%	31.6%	74.2%	31.6%
Terminal rate	2/8 (25%)	3/14 (21%)	7/12 (58%)	3/14 (21%)
First incidence (days)	528	627	638	627
Life table test		P=0.004N		P=0.011N
Logistic regression test		P=0.006N		P=0.008N
Fisher exact test		P=0.007N		P=0.003N

TABLE C2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Preputial Gland: Adenoma				
Overall rate	5/60 (8%)	3/60 (5%)	0/60 (0%)	3/60 (5%)
Adjusted rate	31.1%	18.4%	0.0%	18.4%
Terminal rate	2/8 (25%)	2/14 (14%)	0/12 (0%)	2/14 (14%)
First incidence (days)	528	786	-	786
Life table test		P=0.205N		P=0.121
Logistic regression test		P=0.312N		P=0.084
Fisher exact test		P=0.359N		P=0.122
Preputial Gland: Carcinoma				
Overall rate	2/60 (3%)	5/60 (8%)	0/60 (0%)	5/60 (8%)
Adjusted rate	3.6%	18.4%	0.0%	18.4%
Terminal rate	0/8 (0%)	1/14 (7%)	0/12 (0%)	1/14 (7%)
First incidence (days)	381	520	-	520
Life table test		P=0.287		P=0.027
Logistic regression test		P=0.200		P=0.040
Fisher exact test		P=0.219		P=0.029
Preputial Gland: Adenoma or Carcinoma				
Overall rate	7/60 (12%)	8/60 (13%)	0/60 (0%)	8/60 (13%)
Adjusted rate	33.6%	34.2%	0.0%	34.2%
Terminal rate	2/8 (25%)	3/14 (21%)	0/12 (0%)	3/14 (21%)
First incidence (days)	381	520	-	520
Life table test		P=0.529N		P=0.004
Logistic regression test		P=0.556		P=0.004
Fisher exact test		P=0.500		P=0.003
Prostate Gland: Adenoma				
Overall rate	2/60 (3%)	1/60 (2%)	3/60 (5%)	1/60 (2%)
Adjusted rate			18.8%	7.1%
Terminal rate			2/12 (17%)	1/14 (7%)
First incidence (days)			712	857 (T)
Life table test				P=0.279N
Logistic regression test				P=0.375N
Fisher exact test				P=0.309N
Skin: Keratoacanthoma				
Overall rate	4/60 (7%)	4/60 (7%)	2/60 (3%)	4/60 (7%)
Adjusted rate	28.6%	15.5%	11.0%	15.5%
Terminal rate	2/8 (25%)	1/14 (7%)	1/12 (8%)	1/14 (7%)
First incidence (days)	667	647	730	647
Life table test		P=0.516N		P=0.326
Logistic regression test		P=0.616N		P=0.303
Fisher exact test		P=0.641N		P=0.340

TABLE C2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	6/60 (10%)	6/60 (10%)	2/60 (3%)	6/60 (10%)
Adjusted rate	45.1%	24.2%	11.0%	24.2%
Terminal rate	3/8 (38%)	2/14 (14%)	1/12 (8%)	2/14 (14%)
First incidence (days)	667	647	730	647
Life table test		P=0.423N		P=0.134
Logistic regression test		P=0.566N		P=0.109
Fisher exact test		P=0.619N		P=0.136
Skin: Trichoepithelioma or Basal Cell Carcinoma				
Overall rate	3/60 (5%)	1/60 (2%)	1/60 (2%)	1/60 (2%)
Adjusted rate		2.0%		
Terminal rate		0/14 (0%)		
First incidence (days)		626		
Life table test		P=0.240N		
Logistic regression test		P=0.298N		
Fisher exact test		P=0.309N		
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Carcinoma				
Overall rate	8/60 (13%)	7/60 (12%)	3/60 (5%)	7/60 (12%)
Adjusted rate	50.3%	25.7%	19.0%	25.7%
Terminal rate	3/8 (38%)	2/14 (14%)	2/12 (17%)	2/14 (14%)
First incidence (days)	667	626	730	626
Life table test		P=0.308N		P=0.163
Logistic regression test		P=0.454N		P=0.131
Fisher exact test		P=0.500N		P=0.161
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/60 (7%)	6/60 (10%)	7/60 (12%)	6/60 (10%)
Adjusted rate	30.0%	26.7%	34.3%	26.7%
Terminal rate	1/8 (13%)	2/14 (14%)	3/12 (25%)	2/14 (14%)
First incidence (days)	761	642	577	642
Life table test		P=0.574		P=0.553N
Logistic regression test		P=0.448		P=0.589N
Fisher exact test		P=0.372		P=0.500N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	1/60 (2%)	1/60 (2%)	3/60 (5%)	1/60 (2%)
Adjusted rate			12.1%	3.6%
Terminal rate			0/12 (0%)	0/14 (0%)
First incidence (days)			673	745
Life table test				P=0.344N
Logistic regression test				P=0.316N
Fisher exact test				P=0.309N

TABLE C2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	5/60 (8%)	7/60 (12%)	9/60 (15%)	7/60 (12%)
Adjusted rate	40.0%	29.3%	41.0%	29.3%
Terminal rate	2/8 (25%)	2/14 (14%)	3/12 (25%)	2/14 (14%)
First incidence (days)	761	642	577	642
Life table test		P=0.605		P=0.457N
Logistic regression test		P=0.470		P=0.489N
Fisher exact test		P=0.381		P=0.395N
Testes: Adenoma				
Overall rate	55/60 (92%)	59/60 (98%)	58/60 (97%)	59/60 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	8/8 (100%)	14/14 (100%)	12/12 (100%)	14/14 (100%)
First incidence (days)	489	487	577	487
Life table test		P=0.306N		P=0.273
Logistic regression test		P=0.104		P=0.258
Fisher exact test		P=0.103		P=0.500
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/60 (8%)	4/60 (7%)	5/60 (8%)	4/60 (7%)
Adjusted rate	25.2%	17.6%	26.7%	17.6%
Terminal rate	0/8 (0%)	2/14 (14%)	2/12 (17%)	2/14 (14%)
First incidence (days)	730	603	715	603
Life table test		P=0.355N		P=0.495N
Logistic regression test		P=0.473N		P=0.564N
Fisher exact test		P=0.500N		P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/60 (8%)	6/60 (10%)	6/60 (10%)	6/60 (10%)
Adjusted rate	25.2%	26.5%	34.1%	26.5%
Terminal rate	0/8 (0%)	3/14 (21%)	3/12 (25%)	3/14 (21%)
First incidence (days)	730	603	715	603
Life table test		P=0.575N		P=0.605N
Logistic regression test		P=0.536		P=0.535
Fisher exact test		P=0.500		P=0.619N
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	0/60 (0%)	3/60 (5%)	0/60 (0%)	3/60 (5%)
Adjusted rate	0.0%	18.8%	0.0%	18.8%
Terminal rate	0/8 (0%)	1/14 (7%)	0/12 (0%)	1/14 (7%)
First incidence (days)	-	810	-	810
Life table test		P=0.237		P=0.100
Logistic regression test		P=0.179		P=0.084
Fisher exact test		P=0.122		P=0.122

TABLE C2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Zymbal's Gland: Carcinoma				
Overall rate	2/60 (3%)	3/60 (5%)	1/60 (2%)	3/60 (5%)
Adjusted rate	9.9%	7.8%	8.3%	7.8%
Terminal rate	0/8 (0%)	0/14 (0%)	1/12 (8%)	0/14 (0%)
First incidence (days)	500	487	857 (T)	487
Life table test		P=0.527		P=0.289
Logistic regression test		P=0.483		P=0.348
Fisher exact test		P=0.500		P=0.309
Zymbal's Gland: Adenoma or Carcinoma				
Overall rate	2/60 (3%)	4/60 (7%)	1/60 (2%)	4/60 (7%)
Adjusted rate	9.9%	10.4%	8.3%	10.4%
Terminal rate	0/8 (0%)	0/14 (0%)	1/12 (8%)	0/14 (0%)
First incidence (days)	500	487	857 (T)	487
Life table test		P=0.366		P=0.165
Logistic regression test		P=0.321		P=0.213
Fisher exact test		P=0.340		P=0.182
All Organs: Mononuclear Cell Leukemia				
Overall rate	39/60 (65%)	32/60 (53%)	45/60 (75%)	32/60 (53%)
Adjusted rate	87.2%	75.2%	87.9%	75.2%
Terminal rate	4/8 (50%)	6/14 (43%)	7/12 (58%)	6/14 (43%)
First incidence (days)	534	423	375	423
Life table test		P=0.085N		P=0.170N
Logistic regression test		P=0.168N		P=0.008N
Fisher exact test		P=0.133N		P=0.011N
All Organs: Malignant Mesothelioma				
Overall rate	1/60 (2%)	3/60 (5%)	0/60 (0%)	3/60 (5%)
Adjusted rate	12.5%	7.2%	0.0%	7.2%
Terminal rate	1/8 (13%)	0/14 (0%)	0/12 (0%)	0/14 (0%)
First incidence (days)	857 (T)	626	-	626
Life table test		P=0.366		P=0.108
Logistic regression test		P=0.306		P=0.151
Fisher exact test		P=0.309		P=0.122
All Organs: Benign Neoplasms				
Overall rate	60/60 (100%)	59/60 (98%)	59/60 (98%)	59/60 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	8/8 (100%)	14/14 (100%)	12/12 (100%)	14/14 (100%)
First incidence (days)	381	487	577	487
Life table test		P=0.154N		P=0.307
Logistic regression test		P=0.354N		P=0.318
Fisher exact test		P=0.500N		P=0.752N

TABLE C2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
All Organs: Malignant Neoplasms				
Overall rate	51/60 (85%)	47/60 (78%)	51/60 (85%)	47/60 (78%)
Adjusted rate	95.5%	91.2%	93.9%	91.2%
Terminal rate	6/8 (75%)	10/14 (71%)	9/12 (75%)	10/14 (71%)
First incidence (days)	381	423	375	423
Life table test		P=0.123N		P=0.507
Logistic regression test		P=0.249N		P=0.214N
Fisher exact test		P=0.240N		P=0.240N
All Organs: Benign or Malignant Neoplasms				
Overall rate	60/60 (100%)	60/60 (100%)	60/60 (100%)	60/60 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	8/8 (100%)	14/14 (100%)	12/12 (100%)	14/14 (100%)
First incidence (days)	381	423	375	423
Life table test		P=0.180N		P=0.309
Logistic regression test		-[f]		-
Fisher exact test		P=1.000N		P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreas, pancreatic islets, pituitary gland, preputial gland, prostate gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the *ad libitum*-fed controls or weight-matched controls and the exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE C2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol

	0 ppm	5,000 ppm
Adrenal Medulla: Benign Pheochromocytoma		
Overall rate[a]	12/59 (20%)	12/60 (20%)
Adjusted rate[b]	57.5%	42.5%
Terminal rate[c]	3/10 (30%)	7/22 (32%)
First incidence (days)	707	732
Life table test[d]		P=0.066N
Logistic regression test[d]		P=0.163N
Fisher exact test[d]		P=0.572N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma		
Overall rate	15/59 (25%)	14/60 (23%)
Adjusted rate	65.0%	45.5%
Terminal rate	4/10 (40%)	7/22 (32%)
First incidence (days)	552	712
Life table test		P=0.037N
Logistic regression test		P=0.162N
Fisher exact test		P=0.479N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
Overall rate	1/60 (2%)	3/60 (5%)
Adjusted rate	10.0%	11.8%
Terminal rate	1/10 (10%)	2/22 (9%)
First incidence (days)	911 (T)	820
Life table test		P=0.591
Logistic regression test		P=0.530
Fisher exact test		P=0.309
Mammary Gland: Fibroadenoma		
Overall rate	4/60 (7%)	6/60 (10%)
Adjusted rate	19.9%	19.6%
Terminal rate	1/10 (10%)	3/22 (14%)
First incidence (days)	745	745
Life table test		P=0.565N
Logistic regression test		P=0.512
Fisher exact test		P=0.372
Mammary Gland: Fibroadenoma or Carcinoma		
Overall rate	5/60 (8%)	7/60 (12%)
Adjusted rate	28.8%	23.0%
Terminal rate	2/10 (20%)	3/22 (14%)
First incidence (days)	745	745
Life table test		P=0.463N
Logistic regression test		P=0.595
Fisher exact test		P=0.381

TABLE C2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
Pancreatic Islets: Adenoma		
Overall rate	2/58 (3%)	6/60 (10%)
Adjusted rate	8.3%	20.6%
Terminal rate	0/10 (0%)	3/22 (14%)
First incidence (days)	707	778
Life table test		P=0.394
Logistic regression test		P=0.235
Fisher exact test		P=0.147
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	13/57 (23%)	16/56 (29%)
Adjusted rate	46.6%	47.2%
Terminal rate	2/10 (20%)	6/20 (30%)
First incidence (days)	569	641
Life table test		P=0.286N
Logistic regression test		P=0.382
Fisher exact test		P=0.314
Preputial Gland: Adenoma or Carcinoma		
Overall rate	2/60 (3%)	3/59 (5%)
Adjusted rate	7.7%	8.0%
Terminal rate	0/10 (0%)	0/21 (0%)
First incidence (days)	786	731
Life table test		P=0.647N
Logistic regression test		P=0.509
Fisher exact test		P=0.492
Skin (Subcutaneous Tissue): Fibroma		
Overall rate	6/60 (10%)	3/60 (5%)
Adjusted rate	33.6%	12.5%
Terminal rate	1/10 (10%)	2/22 (9%)
First incidence (days)	730	866
Life table test		P=0.043N
Logistic regression test		P=0.077N
Fisher exact test		P=0.245N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma		
Overall rate	6/60 (10%)	4/60 (7%)
Adjusted rate	33.6%	14.0%
Terminal rate	1/10 (10%)	2/22 (9%)
First incidence (days)	730	671
Life table test		P=0.093N
Logistic regression test		P=0.188N
Fisher exact test		P=0.372N

TABLE C2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
Stomach (Forestomach): Squamous Cell Papilloma		
Overall rate	0/60 (0%)	3/60 (5%)
Adjusted rate	0.0%	9.7%
Terminal rate	0/10 (0%)	1/22 (5%)
First incidence (days)	-[e]	743
Life table test		P=0.235
Logistic regression test		P=0.161
Fisher exact test		P=0.122
Testes: Adenoma		
Overall rate	59/60 (98%)	60/60 (100%)
Adjusted rate	100.0%	100.0%
Terminal rate	10/10 (100%)	22/22 (100%)
First incidence (days)	484	600
Life table test		P=0.002N
Logistic regression test		P=0.600
Fisher exact test		P=0.500
Thyroid Gland (C-cell): Adenoma		
Overall rate	7/60 (12%)	6/59 (10%)
Adjusted rate	30.0%	17.9%
Terminal rate	1/10 (10%)	2/22 (9%)
First incidence (days)	604	730
Life table test		P=0.191N
Logistic regression test		P=0.520N
Fisher exact test		P=0.513N
Thyroid Gland (C-cell): Carcinoma		
Overall rate	0/60 (0%)	5/59 (8%)
Adjusted rate	0.0%	12.1%
Terminal rate	0/10 (0%)	0/22 (0%)
First incidence (days)	-	641
Life table test		P=0.082
Logistic regression test		P=0.013
Fisher exact test		P=0.027
Thyroid Gland (C-cell): Adenoma or Carcinoma		
Overall rate	7/60 (12%)	11/59 (19%)
Adjusted rate	30.0%	27.8%
Terminal rate	1/10 (10%)	2/22 (9%)
First incidence (days)	604	641
Life table test		P=0.595
Logistic regression test		P=0.158
Fisher exact test		P=0.210

TABLE C2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
All Organs: Mononuclear Cell Leukemia		
Overall rate	46/60 (77%)	39/60 (65%)
Adjusted rate	86.9%	78.2%
Terminal rate	4/10 (40%)	12/22 (55%)
First incidence (days)	484	641
Life table test		P=0.002N
Logistic regression test		P=0.234N
Fisher exact test		P=0.114N
All Organs: Malignant Mesothelioma		
Overall rate	3/60 (5%)	4/60 (7%)
Adjusted rate	6.0%	18.2%
Terminal rate	0/10 (0%)	4/22 (18%)
First incidence (days)	552	911 (T)
Life table test		P=0.545N
Logistic regression test		P=0.464
Fisher exact test		P=0.500
All Organs: Benign Neoplasms		
Overall rate	59/60 (98%)	60/60 (100%)
Adjusted rate	100.0%	100.0%
Terminal rate	10/10 (100%)	22/22 (100%)
First incidence (days)	484	600
Life table test		P=0.002N
Logistic regression test		P=0.600
Fisher exact test		P=0.500
All Organs: Malignant Neoplasms		
Overall rate	52/60 (87%)	49/60 (82%)
Adjusted rate	94.0%	86.8%
Terminal rate	7/10 (70%)	15/22 (68%)
First incidence (days)	484	600
Life table test		P=0.003N
Logistic regression test		P=0.596N
Fisher exact test		P=0.309N

TABLE C2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
All Organs: Benign or Malignant Neoplasms		
Overall rate	59/60 (98%)	60/60 (100%)
Adjusted rate	100.0%	100.0%
Terminal rate	10/10 (100%)	22/22 (100%)
First incidence (days)	484	600
Life table test		P=0.002N
Logistic regression test		P=0.600
Fisher exact test		P=0.500

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Disposition Summary			
Animals initially in study	70	70	70
3-Month interim evaluation	10	10	10
Early deaths			
Moribund	48	41	42
Natural deaths	4	7	4
Survivors			
Terminal sacrifice	8	12	14
Animals examined microscopically	70	70	70
3-Month Interim Evaluation			
Alimentary System			
Intestine large, colon	(10)	(10)	(10)
Parasite metazoan			1 (10%)
Intestine large, rectum	(10)	(10)	(10)
Parasite metazoan	1 (10%)	1 (10%)	
Liver	(10)	(10)	(10)
Inflammation, subacute	1 (10%)	2 (20%)	2 (20%)
Necrosis, focal		1 (10%)	
Bile duct, hyperplasia			1 (10%)
Hepatocyte, vacuolization, cytoplasmic		1 (10%)	
Pancreas	(10)	(10)	(10)
Atrophy	1 (10%)		2 (20%)
Cardiovascular System			
Heart	(10)	(10)	(10)
Cardiomyopathy	2 (20%)	4 (40%)	2 (20%)
Endocrine System			
Adrenal cortex	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)	3 (30%)	1 (10%)
Hyperplasia, focal		1 (10%)	
Thyroid gland	(10)	(10)	(10)
Ectopic thymus	1 (10%)	1 (10%)	
Ultimobranchial cyst	1 (10%)		3 (30%)
Genital System			
Prostate	(10)	(10)	(10)
Inflammation, suppurative		1 (10%)	

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

TABLE C3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
3-Month Interim Evaluation (continued)			
Hematopoietic System			
Lymph node		(4)	
Mediastinal, hemorrhage		2 (50%)	
Mediastinal, hyperplasia, lymphoid		1 (25%)	
Pancreatic, hemorrhage		2 (50%)	
Renal, hemorrhage		1 (25%)	
Spleen	(10)	(10)	(10)
Pigmentation, hemosiderin			5 (50%)
Thymus	(10)	(10)	(10)
Hemorrhage		1 (10%)	1 (10%)
Respiratory System			
Lung	(10)	(10)	(10)
Inflammation, subacute	4 (40%)	7 (70%)	7 (70%)
Alveolar epithelium, hyperplasia	3 (30%)	2 (20%)	3 (30%)
Nose	(10)	(10)	(10)
Goblet cell, hyperplasia			7 (70%)
Urinary System			
Kidney	(10)	(10)	(10)
Mineralization	1 (10%)	2 (20%)	
Nephropathy	5 (50%)	8 (80%)	6 (60%)
Systems Examined With No Lesions Observed			
General Body System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Special Senses System			
30-Month Study			
Alimentary System			
Intestine large, colon	(58)	(60)	(60)
Edema			1 (2%)
Parasite metazoan	7 (12%)	6 (10%)	2 (3%)
Intestine large, rectum	(59)	(58)	(59)
Edema	2 (3%)		1 (2%)
Hemorrhage			1 (2%)
Parasite metazoan	5 (8%)	4 (7%)	8 (14%)
Intestine large, cecum	(60)	(60)	(60)
Edema	3 (5%)	2 (3%)	3 (5%)
Parasite metazoan	1 (2%)	2 (3%)	3 (5%)
Intestine small, duodenum	(60)	(60)	(60)
Epithelium, hyperplasia	2 (3%)		4 (7%)

TABLE C3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Alimentary System (continued)			
Intestine small, jejunum	(60)	(59)	(60)
Epithelium, hyperplasia	1 (2%)		1 (2%)
Intestine small, ileum	(60)	(59)	(59)
Diverticulum		1 (2%)	
Liver	(60)	(60)	(60)
Angiectasis	10 (17%)	5 (8%)	7 (12%)
Basophilic focus	7 (12%)	7 (12%)	7 (12%)
Clear cell focus	1 (2%)	1 (2%)	5 (8%)
Congestion		1 (2%)	
Degeneration, cystic	23 (38%)	9 (15%)	5 (8%)
Eosinophilic focus	10 (17%)	6 (10%)	4 (7%)
Eosinophilic focus, multiple	1 (2%)		
Fibrosis	1 (2%)		
Hemorrhage		1 (2%)	
Hematopoietic cell proliferation	1 (2%)		
Hepatodiaphragmatic nodule	7 (12%)	4 (7%)	8 (13%)
Mixed cell focus	2 (3%)		2 (3%)
Necrosis, focal	8 (13%)	6 (10%)	2 (3%)
Thrombosis	1 (2%)	1 (2%)	1 (2%)
Bile duct, cyst	2 (3%)		
Bile duct, hyperplasia	52 (87%)	47 (78%)	25 (42%)
Centrilobular, fibrosis			1 (2%)
Centrilobular, necrosis	2 (3%)	3 (5%)	2 (3%)
Hepatocyte, vacuolization cytoplasmic	6 (10%)	9 (15%)	3 (5%)
Kupffer cell, pigmentation	11 (18%)	15 (25%)	10 (17%)
Mesentery	(20)	(15)	(16)
Accessory spleen	1 (5%)	2 (13%)	4 (25%)
Fat, necrosis	16 (80%)	12 (80%)	13 (81%)
Pancreas	(60)	(60)	(60)
Atrophy	15 (25%)	19 (32%)	15 (25%)
Acinus, cytoplasmic alteration	3 (5%)	1 (2%)	4 (7%)
Acinus, hyperplasia, focal	2 (3%)	1 (2%)	2 (3%)
Salivary gland	(60)	(60)	(60)
Atrophy		1 (2%)	
Stomach, forestomach	(60)	(60)	(59)
Edema	9 (15%)	2 (3%)	6 (10%)
Erosion		2 (3%)	
Hyperplasia	8 (13%)	7 (12%)	12 (20%)
Inflammation, subacute		2 (3%)	
Ulcer	8 (13%)	10 (17%)	7 (12%)
Mucosa, hyperplasia	1 (2%)		
Stomach, glandular	(60)	(60)	(60)
Edema	1 (2%)	2 (3%)	3 (5%)
Erosion	1 (2%)	11 (18%)	1 (2%)
Mineralization	1 (2%)		
Ulcer	3 (5%)	5 (8%)	
Tongue	(1)	(2)	(4)
Epithelium, hyperplasia		1 (50%)	2 (50%)

TABLE C3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Cardiovascular System			
Blood vessel	(60)	(60)	(60)
Hypertrophy	1 (2%)		4 (7%)
Inflammation, subacute	1 (2%)		
Heart	(60)	(60)	(60)
Cardiomyopathy	40 (67%)	38 (63%)	37 (62%)
Necrosis	1 (2%)		
Thrombosis	6 (10%)	9 (15%)	
Endocardium, hyperplasia	1 (2%)		
Schwann cell, hyperplasia		1 (2%)	
Endocrine System			
Adrenal cortex	(60)	(60)	(60)
Accessory adrenal cortical nodule	17 (28%)	14 (23%)	13 (22%)
Degeneration, fatty	9 (15%)	7 (12%)	7 (12%)
Hemorrhage	1 (2%)	3 (5%)	2 (3%)
Hyperplasia, focal	4 (7%)	1 (2%)	3 (5%)
Hypertrophy, focal	6 (10%)	5 (8%)	2 (3%)
Necrosis	1 (2%)	1 (2%)	
Adrenal medulla	(60)	(60)	(60)
Hyperplasia	26 (43%)	30 (50%)	12 (20%)
Islets, pancreatic	(60)	(60)	(60)
Hyperplasia	3 (5%)	3 (5%)	1 (2%)
Parathyroid gland	(55)	(57)	(58)
Hyperplasia	6 (11%)	1 (2%)	9 (16%)
Pituitary gland	(60)	(59)	(60)
Nuclear alteration			1 (2%)
Pars distalis, angiectasis	4 (7%)	2 (3%)	
Pars distalis, cyst	6 (10%)	9 (15%)	7 (12%)
Pars distalis, cyst, hemorrhagic	1 (2%)		
Pars distalis, hyperplasia, focal	10 (17%)	10 (17%)	14 (23%)
Pars intermedia, angiectasis			1 (2%)
Pars intermedia, cyst	1 (2%)	8 (14%)	2 (3%)
Thyroid gland	(60)	(60)	(60)
Ultimobranchial cyst	1 (2%)	3 (5%)	5 (8%)
C-cell, hyperplasia	9 (15%)	6 (10%)	7 (12%)
Follicle, cyst	1 (2%)	1 (2%)	
General Body System			
None			

TABLE C3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Genital System			
Epididymis	(60)	(60)	(60)
Atypia cellular	27 (45%)	29 (48%)	25 (42%)
Granuloma sperm			1 (2%)
Preputial gland	(60)	(60)	(60)
Cyst	3 (5%)		4 (7%)
Hyperplasia	3 (5%)	1 (2%)	2 (3%)
Inflammation, chronic	26 (43%)	12 (20%)	12 (20%)
Inflammation, suppurative	3 (5%)	1 (2%)	5 (8%)
Prostate	(60)	(60)	(60)
Cyst	1 (2%)		
Fibrosis	3 (5%)		
Inflammation, chronic	5 (8%)	2 (3%)	
Inflammation, suppurative	36 (60%)	28 (47%)	23 (38%)
Epithelium, hyperplasia	11 (18%)	12 (20%)	8 (13%)
Testes	(60)	(60)	(60)
Interstitial cell, hyperplasia	4 (7%)	3 (5%)	3 (5%)
Seminiferous tubule, atrophy	7 (12%)	1 (2%)	5 (8%)
Hematopoietic System			
Bone marrow	(60)	(60)	(60)
Depletion cellular		1 (2%)	
Hyperplasia	6 (10%)		7 (12%)
Infiltration cellular, histiocyte			2 (3%)
Myelofibrosis	4 (7%)	2 (3%)	2 (3%)
Lymph node	(33)	(33)	(35)
Iliac, hemorrhage	1 (3%)		
Inguinal, hyperplasia, lymphoid	2 (6%)		1 (3%)
Mediastinal, congestion			2 (6%)
Mediastinal, hemorrhage	3 (9%)	3 (9%)	3 (9%)
Mediastinal, hyperplasia, lymphoid	1 (3%)	2 (6%)	2 (6%)
Mediastinal, pigmentation	13 (39%)	14 (42%)	16 (46%)
Pancreatic, hyperplasia, plasma cell			1 (3%)
Pancreatic, pigmentation	9 (27%)	4 (12%)	3 (9%)
Renal, ectasia			2 (6%)
Renal, hemorrhage	1 (3%)		2 (6%)
Renal, pigmentation	8 (24%)	5 (15%)	7 (20%)
Lymph node, mandibular	(60)	(59)	(60)
Ectasia	3 (5%)	8 (14%)	6 (10%)
Hemorrhage	2 (3%)	1 (2%)	3 (5%)
Hyperplasia, lymphoid	11 (18%)	11 (19%)	17 (28%)
Pigmentation	6 (10%)	8 (14%)	5 (8%)
Lymph node, mesenteric	(60)	(58)	(60)
Ectasia	7 (12%)	1 (2%)	10 (17%)
Hemorrhage	1 (2%)	3 (5%)	2 (3%)
Hyperplasia, lymphoid	3 (5%)	2 (3%)	6 (10%)

TABLE C3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Hematopoietic System (continued)			
Spleen	(60)	(60)	(60)
Angiectasis		1 (2%)	
Congestion	1 (2%)		
Fibrosis	21 (35%)	19 (32%)	13 (22%)
Hematopoietic cell proliferation	7 (12%)	6 (10%)	8 (13%)
Metaplasia, lipocyte	1 (2%)		
Necrosis	2 (3%)	3 (5%)	
Pigmentation, hemosiderin	13 (22%)	11 (18%)	12 (20%)
Lymphoid follicle, atrophy	1 (2%)		
Thymus	(58)	(55)	(56)
Cyst		1 (2%)	
Integumentary System			
Mammary gland	(57)	(58)	(58)
Dilatation	23 (40%)	27 (47%)	10 (17%)
Galactocele	5 (9%)		2 (3%)
Hyperplasia	7 (12%)	12 (21%)	6 (10%)
Skin	(60)	(60)	(60)
Cyst epithelial inclusion	2 (3%)		1 (2%)
Hemorrhage			1 (2%)
Hyperkeratosis		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Epidermis, hyperplasia	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, inflammation suppurative		1 (2%)	
Subcutaneous tissue, thrombosis			1 (2%)
Musculoskeletal System			
Bone	(60)	(60)	(60)
Fibrous osteodystrophy	6 (10%)	1 (2%)	7 (12%)
Hyperostosis	1 (2%)		
Femur, osteopetrosis	1 (2%)	2 (3%)	
Nervous System			
Brain	(60)	(60)	(60)
Angiectasis		1 (2%)	
Atrophy	12 (20%)	6 (10%)	3 (5%)
Hemorrhage	2 (3%)		1 (2%)
Hydrocephalus	4 (7%)	3 (5%)	
Necrosis	1 (2%)	2 (3%)	1 (2%)

TABLE C3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Respiratory System			
Lung	(60)	(60)	(60)
Congestion	2 (3%)		
Edema	1 (2%)	1 (2%)	1 (2%)
Hemorrhage	3 (5%)	2 (3%)	2 (3%)
Infiltration cellular, histiocyte	19 (32%)	17 (28%)	14 (23%)
Inflammation, subacute			1 (2%)
Metaplasia, osseous	1 (2%)		
Alveolar epithelium, hyperplasia	4 (7%)	6 (10%)	7 (12%)
Nose	(60)	(60)	(60)
Foreign body	6 (10%)	5 (8%)	2 (3%)
Inflammation, suppurative	17 (28%)	10 (17%)	11 (18%)
Goblet cell, hyperplasia	5 (8%)	4 (7%)	13 (22%)
Mucosa, hyperplasia	14 (23%)	8 (13%)	10 (17%)
Mucosa, metaplasia, squamous	8 (13%)	4 (7%)	7 (12%)
Special Senses System			
Eye	(4)	(4)	(2)
Atrophy	2 (50%)		1 (50%)
Cataract	1 (25%)	2 (50%)	1 (50%)
Inflammation, chronic		1 (25%)	
Retina, degeneration	1 (25%)	2 (50%)	1 (50%)
Urinary System			
Kidney	(60)	(60)	(60)
Cyst	2 (3%)	1 (2%)	11 (18%)
Inflammation, suppurative	9 (15%)		20 (33%)
Mineralization	12 (20%)	11 (18%)	1 (2%)
Nephropathy	60 (100%)	56 (93%)	60 (100%)
Renal tubule, accumulation, hyaline droplet	1 (2%)	3 (5%)	1 (2%)
Renal tubule, atrophy		1 (2%)	1 (2%)
Renal tubule, necrosis	3 (5%)	1 (2%)	
Renal tubule, pigmentation	18 (30%)	23 (38%)	15 (25%)
Transitional epithelium, hyperplasia	13 (22%)	2 (3%)	21 (35%)
Urinary bladder	(60)	(60)	(60)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	
Transitional epithelium, hyperplasia	2 (3%)		

TABLE C3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol[a]

	0 ppm	5,000 ppm
Disposition Summary		
Animals initially in study	70	70
3-Month interim evaluation	10	10
Early deaths		
Moribund	43	33
Natural deaths	7	5
Survivors		
Terminal sacrifice	10	22
Animals examined microscopically	70	70
3-Month Interim Evaluation		
Cardiovascular System		
Heart	(10)	(10)
Cardiomyopathy	3 (30%)	2 (20%)
Endocrine System		
Adrenal cortex	(10)	(10)
Accessory adrenal cortical nodule	2 (20%)	
Pituitary gland	(10)	(10)
Pars distalis, cyst	1 (10%)	1 (10%)
Pars intermedia, cyst	1 (10%)	
Thyroid gland	(10)	(10)
Ultimobranchial cyst	2 (20%)	
Genital System		
Prostate	(10)	(10)
Inflammation, suppurative	2 (20%)	1 (10%)
Hematopoietic System		
Lymph node, mesenteric	(10)	(10)
Hemorrhage	1 (10%)	
Spleen	(10)	(10)
Pigmentation, hemosiderin		3 (30%)
Thymus	(10)	(9)
Hemorrhage	1 (10%)	
Respiratory System		
Lung	(10)	(10)
Alveolar epithelium, hyperplasia	1 (10%)	
Nose	(10)	(10)
Goblet cell, hyperplasia		6 (60%)

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

TABLE C3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
3-Month Interim Evaluation (continued)		
Urinary System		
Kidney	(10)	(10)
Nephropathy	2 (20%)	1 (10%)
Systems Examined With No Lesions Observed		
Alimentary System		
General Body System		
Integumentary System		
Musculoskeletal System		
Nervous System		
Special Senses System		
30-Month Study		
Alimentary System		
Intestine large, colon	(60)	(60)
Parasite metazoan	7 (12%)	8 (13%)
Intestine large, rectum	(59)	(60)
Erosion		1 (2%)
Parasite metazoan	4 (7%)	7 (12%)
Intestine large, cecum	(60)	(60)
Edema	3 (5%)	2 (3%)
Parasite metazoan		3 (5%)
Intestine small, duodenum	(60)	(60)
Ulcer	3 (5%)	
Liver	(60)	(60)
Angiectasis	5 (8%)	6 (10%)
Basophilic focus	5 (8%)	1 (2%)
Clear cell focus		3 (5%)
Cyst		1 (2%)
Degeneration, cystic	6 (10%)	12 (20%)
Eosinophilic focus	6 (10%)	9 (15%)
Hematopoietic cell proliferation	1 (2%)	
Hepatodiaphragmatic nodule	2 (3%)	5 (8%)
Inflammation, subacute		1 (2%)
Mixed cell focus		3 (5%)
Necrosis, focal	7 (12%)	6 (10%)
Thrombosis		2 (3%)
Bile duct, hyperplasia	45 (75%)	30 (50%)
Centrilobular, necrosis		2 (3%)
Hepatocyte, vacuolization cytoplasmic	2 (3%)	2 (3%)
Kupffer cell, hyperplasia	1 (2%)	
Kupffer cell, pigmentation	19 (32%)	14 (23%)
Mesentery	(8)	(5)
Accessory spleen	2 (25%)	1 (20%)
Fat, necrosis	4 (50%)	1 (20%)
Pancreas	(58)	(60)
Atrophy	21 (36%)	19 (32%)
Acinus, cytoplasmic alteration		1 (2%)

TABLE C3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Alimentary System (continued)		
Salivary glands	(60)	(60)
Atrophy	1 (2%)	1 (2%)
Stomach, forestomach	(60)	(60)
Erosion		2 (3%)
Hyperplasia	5 (8%)	3 (5%)
Ulcer	1 (2%)	1 (2%)
Stomach, glandular	(60)	(60)
Edema	1 (2%)	1 (2%)
Erosion	1 (2%)	2 (3%)
Mineralization		1 (2%)
Ulcer	1 (2%)	
Tongue	(1)	(2)
Epithelium, hyperplasia		1 (50%)
Cardiovascular System		
Blood vessel	(60)	(60)
Hypertrophy	1 (2%)	1 (2%)
Inflammation, subacute	1 (2%)	1 (2%)
Thrombosis	1 (2%)	
Heart	(60)	(60)
Cardiomyopathy	34 (57%)	43 (72%)
Thrombosis	5 (8%)	6 (10%)
Endocrine System		
Adrenal cortex	(60)	(60)
Accessory adrenal cortical nodule	13 (22%)	7 (12%)
Angiectasis	1 (2%)	1 (2%)
Degeneration, fatty	13 (22%)	5 (8%)
Hematopoietic cell proliferation		1 (2%)
Hemorrhage	1 (2%)	
Hyperplasia, diffuse	1 (2%)	
Hyperplasia, focal	2 (3%)	2 (3%)
Hypertrophy, focal	5 (8%)	5 (8%)
Necrosis		1 (2%)
Adrenal medulla	(59)	(60)
Hyperplasia	18 (31%)	15 (25%)
Islets, pancreatic	(58)	(60)
Hyperplasia	2 (3%)	1 (2%)
Parathyroid gland	(56)	(57)
Hyperplasia		1 (2%)
Pituitary gland	(57)	(56)
Pars distalis, angiectasis	3 (5%)	3 (5%)
Pars distalis, cyst	7 (12%)	7 (13%)
Pars distalis, hyperplasia, focal	14 (25%)	7 (13%)
Pars distalis, hypertrophy		1 (2%)
Pars intermedia, cyst	2 (4%)	4 (7%)
Thyroid gland	(60)	(59)
Ultimobranchial cyst		2 (3%)
C-cell, hyperplasia	5 (8%)	5 (8%)
Follicle, cyst	2 (3%)	2 (3%)

TABLE C3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
General Body System		
None		
Genital System		
Epididymis	(60)	(60)
Atypia cellular	25 (42%)	19 (32%)
Preputial gland	(60)	(59)
Cyst	3 (5%)	1 (2%)
Hyperplasia	1 (2%)	2 (3%)
Inflammation, chronic	9 (15%)	13 (22%)
Inflammation, suppurative	1 (2%)	
Prostate	(60)	(60)
Inflammation, suppurative	28 (47%)	22 (37%)
Epithelium, hyperplasia	3 (5%)	5 (8%)
Testes	(60)	(60)
Atrophy	2 (3%)	4 (7%)
Interstitial cell, hyperplasia	3 (5%)	
Hematopoietic System		
Bone marrow	(60)	(60)
Hyperplasia	2 (3%)	2 (3%)
Myelofibrosis	8 (13%)	3 (5%)
Lymph node	(36)	(23)
Iliac, hyperplasia, lymphoid		1 (4%)
Iliac, pigmentation		2 (9%)
Mediastinal, hemorrhage	2 (6%)	
Mediastinal, pigmentation	19 (53%)	11 (48%)
Pancreatic, pigmentation	8 (22%)	4 (17%)
Renal, hemorrhage	1 (3%)	
Renal, pigmentation	7 (19%)	3 (13%)
Lymph node, mandibular	(60)	(60)
Ectasia	2 (3%)	2 (3%)
Hemorrhage	1 (2%)	3 (5%)
Hyperplasia, lymphoid	5 (8%)	4 (7%)
Hyperplasia, plasma cell	1 (2%)	2 (3%)
Pigmentation	13 (22%)	14 (23%)
Lymph node, mesenteric	(60)	(60)
Ectasia	2 (3%)	4 (7%)
Hemorrhage	1 (2%)	
Hyperplasia, lymphoid	1 (2%)	2 (3%)
Spleen	(60)	(60)
Fibrosis	13 (22%)	16 (27%)
Hematopoietic cell proliferation	2 (3%)	7 (12%)
Necrosis	2 (3%)	2 (3%)
Pigmentation, hemosiderin	3 (5%)	15 (25%)
Lymphoid follicle, atrophy	2 (3%)	1 (2%)

TABLE C3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Integumentary System		
Mammary gland	(58)	(58)
Dilatation	16 (28%)	14 (24%)
Galactocele		1 (2%)
Hyperplasia	7 (12%)	9 (16%)
Skin	(60)	(60)
Cyst epithelial inclusion		1 (2%)
Hyperkeratosis	1 (2%)	
Hyperplasia	1 (2%)	
Subcutaneous tissue, edema		1 (2%)
Musculoskeletal System		
Bone	(60)	(60)
Hyperostosis		1 (2%)
Cranium, osteopetrosis		1 (2%)
Femur, osteopetrosis	2 (3%)	2 (3%)
Nervous System		
Brain	(60)	(60)
Atrophy	3 (5%)	8 (13%)
Hemorrhage	1 (2%)	
Hydrocephalus	1 (2%)	2 (3%)
Necrosis	1 (2%)	1 (2%)
Respiratory System		
Lung	(60)	(60)
Congestion	1 (2%)	
Edema	3 (5%)	
Hemorrhage	4 (7%)	6 (10%)
Infiltration cellular, histiocyte	14 (23%)	21 (35%)
Inflammation, subacute		2 (3%)
Alveolar epithelium, hyperplasia	5 (8%)	8 (13%)
Nose	(60)	(60)
Foreign body	3 (5%)	2 (3%)
Inflammation	1 (2%)	
Inflammation, suppurative	5 (8%)	2 (3%)
Goblet cell, hyperplasia	8 (13%)	11 (18%)
Mucosa, hyperplasia	8 (13%)	2 (3%)
Mucosa, metaplasia, squamous	7 (12%)	1 (2%)
Special Senses System		
Eye	(1)	(3)
Cataract	1 (100%)	3 (100%)
Hemorrhage		1 (33%)
Retina, degeneration	1 (100%)	3 (100%)

TABLE C3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Urinary System		
Kidney	(60)	(60)
Calculus, microscopic observation only		2 (3%)
Cyst	2 (3%)	
Hydronephrosis		1 (2%)
Infiltration cellular, lipocyte	1 (2%)	
Inflammation, suppurative		3 (5%)
Mineralization	4 (7%)	
Nephropathy	51 (85%)	59 (98%)
Renal tubule, accumulation, hyaline droplet	1 (2%)	1 (2%)
Renal tubule, atrophy	1 (2%)	4 (7%)
Renal tubule, dilatation		1 (2%)
Renal tubule, necrosis	3 (5%)	
Renal tubule, pigmentation	17 (28%)	18 (30%)
Transitional epithelium, hyperplasia	1 (2%)	5 (8%)
Urinary bladder	(60)	(60)
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE RATS IN THE DIETARY RESTRICTION STUDY OF *t*-BUTYLHYDROQUINONE

TABLE D1a
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Disposition Summary			
Animals initially in study	70	70	70
3-Month interim evaluation	10	10	10
Early deaths			
Moribund	40	31	36
Natural deaths	10	7	7
Survivors			
Terminal sacrifice	10	22	17
Animals examined microscopically	70	70	70
Systems Examined At 3 Months With No Neoplasms Observed			
Alimentary System			
Cardiovascular System			
Endocrine System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			
30-Month Study			
Alimentary System			
Intestine large, colon	(60)	(60)	(59)
Intestine large, cecum	(60)	(60)	(60)
Intestine small, ileum	(60)	(60)	(58)
Liver	(60)	(60)	(60)
Fibrous histiocytoma, metastatic, skin		1 (2%)	
Hepatocellular adenoma			1 (2%)
Hepatocellular adenoma, multiple			1 (2%)
Mesentery	(11)	(5)	(7)
Sarcoma stromal, metastatic, uterus	1 (9%)		
Pancreas	(60)	(60)	(59)
Sarcoma stromal, metastatic, uterus	1 (2%)		
Salivary glands	(60)	(60)	(60)
Carcinoma		1 (2%)	
Stomach, forestomach	(60)	(60)	(60)
Stomach, glandular	(60)	(60)	(60)
Tongue	(1)		(1)
Squamous cell papilloma	1 (100%)		

TABLE D1a
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Cardiovascular System			
Heart	(60)	(60)	(60)
Schwannoma benign			1 (2%)
Endocrine System			
Adrenal cortex	(60)	(60)	(60)
Adenoma	4 (7%)		
Adrenal medulla	(60)	(60)	(60)
Pheochromocytoma malignant		1 (2%)	1 (2%)
Pheochromocytoma benign	2 (3%)	2 (3%)	3 (5%)
Islets, pancreatic	(60)	(60)	(59)
Adenoma	2 (3%)	1 (2%)	2 (3%)
Parathyroid gland	(52)	(55)	(54)
Adenoma	2 (4%)	1 (2%)	1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)
Pituitary gland	(60)	(59)	(60)
Pars distalis, adenoma	26 (43%)	31 (53%)	28 (47%)
Pars distalis, carcinoma	2 (3%)	2 (3%)	3 (5%)
Thyroid gland	(60)	(59)	(60)
C-cell, adenoma	7 (12%)	6 (10%)	6 (10%)
C-cell, carcinoma	1 (2%)	2 (3%)	1 (2%)
Follicular cell, carcinoma	1 (2%)	1 (2%)	2 (3%)
General Body System			
Peritoneum	(1)		
Genital System			
Clitoral gland	(58)	(59)	(60)
Adenoma	6 (10%)	3 (5%)	6 (10%)
Adenoma, multiple		1 (2%)	1 (2%)
Carcinoma	6 (10%)	1 (2%)	8 (13%)
Carcinoma, multiple		1 (2%)	
Ovary	(60)	(60)	(60)
Granulosa cell tumor benign	1 (2%)		1 (2%)
Uterus	(60)	(60)	(60)
Adenoma			1 (2%)
Carcinoma			1 (2%)
Leiomyoma	1 (2%)		
Polyp stromal	6 (10%)	9 (15%)	9 (15%)
Polyp stromal, multiple	1 (2%)		
Sarcoma stromal	2 (3%)	1 (2%)	

TABLE D1a
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Hematopoietic System			
Bone marrow	(60)	(60)	(60)
Lymph node	(20)	(14)	(18)
Lymph node, mandibular	(59)	(60)	(60)
Lymph node, mesenteric	(58)	(59)	(60)
Spleen	(60)	(60)	(60)
Hemangiosarcoma	1 (2%)		
Thymus	(56)	(56)	(57)
Fibrous histiocytoma, metastatic, skin		1 (2%)	
Integumentary System			
Mammary gland	(60)	(60)	(60)
Adenoma	3 (5%)	3 (5%)	2 (3%)
Carcinoma	8 (13%)	1 (2%)	3 (5%)
Carcinoma, multiple			1 (2%)
Fibroadenoma	28 (47%)	21 (35%)	20 (33%)
Fibroadenoma, multiple	15 (25%)	2 (3%)	7 (12%)
Skin	(60)	(59)	(60)
Basal cell carcinoma	1 (2%)		
Keratoacanthoma		1 (2%)	
Squamous cell papilloma			2 (3%)
Subcutaneous tissue, fibroma	3 (5%)	2 (3%)	1 (2%)
Subcutaneous tissue, fibrous histiocytoma		1 (2%)	
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)
Subcutaneous tissue, lipoma	1 (2%)		
Subcutaneous tissue, sarcoma			1 (2%)
Subcutaneous tissue, schwannoma benign		1 (2%)	
Subcutaneous tissue, schwannoma malignant			1 (2%)
Musculoskeletal System			
Skeletal muscle	(1)	(1)	(1)
Fibrous histiocytoma, metastatic, skin		1 (100%)	
Sarcoma			1 (100%)
Sarcoma stromal, metastatic, uterus	1 (100%)		
Nervous System			
Brain	(60)	(60)	(60)
Carcinoma, metastatic, mammary gland			1 (2%)
Carcinoma, metastatic, pituitary gland		1 (2%)	1 (2%)
Oligodendroglioma malignant	1 (2%)		
Spinal cord	(2)	(1)	(4)
Astrocytoma malignant			1 (25%)

TABLE D1a
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Respiratory System			
Lung	(60)	(60)	(60)
Alveolar/bronchiolar adenoma	2 (3%)		1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)
Fibrous histiocytoma, metastatic, skin		1 (2%)	
Nose	(60)	(60)	(60)
Special Senses System			
None			
Urinary System			
Kidney	(60)	(60)	(60)
Fibrous histiocytoma, metastatic, skin		1 (2%)	
Sarcoma stromal, metastatic, uterus	1 (2%)		
Renal tubule, adenoma	1 (2%)		
Urinary bladder	(59)	(60)	(59)
Papilloma			1 (2%)
Systemic Lesions			
Multiple organs[b]	(60)	(60)	(60)
Leukemia mononuclear	27 (45%)	25 (42%)	27 (45%)
Mesothelioma malignant	1 (2%)		
Neoplasm Summary			
Total animals with primary neoplasms[c]			
30-Month study	59	54	59
Total primary neoplasms			
30-Month study	164	121	148
Total animals with benign neoplasms			
30-Month study	52	45	50
Total benign neoplasms			
30-Month study	112	84	95
Total animals with malignant neoplasms			
30-Month study	41	32	38
Total malignant neoplasms			
30-Month study	52	37	53
Total animals with metastatic neoplasms			
30-Month study	2	2	4
Total metastatic neoplasms			
30-Month study	5	6	4

[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 D1b
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol[a]

	0 ppm	5,000 ppm
Disposition Summary		
Animals initially in study	70	70
3-Month interim evaluation	10	10
Early deaths		
Moribund	39	32
Natural deaths	3	4
Survivors		
Terminal sacrifice	18	24
Animals examined microscopically	70	70
Systems Examined At 3 Months With No Neoplasms Observed		
Alimentary System		
Cardiovascular System		
Endocrine System		
General Body System		
Genital System		
Hematopoietic System		
Integumentary System		
Musculoskeletal System		
Nervous System		
Respiratory System		
Special Senses System		
Urinary System		
30-Month Study		
Alimentary System		
Intestine small, duodenum	(59)	(59)
Intestine small, jejunum	(60)	(59)
Intestine small, ileum	(60)	(59)
Liver	(60)	(60)
Hepatocellular adenoma	1 (2%)	
Mesentery	(8)	(6)
Pancreas	(60)	(59)
Salivary glands	(60)	(60)
Schwannoma malignant		1 (2%)
Stomach, forestomach	(59)	(59)
Squamous cell papilloma		2 (3%)
Stomach, glandular	(59)	(60)
Cardiovascular System		
Heart	(60)	(60)
Schwannoma benign		1 (2%)

TABLE D1b
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Endocrine System		
Adrenal cortex	(60)	(60)
Adenoma		1 (2%)
Adrenal medulla	(57)	(60)
Pheochromocytoma malignant		1 (2%)
Pheochromocytoma benign	3 (5%)	4 (7%)
Pheochromocytoma benign, multiple	1 (2%)	
Islets, pancreatic	(60)	(59)
Adenoma	1 (2%)	2 (3%)
Pituitary gland	(59)	(60)
Pars distalis, adenoma	30 (51%)	18 (30%)
Thyroid gland	(60)	(59)
C-cell, adenoma	3 (5%)	6 (10%)
C-cell, carcinoma		1 (2%)
General Body System		
None		
Genital System		
Clitoral gland	(59)	(59)
Adenoma	3 (5%)	10 (17%)
Carcinoma	2 (3%)	5 (8%)
Ovary	(60)	(60)
Granulosa cell tumor malignant	1 (2%)	
Granulosa cell tumor benign	2 (3%)	1 (2%)
Uterus	(60)	(60)
Polyp stromal	8 (13%)	6 (10%)
Sarcoma stromal		1 (2%)
Vagina	(1)	
Squamous cell papilloma	1 (100%)	
Hematopoietic System		
Bone marrow	(60)	(60)
Lymph node	(19)	(23)
Lymph node, mandibular	(60)	(59)
Lymph node, mesenteric	(59)	(59)
Spleen	(60)	(60)
Thymus	(57)	(59)
Thymoma benign	1 (2%)	
Integumentary System		
Mammary gland	(60)	(59)
Carcinoma	1 (2%)	
Fibroadenoma	22 (37%)	16 (27%)
Fibroadenoma, multiple	8 (13%)	1 (2%)
Skin	(60)	(60)
Basal cell carcinoma	1 (2%)	
Trichoepithelioma	1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)

TABLE D1b
Summary of the Incidence of Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Musculoskeletal System		
Skeletal muscle	(1)	
Nervous System		
Brain	(60)	(60)
Astrocytoma malignant	1 (2%)	
Spinal cord	(4)	(2)
Respiratory System		
Lung	(60)	(60)
Alveolar/bronchiolar adenoma	2 (3%)	2 (3%)
Alveolar/bronchiolar carcinoma	1 (2%)	
Nose	(60)	(60)
Special Senses System		
Zymbal's gland	(1)	
Carcinoma	1 (100%)	
Urinary System		
Kidney	(60)	(60)
Urinary bladder	(60)	(60)
Systemic Lesions		
Multiple organs[b]	(60)	(60)
Leukemia mononuclear	37 (62%)	34 (57%)
Neoplasm Summary		
Total animals with primary neoplasms[c]		
30-Month Study	59	57
Total primary neoplasms		
30-Month Study	133	114
Total animals with benign neoplasms		
30-Month Study	46	42
Total benign neoplasms		
30-Month Study	88	71
Total animals with malignant neoplasms		
30-Month Study	40	41
Total malignant neoplasms		
30-Month Study	45	43

[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 D2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Adrenal Cortex: Adenoma				
Overall rate[a]	4/60 (7%)	0/60 (0%)	0/60 (0%)	0/60 (0%)
Adjusted rate[b]	25.9%	0.0%		
Terminal rate[c]	1/10 (10%)	0/17 (0%)		
First incidence (days)	795	-[e]		
Life table test[d]		P=0.019N		
Logistic regression test[d]		P=0.024N		
Fisher exact test[d]		P=0.059N		
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	2/60 (3%)	3/60 (5%)	2/60 (3%)	3/60 (5%)
Adjusted rate	16.4%	12.3%	7.2%	12.3%
Terminal rate	1/10 (10%)	1/17 (6%)	1/22 (5%)	1/17 (6%)
First incidence (days)	856	750	817	750
Life table test		P=0.630N		P=0.440
Logistic regression test		P=0.673		P=0.480
Fisher exact test		P=0.500		P=0.500
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	2/60 (3%)	4/60 (7%)	3/60 (5%)	4/60 (7%)
Adjusted rate	16.4%	16.9%	10.9%	16.9%
Terminal rate	1/10 (10%)	1/17 (6%)	1/22 (5%)	1/17 (6%)
First incidence (days)	856	750	817	750
Life table test		P=0.601		P=0.435
Logistic regression test		P=0.539		P=0.470
Fisher exact test		P=0.340		P=0.500
Clitoral Gland: Adenoma				
Overall rate	6/58 (10%)	7/60 (12%)	4/59 (7%)	7/60 (12%)
Adjusted rate	38.3%	27.0%	14.5%	27.0%
Terminal rate	3/10 (30%)	2/17 (12%)	2/22 (9%)	2/17 (12%)
First incidence (days)	579	628	817	628
Life table test		P=0.375N		P=0.195
Logistic regression test		P=0.513N		P=0.247
Fisher exact test		P=0.526		P=0.274
Clitoral Gland: Carcinoma				
Overall rate	6/58 (10%)	8/60 (13%)	2/59 (3%)	8/60 (13%)
Adjusted rate	43.2%	29.0%	4.0%	29.0%
Terminal rate	4/10 (40%)	2/17 (12%)	0/22 (0%)	2/17 (12%)
First incidence (days)	649	750	648	750
Life table test		P=0.465N		P=0.041
Logistic regression test		P=0.579N		P=0.050
Fisher exact test		P=0.415		P=0.050

TABLE D2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	12/58 (21%)	14/60 (23%)	6/59 (10%)	14/60 (23%)
Adjusted rate	74.9%	47.4%	17.9%	47.4%
Terminal rate	7/10 (70%)	4/17 (24%)	2/22 (9%)	4/17 (24%)
First incidence (days)	579	628	648	628
Life table test		P=0.248N		P=0.029
Logistic regression test		P=0.402N		P=0.040
Fisher exact test		P=0.451		P=0.046
Mammary Gland: Fibroadenoma				
Overall rate	43/60 (72%)	27/60 (45%)	23/60 (38%)	27/60 (45%)
Adjusted rate	100.0%	74.4%	62.8%	74.4%
Terminal rate	10/10 (100%)	9/17 (53%)	10/22 (45%)	9/17 (53%)
First incidence (days)	418	596	600	596
Life table test		P<0.001N		P=0.157
Logistic regression test		P<0.001N		P=0.252
Fisher exact test		P=0.003N		P=0.289
Mammary Gland: Adenoma				
Overall rate	3/60 (5%)	2/60 (3%)	3/60 (5%)	2/60 (3%)
Adjusted rate	9.9%	8.6%	8.5%	8.6%
Terminal rate	0/10 (0%)	1/17 (6%)	1/22 (5%)	1/17 (6%)
First incidence (days)	613	807	668	807
Life table test		P=0.326N		P=0.563N
Logistic regression test		P=0.503N		P=0.501N
Fisher exact test		P=0.500N		P=0.500N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	45/60 (75%)	27/60 (45%)	25/60 (42%)	27/60 (45%)
Adjusted rate	100.0%	74.4%	66.6%	74.4%
Terminal rate	10/10 (100%)	9/17 (53%)	11/22 (50%)	9/17 (53%)
First incidence (days)	418	596	600	596
Life table test		P<0.001N		P=0.239
Logistic regression test		P<0.001N		P=0.389
Fisher exact test		P<0.001N		P=0.427
Mammary Gland: Carcinoma				
Overall rate	8/60 (13%)	4/60 (7%)	1/60 (2%)	4/60 (7%)
Adjusted rate	29.3%	10.5%	2.1%	10.5%
Terminal rate	1/10 (10%)	0/17 (0%)	0/22 (0%)	0/17 (0%)
First incidence (days)	540	690	729	690
Life table test		P=0.070N		P=0.168
Logistic regression test		P=0.177N		P=0.181
Fisher exact test		P=0.181N		P=0.182

TABLE D2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Mammary Gland: Adenoma or Carcinoma				
Overall rate	10/60 (17%)	6/60 (10%)	4/60 (7%)	6/60 (10%)
Adjusted rate	34.9%	18.2%	10.4%	18.2%
Terminal rate	1/10 (10%)	1/17 (6%)	1/22 (5%)	1/17 (6%)
First incidence (days)	540	690	668	690
Life table test		P=0.064N		P=0.317
Logistic regression test		P=0.193N		P=0.347
Fisher exact test		P=0.211N		P=0.372
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	48/60 (80%)	30/60 (50%)	26/60 (43%)	30/60 (50%)
Adjusted rate	100.0%	76.3%	67.3%	76.3%
Terminal rate	10/10 (100%)	9/17 (53%)	11/22 (50%)	9/17 (53%)
First incidence (days)	418	596	600	596
Life table test		P<0.001N		P=0.160
Logistic regression test		P<0.001N		P=0.264
Fisher exact test		P<0.001N		P=0.292
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	26/60 (43%)	28/60 (47%)	31/59 (53%)	28/60 (47%)
Adjusted rate	80.9%	69.8%	70.1%	69.8%
Terminal rate	5/10 (50%)	7/17 (41%)	10/22 (45%)	7/17 (41%)
First incidence (days)	540	501	523	501
Life table test		P=0.103N		P=0.537
Logistic regression test		P=0.481N		P=0.330N
Fisher exact test		P=0.427		P=0.324N
Pituitary Gland (Pars Distalis): Carcinoma				
Overall rate	2/60 (3%)	3/60 (5%)	2/59 (3%)	3/60 (5%)
Adjusted rate	5.0%	10.1%	6.5%	10.1%
Terminal rate	0/10 (0%)	1/17 (6%)	1/22 (5%)	1/17 (6%)
First incidence (days)	540	666	729	666
Life table test		P=0.609		P=0.434
Logistic regression test		P=0.441		P=0.508
Fisher exact test		P=0.500		P=0.508
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	28/60 (47%)	31/60 (52%)	33/59 (56%)	31/60 (52%)
Adjusted rate	81.9%	74.0%	73.1%	74.0%
Terminal rate	5/10 (50%)	8/17 (47%)	11/22 (50%)	8/17 (47%)
First incidence (days)	540	501	523	501
Life table test		P=0.124N		P=0.462
Logistic regression test		P=0.573		P=0.395N
Fisher exact test		P=0.358		P=0.389N

TABLE D2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/60 (5%)	1/60 (2%)	2/60 (3%)	1/60 (2%)
Adjusted rate	13.8%	4.2%		
Terminal rate	1/10 (10%)	0/17 (0%)		
First incidence (days)	540	869		
Life table test		P=0.200N		
Logistic regression test		P=0.313N		
Fisher exact test		P=0.309N		
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma				
Overall rate	4/60 (7%)	3/60 (5%)	3/60 (5%)	3/60 (5%)
Adjusted rate	19.9%	15.4%	8.4%	15.4%
Terminal rate	1/10 (10%)	2/17 (12%)	1/22 (5%)	2/17 (12%)
First incidence (days)	540	869	648	869
Life table test		P=0.279N		P=0.589
Logistic regression test		P=0.410N		P=0.654
Fisher exact test		P=0.500N		P=0.660N
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/60 (12%)	6/60 (10%)	6/59 (10%)	6/60 (10%)
Adjusted rate	44.9%	24.2%	22.5%	24.2%
Terminal rate	4/10 (40%)	3/17 (18%)	3/22 (14%)	3/17 (18%)
First incidence (days)	540	633	830	633
Life table test		P=0.208N		P=0.503
Logistic regression test		P=0.351N		P=0.592
Fisher exact test		P=0.500N		P=0.607N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/60 (13%)	7/60 (12%)	7/59 (12%)	7/60 (12%)
Adjusted rate	54.1%	27.6%	24.3%	27.6%
Terminal rate	5/10 (50%)	3/17 (18%)	3/22 (14%)	3/17 (18%)
First incidence (days)	540	633	744	633
Life table test		P=0.174N		P=0.498
Logistic regression test		P=0.309N		P=0.587
Fisher exact test		P=0.500N		P=0.598N
Uterus: Stromal Polyp				
Overall rate	7/60 (12%)	9/60 (15%)	9/60 (15%)	9/60 (15%)
Adjusted rate	28.7%	24.8%	26.4%	24.8%
Terminal rate	1/10 (10%)	2/17 (12%)	3/22 (14%)	2/17 (12%)
First incidence (days)	649	591	633	591
Life table test		P=0.554N		P=0.497
Logistic regression test		P=0.388		P=0.598N
Fisher exact test		P=0.395		P=0.601N

TABLE D2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	9/60 (15%)	9/60 (15%)	9/60 (15%)	9/60 (15%)
Adjusted rate	34.9%	24.8%	26.4%	24.8%
Terminal rate	1/10 (10%)	2/17 (12%)	3/22 (14%)	2/17 (12%)
First incidence (days)	302	591	633	591
Life table test		P=0.332N		P=0.497
Logistic regression test		P=0.536		P=0.598N
Fisher exact test		P=0.601N		P=0.601N
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/60 (45%)	27/60 (45%)	25/60 (42%)	27/60 (45%)
Adjusted rate	76.5%	63.2%	59.0%	63.2%
Terminal rate	5/10 (50%)	5/17 (29%)	7/22 (32%)	5/17 (29%)
First incidence (days)	421	501	509	501
Life table test		P=0.106N		P=0.297
Logistic regression test		P=0.529N		P=0.424
Fisher exact test		P=0.573N		P=0.427
All Organs: Benign Neoplasms				
Overall rate	52/60 (87%)	50/60 (83%)	45/60 (75%)	50/60 (83%)
Adjusted rate	100.0%	95.8%	89.7%	95.8%
Terminal rate	10/10 (100%)	15/17 (88%)	17/22 (77%)	15/17 (88%)
First incidence (days)	418	501	523	501
Life table test		P=0.009N		P=0.118
Logistic regression test		P=0.085N		P=0.175
Fisher exact test		P=0.399N		P=0.184
All Organs: Malignant Neoplasms				
Overall rate	41/60 (68%)	39/60 (65%)	32/60 (53%)	39/60 (65%)
Adjusted rate	100.0%	82.8%	66.8%	82.8%
Terminal rate	10/10 (100%)	10/17 (59%)	8/22 (36%)	10/17 (59%)
First incidence (days)	302	501	509	501
Life table test		P=0.024N		P=0.105
Logistic regression test		P=0.343N		P=0.191
Fisher exact test		P=0.423N		P=0.133

TABLE D2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	5,000 ppm × *Ad Libitum*-Fed Control	Weight-Matched Control	5,000 ppm × Weight-Matched Control
All Organs: Benign or Malignant Neoplasms				
Overall rate	59/60 (98%)	59/60 (98%)	54/60 (90%)	59/60 (98%)
Adjusted rate	100.0%	98.3%	93.1%	98.3%
Terminal rate	10/10 (100%)	16/17 (94%)	18/22 (82%)	16/17 (94%)
First incidence (days)	302	501	509	501
Life table test		P=0.016N		P=0.120
Logistic regression test		P=0.624N		P=0.059
Fisher exact test		P=0.752N		P=0.057

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the *ad libitum*-fed controls or weight-matched controls and the exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol

	0 ppm	5,000 ppm
Adrenal Medulla: Benign Pheochromocytoma		
Overall rate[a]	4/57 (7%)	4/60 (7%)
Adjusted rate[b]	17.1%	12.9%
Terminal rate[c]	2/18 (11%)	2/24 (8%)
First incidence (days)	677	499
Life table test[d]		P=0.530N
Logistic regression test[d]		P=0.613N
Fisher exact test[d]		P=0.612N
Adrenal Medulla: Benign or Malignant Pheochromocytoma		
Overall rate	4/57 (7%)	5/60 (8%)
Adjusted rate	17.1%	15.1%
Terminal rate	2/18 (11%)	2/24 (8%)
First incidence (days)	677	499
Life table test		P=0.619
Logistic regression test		P=0.535
Fisher exact test		P=0.533
Clitoral Gland: Adenoma		
Overall rate	3/59 (5%)	10/59 (17%)
Adjusted rate	13.4%	27.5%
Terminal rate	1/18 (6%)	3/23 (13%)
First incidence (days)	866	673
Life table test		P=0.093
Logistic regression test		P=0.044
Fisher exact test		P=0.037
Clitoral Gland: Carcinoma		
Overall rate	2/59 (3%)	5/59 (8%)
Adjusted rate	6.2%	21.7%
Terminal rate	0/18 (0%)	5/23 (22%)
First incidence (days)	788	911 (T)
Life table test		P=0.310
Logistic regression test		P=0.279
Fisher exact test		P=0.219
Clitoral Gland: Adenoma or Carcinoma		
Overall rate	5/59 (8%)	15/59 (25%)
Adjusted rate	18.8%	45.6%
Terminal rate	1/18 (6%)	8/23 (35%)
First incidence (days)	788	673
Life table test		P=0.051
Logistic regression test		P=0.019
Fisher exact test		P=0.013

TABLE D2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
Overall rate	3/60 (5%)	2/60 (3%)
Adjusted rate	11.0%	5.5%
Terminal rate	0/18 (0%)	0/24 (0%)
First incidence (days)	711	841
Life table test		P=0.402N
Logistic regression test		P=0.490N
Fisher exact test		P=0.500N
Mammary Gland: Fibroadenoma		
Overall rate	30/60 (50%)	17/60 (28%)
Adjusted rate	86.8%	56.1%
Terminal rate	14/18 (78%)	12/24 (50%)
First incidence (days)	688	780
Life table test		P<0.001N
Logistic regression test		P=0.002N
Fisher exact test		P=0.012N
Mammary Gland: Fibroadenoma or Carcinoma		
Overall rate	31/60 (52%)	17/60 (28%)
Adjusted rate	87.5%	56.1%
Terminal rate	14/18 (78%)	12/24 (50%)
First incidence (days)	688	780
Life table test		P<0.001N
Logistic regression test		P<0.001N
Fisher exact test		P=0.008N
Ovary: Benign or Malignant Granulosa Cell Neoplasm		
Overall rate	3/60 (5%)	1/60 (2%)
Adjusted rate	9.7%	4.2%
Terminal rate	0/18 (0%)	1/24 (4%)
First incidence (days)	820	911 (T)
Life table test		P=0.234N
Logistic regression test		P=0.277N
Fisher exact test		P=0.309N
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	30/59 (51%)	18/60 (30%)
Adjusted rate	81.1%	50.8%
Terminal rate	11/17 (65%)	9/24 (38%)
First incidence (days)	638	649
Life table test		P=0.004N
Logistic regression test		P=0.007N
Fisher exact test		P=0.016N

TABLE D2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
Thyroid Gland (C-cell): Adenoma		
Overall rate	3/60 (5%)	6/59 (10%)
Adjusted rate	11.4%	16.5%
Terminal rate	1/18 (6%)	1/24 (4%)
First incidence (days)	677	499
Life table test		P=0.348
Logistic regression test		P=0.221
Fisher exact test		P=0.237
Thyroid Gland (C-cell): Adenoma or Carcinoma		
Overall rate	3/60 (5%)	7/59 (12%)
Adjusted rate	11.4%	20.1%
Terminal rate	1/18 (6%)	2/24 (8%)
First incidence (days)	677	499
Life table test		P=0.259
Logistic regression test		P=0.149
Fisher exact test		P=0.154
Uterus: Stromal Polyp		
Overall rate	8/60 (13%)	6/60 (10%)
Adjusted rate	21.2%	18.5%
Terminal rate	1/18 (6%)	2/24 (8%)
First incidence (days)	562	672
Life table test		P=0.281N
Logistic regression test		P=0.400N
Fisher exact test		P=0.389N
Uterus: Stromal Polyp or Stromal Sarcoma		
Overall rate	8/60 (13%)	7/60 (12%)
Adjusted rate	21.2%	22.2%
Terminal rate	1/18 (6%)	3/24 (13%)
First incidence (days)	562	672
Life table test		P=0.368N
Logistic regression test		P=0.507N
Fisher exact test		P=0.500N
All Organs: Mononuclear Cell Leukemia		
Overall rate	37/60 (62%)	34/60 (57%)
Adjusted rate	74.3%	64.6%
Terminal rate	8/18 (44%)	7/24 (29%)
First incidence (days)	504	540
Life table test		P=0.178N
Logistic regression test		P=0.552
Fisher exact test		P=0.355N

TABLE D2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
All Organs: Benign Neoplasms		
Overall rate	46/60 (77%)	42/60 (70%)
Adjusted rate	95.6%	86.9%
Terminal rate	16/18 (89%)	18/24 (75%)
First incidence (days)	562	499
Life table test		P=0.061N
Logistic regression test		P=0.189N
Fisher exact test		P=0.268N
All Organs: Malignant Neoplasms		
Overall rate	40/60 (67%)	41/60 (68%)
Adjusted rate	76.7%	77.6%
Terminal rate	8/18 (44%)	13/24 (54%)
First incidence (days)	504	540
Life table test		P=0.293N
Logistic regression test		P=0.271
Fisher exact test		P=0.500
All Organs: Benign or Malignant Neoplasms		
Overall rate	59/60 (98%)	57/60 (95%)
Adjusted rate	98.3%	96.6%
Terminal rate	17/18 (94%)	22/24 (92%)
First incidence (days)	504	499
Life table test		P=0.098N
Logistic regression test		P=0.297N
Fisher exact test		P=0.309N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, lung, ovary, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and the exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the exposed group is indicated by N.

TABLE D3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
Disposition Summary			
Animals initially in study	70	70	70
3-Month interim evaluation	10	10	10
Early deaths			
Moribund	40	31	36
Natural deaths	10	7	7
Survivors			
Terminal sacrifice	10	22	17
Animals examined microscopically	70	70	70
3-Month Interim Evaluation			
Alimentary System			
Intestine large, rectum	(10)	(10)	(10)
Parasite metazoan			1 (10%)
Intestine large, cecum	(10)	(10)	(10)
Parasite metazoan		1 (10%)	
Liver	(10)	(10)	(10)
Angiectasis			1 (10%)
Hepatodiaphragmatic nodule	2 (20%)		1 (10%)
Endocrine System			
Adrenal cortex	(10)	(10)	(10)
Accessory adrenal cortical nodule	3 (30%)	1 (10%)	1 (10%)
Hyperplasia, focal	1 (10%)		
Pituitary gland	(10)	(10)	(10)
Pars distalis, cyst	2 (20%)		
Thyroid gland	(10)	(10)	(10)
Ectopic thymus	1 (10%)	1 (10%)	
Ultimobranchial cyst	2 (20%)		1 (10%)
Genital System			
Clitoral gland	(10)	(10)	(10)
Inflammation, chronic	1 (10%)		
Ovary	(10)	(10)	(10)
Cyst			1 (10%)
Uterus	(10)	(10)	(10)
Hydrometra	1 (10%)	4 (40%)	2 (20%)

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

TABLE D3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
3-Month Interim Evaluation (continued)			
Hematopoietic System			
Lymph node, mandibular	(10)	(10)	(10)
Hemorrhage	2 (20%)		2 (20%)
Spleen	(10)	(10)	(10)
Developmental malformation		1 (10%)	
Pigmentation, hemosiderin	5 (50%)	3 (30%)	10 (100%)
Thymus	(10)	(10)	(10)
Hemorrhage		1 (10%)	
Respiratory System			
Lung	(10)	(10)	(10)
Inflammation, subacute	4 (40%)	3 (30%)	2 (20%)
Alveolar epithelium, hyperplasia	1 (10%)		1 (10%)
Nose	(10)	(10)	(10)
Goblet cell, hyperplasia			1 (10%)
Urinary System			
Kidney	(10)	(10)	(10)
Cyst			1 (10%)
Mineralization	10 (100%)	10 (100%)	10 (100%)
Systems Examined With No Lesions Observed			
Cardiovascular System			
General Body System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Special Senses System			
30-Month Study			
Alimentary System			
Esophagus	(58)	(59)	(60)
Inflammation, subacute		1 (2%)	
Intestine large, colon	(60)	(60)	(59)
Edema			1 (2%)
Parasite metazoan	6 (10%)	3 (5%)	5 (8%)
Ulcer			1 (2%)
Intestine large, rectum	(59)	(60)	(59)
Edema	1 (2%)		
Parasite metazoan	2 (3%)		8 (14%)
Intestine large, cecum	(60)	(60)	(60)
Edema		1 (2%)	2 (3%)
Parasite metazoan	2 (3%)	1 (2%)	1 (2%)

TABLE D3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Alimentary System (continued)			
Liver	(60)	(60)	(60)
Angiectasis	1 (2%)	2 (3%)	1 (2%)
Basophilic focus	26 (43%)	34 (57%)	29 (48%)
Clear cell focus	2 (3%)	4 (7%)	5 (8%)
Degeneration, cystic	1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus	10 (17%)	12 (20%)	17 (28%)
Eosinophilic focus, multiple			1 (2%)
Hematopoietic cell proliferation	1 (2%)	3 (5%)	2 (3%)
Hepatodiaphragmatic nodule	12 (20%)	12 (20%)	18 (30%)
Inflammation, granulomatous	12 (20%)	9 (15%)	10 (17%)
Mixed cell focus	2 (3%)	3 (5%)	7 (12%)
Necrosis, focal	6 (10%)	2 (3%)	3 (5%)
Bile duct, cyst			1 (2%)
Bile duct, hyperplasia	17 (28%)	18 (30%)	24 (40%)
Centrilobular, atrophy		1 (2%)	
Centrilobular, necrosis		1 (2%)	1 (2%)
Hepatocyte, vacuolization cytoplasmic	14 (23%)	7 (12%)	3 (5%)
Kupffer cell, pigmentation	12 (20%)	9 (15%)	9 (15%)
Mesentery	(11)	(5)	(7)
Accessory spleen	1 (9%)	3 (60%)	2 (29%)
Fat, necrosis	9 (82%)	2 (40%)	5 (71%)
Pancreas	(60)	(60)	(59)
Atrophy	20 (33%)	20 (33%)	13 (22%)
Metaplasia, hepatocyte	1 (2%)		
Acinus, cytoplasmic alteration		1 (2%)	1 (2%)
Salivary glands	(60)	(60)	(60)
Atrophy	2 (3%)		
Cyst		1 (2%)	
Inflammation, chronic		1 (2%)	
Stomach, forestomach	(60)	(60)	(60)
Edema	4 (7%)	2 (3%)	
Erosion	1 (2%)	2 (3%)	1 (2%)
Hyperplasia			1 (2%)
Ulcer	2 (3%)	4 (7%)	2 (3%)
Mucosa, hyperplasia	5 (8%)	9 (15%)	5 (8%)
Stomach, glandular	(60)	(60)	(60)
Edema	1 (2%)	1 (2%)	
Erosion	3 (5%)	1 (2%)	2 (3%)
Ulcer	2 (3%)	4 (7%)	
Tongue	(1)		(1)
Epithelium, hyperplasia			1 (100%)
Cardiovascular System			
Blood vessel	(60)	(60)	(60)
Inflammation, subacute		1 (2%)	
Heart	(60)	(60)	(60)
Cardiomyopathy	28 (47%)	35 (58%)	28 (47%)
Thrombosis	3 (5%)	1 (2%)	
Valve, inflammation, chronic	1 (2%)		

TABLE D3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Endocrine System			
Adrenal cortex	(60)	(60)	(60)
Accessory adrenal cortical nodule	11 (18%)	8 (13%)	9 (15%)
Atrophy	1 (2%)		
Degeneration, fatty	9 (15%)	8 (13%)	12 (20%)
Fibrosis		1 (2%)	
Hemorrhage	1 (2%)		1 (2%)
Hyperplasia, diffuse	3 (5%)		1 (2%)
Hyperplasia, focal	3 (5%)	6 (10%)	2 (3%)
Hypertrophy, focal	9 (15%)	8 (13%)	7 (12%)
Necrosis		2 (3%)	
Adrenal medulla	(60)	(60)	(60)
Hyperplasia	5 (8%)	7 (12%)	7 (12%)
Islets, pancreatic	(60)	(60)	(59)
Hyperplasia	1 (2%)	1 (2%)	
Parathyroid gland	(52)	(55)	(54)
Hyperplasia	1 (2%)		1 (2%)
Pituitary gland	(60)	(59)	(60)
Pars distalis, angiectasis	8 (13%)	7 (12%)	7 (12%)
Pars distalis, atypia cellular		1 (2%)	
Pars distalis, cyst	14 (23%)	11 (19%)	19 (32%)
Pars distalis, hyperplasia, focal	9 (15%)	7 (12%)	9 (15%)
Pars intermedia, angiectasis		2 (3%)	
Pars intermedia, cyst	2 (3%)		3 (5%)
Thyroid gland	(60)	(59)	(60)
Ultimobranchial cyst	2 (3%)	2 (3%)	1 (2%)
C-cell, hyperplasia	8 (13%)	9 (15%)	8 (13%)
Follicle, cyst	1 (2%)		1 (2%)
Follicular cell, hyperplasia		1 (2%)	1 (2%)
General Body System			
None			
Genital System			
Clitoral gland	(58)	(59)	(60)
Cyst	2 (3%)	5 (8%)	5 (8%)
Cyst, multiple	1 (2%)		
Fibrosis		1 (2%)	
Hyperplasia	3 (5%)	4 (7%)	4 (7%)
Inflammation, chronic	2 (3%)	1 (2%)	2 (3%)
Inflammation, suppurative	2 (3%)		1 (2%)
Ovary	(60)	(60)	(60)
Angiectasis		1 (2%)	
Cyst	17 (28%)	9 (15%)	17 (28%)
Uterus	(60)	(60)	(60)
Hydrometra	3 (5%)	5 (8%)	7 (12%)
Hyperplasia, cystic	4 (7%)	4 (7%)	3 (5%)

TABLE D3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Hematopoietic System			
Bone marrow	(60)	(60)	(60)
Depletion cellular	1 (2%)		
Fibrosis			1 (2%)
Hyperplasia	1 (2%)	1 (2%)	
Myelofibrosis	2 (3%)	1 (2%)	3 (5%)
Stromal cell, hyperplasia		1 (2%)	
Lymph node	(20)	(14)	(18)
Iliac, hemorrhage		1 (7%)	
Iliac, hyperplasia, lymphoid		1 (7%)	
Mediastinal, ectasia	1 (5%)		
Mediastinal, hemorrhage	3 (15%)	1 (7%)	
Mediastinal, hyperplasia, lymphoid	1 (5%)		
Mediastinal, pigmentation	14 (70%)	3 (21%)	6 (33%)
Pancreatic, pigmentation	1 (5%)	2 (14%)	4 (22%)
Renal, hemorrhage			2 (11%)
Renal, pigmentation	1 (5%)	3 (21%)	7 (39%)
Lymph node, mandibular	(59)	(60)	(60)
Ectasia	2 (3%)	2 (3%)	1 (2%)
Hemorrhage	3 (5%)	3 (5%)	
Hyperplasia, lymphoid	13 (22%)	12 (20%)	7 (12%)
Hyperplasia, plasma cell	1 (2%)		1 (2%)
Pigmentation	20 (34%)	27 (45%)	25 (42%)
Lymph node, mesenteric	(58)	(59)	(60)
Ectasia	2 (3%)		2 (3%)
Hemorrhage		4 (7%)	7 (12%)
Hyperplasia, lymphoid	2 (3%)	4 (7%)	4 (7%)
Pigmentation		1 (2%)	1 (2%)
Spleen	(60)	(60)	(60)
Fibrosis	3 (5%)	4 (7%)	3 (5%)
Hematopoietic cell proliferation	15 (25%)	12 (20%)	11 (18%)
Hemorrhage			1 (2%)
Hyperplasia, lymphoid			1 (2%)
Metaplasia, lipocyte			1 (2%)
Necrosis			1 (2%)
Pigmentation, hemosiderin	24 (40%)	28 (47%)	41 (68%)
Lymphoid follicle, atrophy	1 (2%)		
Red pulp, atrophy	1 (2%)	1 (2%)	1 (2%)
Integumentary System			
Mammary gland	(60)	(60)	(60)
Dilatation	37 (62%)	33 (55%)	34 (57%)
Galactocele	5 (8%)	1 (2%)	5 (8%)
Hyperplasia	12 (20%)	12 (20%)	15 (25%)
Inflammation, suppurative			1 (2%)
Skin	(60)	(59)	(60)
Cyst epithelial inclusion	1 (2%)		1 (2%)
Hyperkeratosis	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)	2 (3%)	
Ulcer		2 (3%)	2 (3%)
Epidermis, hyperplasia	1 (2%)	2 (3%)	2 (3%)

TABLE D3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Musculoskeletal System			
Bone	(60)	(60)	(60)
Fibrous osteodystrophy			1 (2%)
Hyperostosis			1 (2%)
Cranium, osteopetrosis	8 (13%)	17 (28%)	9 (15%)
Femur, osteopetrosis	9 (15%)	17 (28%)	5 (8%)
Nervous System			
Brain	(60)	(60)	(60)
Atrophy	19 (32%)	22 (37%)	22 (37%)
Gliosis		1 (2%)	
Hemorrhage			1 (2%)
Hydrocephalus	4 (7%)	4 (7%)	8 (13%)
Necrosis		1 (2%)	
Respiratory System			
Lung	(60)	(60)	(60)
Congestion	1 (2%)		
Edema		2 (3%)	
Hemorrhage	2 (3%)	1 (2%)	2 (3%)
Infiltration cellular, histiocyte	28 (47%)	33 (55%)	23 (38%)
Inflammation, subacute	3 (5%)	1 (2%)	
Thrombosis	1 (2%)		
Alveolar epithelium, hyperplasia	4 (7%)	6 (10%)	4 (7%)
Nose	(60)	(60)	(60)
Foreign body	3 (5%)	1 (2%)	
Inflammation, suppurative	5 (8%)	3 (5%)	3 (5%)
Goblet cell, hyperplasia	10 (17%)	8 (13%)	6 (10%)
Mucosa, hyperplasia	5 (8%)	1 (2%)	1 (2%)
Mucosa, metaplasia, squamous	3 (5%)	2 (3%)	
Special Senses System			
Eye	(4)		(1)
Cataract	3 (75%)		1 (100%)
Hemorrhage	1 (25%)		
Retina, degeneration	4 (100%)		1 (100%)

TABLE D3a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
30-Month Study (continued)			
Urinary System			
Kidney	(60)	(60)	(60)
Cyst			2 (3%)
Hydronephrosis		1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	5 (8%)
Inflammation, suppurative	2 (3%)	1 (2%)	
Mineralization	57 (95%)	52 (87%)	48 (80%)
Nephropathy	37 (62%)	38 (63%)	39 (65%)
Renal tubule, atrophy	1 (2%)	1 (2%)	5 (8%)
Renal tubule, cytoplasmic alteration	5 (8%)	3 (5%)	2 (3%)
Renal tubule, dilatation			1 (2%)
Renal tubule, necrosis	2 (3%)	1 (2%)	2 (3%)
Renal tubule, pigmentation	15 (25%)	9 (15%)	16 (27%)
Transitional epithelium, hyperplasia	2 (3%)	4 (7%)	3 (5%)
Urinary bladder	(59)	(60)	(59)
Transitional epithelium, hyperplasia		1 (2%)	2 (3%)

TABLE D3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydoquinone: Restricted Feed Protocol[a]

	0 ppm	5,000 ppm
Disposition Summary		
Animals initially in study	70	70
3-Month interim evaluation	10	10
Early deaths		
Moribund	39	32
Natural deaths	3	4
Survivors		
Terminal sacrifice	18	24
Animals examined microscopically	70	70
3-Month Interim Evaluation		
Alimentary System		
Intestine large, colon	(10)	(10)
Parasite metazoan	1 (10%)	
Intestine large, rectum	(10)	(10)
Parasite metazoan		1 (10%)
Liver	(10)	(10)
Hepatodiaphragmatic nodule		2 (20%)
Cardiovascular System		
Heart	(10)	(10)
Cardiomyopathy	1 (10%)	
Endocrine System		
Adrenal cortex	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)	
Thyroid gland	(10)	(10)
Ectopic thymus		1 (10%)
Ultimobranchial cyst		1 (10%)
Genital System		
Clitoral gland	(10)	(10)
Cyst		1 (10%)
Ovary	(10)	(10)
Cyst		2 (20%)
Uterus	(10)	(10)
Hydrometra	1 (10%)	
Hematopoietic System		
Spleen	(10)	(10)
Pigmentation, hemosiderin		8 (80%)

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

TABLE D3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydoquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
3-Month Interim Evaluation (continued)		
Respiratory System		
Nose	(10)	(10)
Goblet cell, hyperplasia		4 (40%)
Urinary System		
Kidney	(10)	(10)
Mineralization	10 (100%)	10 (100%)
Systems Examined With No Lesions Observed		
General Body System		
Integumentary System		
Musculoskeletal System		
Nervous System		
Special Senses System		
30-Month Study		
Alimentary System		
Esophagus	(58)	(59)
Epithelium, hyperplasia	1 (2%)	
Intestine large, colon	(59)	(60)
Parasite metazoan	4 (7%)	6 (10%)
Intestine large, rectum	(60)	(60)
Parasite metazoan	5 (8%)	6 (10%)
Intestine large, cecum	(60)	(59)
Edema	1 (2%)	1 (2%)
Parasite metazoan	1 (2%)	
Intestine small, duodenum	(59)	(59)
Erosion	1 (2%)	
Epithelium, hyperplasia	1 (2%)	
Liver	(60)	(60)
Angiectasis		5 (8%)
Basophilic focus	26 (43%)	23 (38%)
Clear cell focus	2 (3%)	2 (3%)
Cyst		1 (2%)
Eosinophilic focus	7 (12%)	13 (22%)
Hematopoietic cell proliferation	2 (3%)	
Hepatodiaphragmatic nodule	2 (3%)	3 (5%)
Inflammation, granulomatous	7 (12%)	3 (5%)
Inflammation, subacute	1 (2%)	
Mixed cell focus	8 (13%)	1 (2%)
Necrosis, focal	7 (12%)	2 (3%)
Bile duct, hyperplasia	23 (38%)	24 (40%)
Centrilobular, necrosis		1 (2%)
Hepatocyte, vacuolization cytoplasmic	7 (12%)	9 (15%)
Kupffer cell, pigmentation	14 (23%)	19 (32%)
Mesentery	(8)	(6)
Accessory spleen	2 (25%)	
Fat, necrosis	5 (63%)	5 (83%)

TABLE D3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydoquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Alimentary System (continued)		
Pancreas	(60)	(59)
Atrophy	15 (25%)	11 (19%)
Acinus, cytoplasmic alteration	1 (2%)	1 (2%)
Stomach, forestomach	(59)	(59)
Edema	1 (2%)	1 (2%)
Erosion	1 (2%)	2 (3%)
Ulcer	4 (7%)	
Epithelium, hyperplasia	5 (8%)	5 (8%)
Stomach, glandular	(59)	(60)
Edema	1 (2%)	
Erosion	1 (2%)	2 (3%)
Mineralization	1 (2%)	
Ulcer	2 (3%)	
Tongue		(3)
Epithelium, hyperplasia		1 (33%)
Cardiovascular System		
Heart	(60)	(60)
Cardiomyopathy	29 (48%)	30 (50%)
Mineralization	1 (2%)	
Thrombosis	2 (3%)	2 (3%)
Endocardium, hyperplasia		1 (2%)
Schwann cell, hyperplasia	1 (2%)	
Endocrine System		
Adrenal cortex	(60)	(60)
Accessory adrenal cortical nodule	9 (15%)	10 (17%)
Atrophy		2 (3%)
Degeneration, fatty	11 (18%)	10 (17%)
Hemorrhage	1 (2%)	
Hyperplasia, diffuse	1 (2%)	
Hyperplasia, focal	7 (12%)	1 (2%)
Hypertrophy, focal	5 (8%)	8 (13%)
Necrosis	1 (2%)	
Adrenal medulla	(57)	(60)
Hyperplasia	5 (9%)	15 (25%)
Islets, pancreatic	(60)	(59)
Hyperplasia		1 (2%)
Parathyroid gland	(55)	(57)
Hyperplasia	2 (4%)	
Pituitary gland	(59)	(60)
Pars distalis, angiectasis	2 (3%)	10 (17%)
Pars distalis, cyst	9 (15%)	11 (18%)
Pars distalis, hyperplasia, focal	11 (19%)	13 (22%)
Pars intermedia, angiectasis	2 (3%)	4 (7%)
Pars intermedia, cyst	4 (7%)	6 (10%)

TABLE D3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydoquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Endocrine System (continued)		
Thyroid gland	(60)	(59)
Ultimobranchial cyst	2 (3%)	3 (5%)
C-cell, hyperplasia	4 (7%)	3 (5%)
Follicle, cyst	1 (2%)	1 (2%)
General Body System		
None		
Genital System		
Clitoral gland	(59)	(59)
Cyst	5 (8%)	5 (8%)
Hyperplasia	5 (8%)	6 (10%)
Inflammation, chronic	3 (5%)	2 (3%)
Inflammation, suppurative	2 (3%)	
Ovary	(60)	(60)
Angiectasis	2 (3%)	
Cyst	6 (10%)	12 (20%)
Uterus	(60)	(60)
Hydrometra	4 (7%)	3 (5%)
Hyperplasia, cystic	1 (2%)	
Hematopoietic System		
Bone marrow	(60)	(60)
Hyperplasia	1 (2%)	
Infiltration cellular, histiocyte		1 (2%)
Inflammation, granulomatous	1 (2%)	1 (2%)
Myelofibrosis	1 (2%)	5 (8%)
Stromal cell, hyperplasia		1 (2%)
Lymph node	(19)	(23)
Iliac, ectasia	1 (5%)	
Iliac, hemorrhage		1 (4%)
Iliac, pigmentation		1 (4%)
Mediastinal, hemorrhage		3 (13%)
Mediastinal, hyperplasia, lymphoid		1 (4%)
Mediastinal, pigmentation	8 (42%)	11 (48%)
Pancreatic, ectasia	1 (5%)	
Pancreatic, pigmentation	2 (11%)	4 (17%)
Renal, pigmentation	6 (32%)	5 (22%)
Lymph node, mandibular	(60)	(59)
Ectasia	3 (5%)	2 (3%)
Hemorrhage	5 (8%)	5 (8%)
Hyperplasia, lymphoid	9 (15%)	3 (5%)
Hyperplasia, plasma cell	1 (2%)	1 (2%)
Pigmentation	22 (37%)	22 (37%)

TABLE D3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydoquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Hematopoietic System (continued)		
Lymph node, mesenteric	(59)	(59)
Ectasia	1 (2%)	2 (3%)
Hemorrhage	2 (3%)	6 (10%)
Hyperplasia, lymphoid	1 (2%)	
Pigmentation		1 (2%)
Spleen	(60)	(60)
Fibrosis	4 (7%)	2 (3%)
Hematopoietic cell proliferation	9 (15%)	12 (20%)
Hyperplasia, lymphoid		1 (2%)
Necrosis	1 (2%)	1 (2%)
Pigmentation, hemosiderin	30 (50%)	30 (50%)
Lymphoid follicle, atrophy		2 (3%)
Red pulp, atrophy		1 (2%)
Integumentary System		
Mammary gland	(60)	(59)
Dilatation	51 (85%)	34 (58%)
Galactocele	1 (2%)	4 (7%)
Hyperplasia	3 (5%)	2 (3%)
Skin	(60)	(60)
Inflammation, chronic		2 (3%)
Ulcer	1 (2%)	2 (3%)
Epidermis, hyperplasia	1 (2%)	3 (5%)
Subcutaneous tissue, edema	1 (2%)	3 (5%)
Musculoskeletal System		
Bone	(60)	(60)
Fibrous osteodystrophy	2 (3%)	
Cranium, osteopetrosis	3 (5%)	2 (3%)
Femur, osteopetrosis	3 (5%)	7 (12%)
Nervous System		
Brain	(60)	(60)
Atrophy	17 (28%)	15 (25%)
Gliosis		1 (2%)
Hemorrhage	1 (2%)	
Hydrocephalus	1 (2%)	3 (5%)
Respiratory System		
Lung	(60)	(60)
Edema	1 (2%)	3 (5%)
Fibrosis		1 (2%)
Foreign body	1 (2%)	
Hemorrhage	2 (3%)	3 (5%)
Infiltration cellular, histiocyte	33 (55%)	30 (50%)
Inflammation, subacute	1 (2%)	
Mineralization	1 (2%)	
Alveolar epithelium, hyperplasia	3 (5%)	4 (7%)

TABLE D3b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Dietary Restriction Study of *t*-Butylhydoquinone: Restricted Feed Protocol (continued)

	0 ppm	5,000 ppm
30-Month Study (continued)		
Respiratory System (continued)		
Nose	(60)	(60)
Foreign body	1 (2%)	1 (2%)
Inflammation, suppurative	3 (5%)	2 (3%)
Goblet cell, hyperplasia	7 (12%)	9 (15%)
Mucosa, hyperplasia	4 (7%)	3 (5%)
Mucosa, metaplasia, squamous	1 (2%)	1 (2%)
Special Senses System		
Ear	(2)	
Inflammation, chronic	1 (50%)	
Eye		(1)
Cataract		1 (100%)
Retina, degeneration		1 (100%)
Urinary System		
Kidney	(60)	(60)
Glomerulosclerosis	1 (2%)	
Hydronephrosis		2 (3%)
Inflammation, chronic		2 (3%)
Inflammation, suppurative		1 (2%)
Mineralization	59 (98%)	56 (93%)
Nephropathy	38 (63%)	41 (68%)
Renal tubule, atrophy	1 (2%)	14 (23%)
Renal tubule, cytoplasmic alteration	5 (8%)	1 (2%)
Renal tubule, dilatation	2 (3%)	7 (12%)
Renal tubule, necrosis	1 (2%)	
Renal tubule, pigmentation	17 (28%)	17 (28%)
Transitional epithelium, hyperplasia	5 (8%)	5 (8%)
Urinary bladder	(60)	(60)
Transitional epithelium, hyperplasia	1 (2%)	

APPENDIX E
SUMMARY OF LESIONS IN MALE RATS IN THE DIETARY RESTRICTION STUDY OF SALICYLAZOSULFAPRYRIDINE

TABLE E1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
Disposition Summary			
Animals initially in study	70[b]	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths	1	2	2
Moribund	13	16	15
Natural deaths	1	1	10
Survivors			
Terminal sacrifice	35	31	23
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Intestine large, colon	(10)	(10)	(10)
Carcinoma	1 (10%)		
Endocrine System			
Islets, pancreatic	(10)	(10)	(10)
Adenoma		1 (10%)	
Pituitary gland	(10)	(10)	(10)
Pars distalis, adenoma	1 (10%)	4 (40%)	
Genital System			
Testes	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	6 (60%)	3 (30%)	9 (90%)
Interstitial cell, adenoma	3 (30%)	5 (50%)	1 (10%)
Respiratory System			
Lung	(10)	(10)	(10)
Alveolar/bronchiolar carcinoma	1 (10%)		
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
General Body System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Special Senses System			
Urinary System			

TABLE E1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study			
Alimentary System			
Intestine large, colon	(49)	(50)	(48)
Adenoma		1 (2%)	
Intestine large, rectum	(50)	(50)	(49)
Polyp		1 (2%)	
Intestine large, cecum	(50)	(50)	(50)
Sarcoma		1 (2%)	
Intestine small, jejunum	(50)	(50)	(49)
Intestine small, ileum	(49)	(50)	(50)
Leiomyosarcoma	1 (2%)		
Liver	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)
Hepatocellular adenoma	2 (4%)	2 (4%)	
Leiomyosarcoma, metastatic, stomach, forestomach	1 (2%)		
Osteosarcoma, metastatic, bone			1 (2%)
Sarcoma, metastatic, intestine large, cecum		1 (2%)	
Mesentery	(17)	(16)	(12)
Fibrous histiocytoma	1 (6%)		
Leiomyosarcoma, metastatic, stomach, forestomach	1 (6%)		
Sarcoma, metastatic, intestine large, cecum		1 (6%)	
Pancreas	(50)	(50)	(50)
Fibrous histiocytoma	1 (2%)		
Leiomyosarcoma, metastatic, stomach, forestomach	1 (2%)		
Mixed tumor benign			1 (2%)
Sarcoma, metastatic, intestine large, cecum		1 (2%)	
Acinar cell, adenoma	9 (18%)	10 (20%)	10 (20%)
Acinar cell, adenoma, multiple	3 (6%)	2 (4%)	
Acinar cell, carcinoma, multiple	1 (2%)		
Salivary glands	(50)	(50)	(50)
Adenoma			1 (2%)
Schwannoma malignant		1 (2%)	
Stomach, forestomach	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)		
Squamous cell carcinoma			1 (2%)
Squamous cell papilloma	1 (2%)		
Tongue			(1)
Squamous cell carcinoma			1 (100%)
Cardiovascular System			
Heart	(50)	(50)	(50)
Schwannoma benign		1 (2%)	2 (4%)

TABLE E1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study (continued)			
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma malignant		1 (2%)	
Pheochromocytoma complex	1 (2%)		
Pheochromocytoma benign	12 (24%)	7 (14%)	7 (14%)
Bilateral, pheochromocytoma benign	3 (6%)	2 (4%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	5 (10%)
Carcinoma	1 (2%)	1 (2%)	
Pituitary gland	(50)	(48)	(49)
Ganglioneuroma	1 (2%)		
Pars distalis, adenoma	14 (28%)	19 (40%)	18 (37%)
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	3 (6%)	6 (12%)	6 (12%)
C-cell, carcinoma	2 (4%)		1 (2%)
Follicular cell, adenoma	4 (8%)		1 (2%)
Follicular cell, carcinoma	1 (2%)		
General Body System			
Tissue NOS	(1)	(1)	
Sarcoma, metastatic, intestine large, cecum		1 (100%)	
Genital System			
Epididymis	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)
Adenoma	1 (2%)		
Carcinoma	2 (4%)		
Prostate	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(49)
Testes	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	44 (88%)	37 (74%)	43 (86%)
Interstitial cell, adenoma	1 (2%)	8 (16%)	2 (4%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Lymph node	(9)	(15)	(10)
Inguinal, fibrous histiocytoma, metastatic, skin			1 (10%)
Mediastinal, sarcoma, metastatic, intestine large, cecum		1 (7%)	
Lymph node, mandibular	(50)	(49)	(49)
Lymph node, mesenteric	(50)	(50)	(49)
Sarcoma, metastatic, intestine large, cecum		1 (2%)	

TABLE E1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study (continued)			
Hematopoietic System (continued)			
Spleen	(50)	(50)	(50)
Fibrosarcoma		1 (2%)	
Leiomyosarcoma, metastatic, stomach, forestomach	1 (2%)		
Sarcoma, metastatic, intestine large, cecum		1 (2%)	
Thymus	(47)	(50)	(49)
Thymoma benign	1 (2%)		
Integumentary System			
Mammary gland	(48)	(50)	(49)
Fibroadenoma	3 (6%)	1 (2%)	3 (6%)
Skin	(50)	(50)	(50)
Basal cell adenoma	2 (4%)		
Keratoacanthoma	3 (6%)	2 (4%)	2 (4%)
Squamous cell papilloma	1 (2%)	2 (4%)	1 (2%)
Trichoepithelioma		1 (2%)	
Subcutaneous tissue, fibroma	2 (4%)	3 (6%)	3 (6%)
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, fibrous histiocytoma			1 (2%)
Subcutaneous tissue, schwannoma malignant		1 (2%)	
Musculoskeletal System			
Bone	(50)	(50)	(50)
Osteosarcoma			1 (2%)
Skeletal muscle	(1)	(1)	(1)
Fibrous histiocytoma	1 (100%)		
Sarcoma, metastatic, intestine large, cecum		1 (100%)	
Nervous System			
Brain	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)		
Granular cell tumor benign		1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)
Sarcoma, metastatic, intestine large, cecum		1 (2%)	
Nose	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		

TABLE E1a
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study (continued)			
Special Senses System			
Zymbal's gland	(1)	(2)	
Carcinoma	1 (100%)	2 (100%)	
Urinary System			
Kidney	(50)	(50)	(50)
Renal tubule, adenoma		1 (2%)	
Urinary bladder	(50)	(50)	(50)
Papilloma			4 (8%)
Papilloma, multiple			2 (4%)
Systemic Lesions			
Multiple organs[c]	(50)	(50)	(50)
Leukemia mononuclear	13 (26%)	10 (20%)	3 (6%)
Mesothelioma malignant	1 (2%)	1 (2%)	3 (6%)
Neoplasm Summary			
Total animals with primary neoplasms[d]			
15-Month interim evaluation	9	10	10
2-Year study	49	49	48
Total primary neoplasms			
15-Month interim evaluation	12	13	10
2-Year study	144	128	124
Total animals with benign neoplasms			
15-Month interim evaluation	9	10	10
2-Year study	49	49	47
Total benign neoplasms			
15-Month interim evaluation	10	13	10
2-Year study	114	109	112
Total animals with malignant neoplasms			
15-Month interim evaluation	2		
2-Year study	23	16	9
Total malignant neoplasms			
15-Month interim evaluation	2		
2-Year study	30	19	12
Total animals with metastatic neoplasms			
2-Year study	2	1	5
Total metastatic neoplasms			
2-Year study	5	9	13

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Ten control animals were examined at 6 months for comparisons with a stop-exposure group that was not included in the dietary restriction study.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE E1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols[a]

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Disposition Summary				
Animals initially in study	61	60	49	50
15-Month interim evaluation	10	10		
Early deaths				
Accidental deaths	2	2	4	2
Moribund	13	6	28	14
Natural deaths	2	3	7	10
Survivors				
Died last week of study				1
Terminal sacrifice	34	39	10	23
Animals examined microscopically	61	60	49	50
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(10)	(10)		
Pars distalis, adenoma	1 (10%)	1 (10%)		
Genital System				
Testes	(10)	(10)		
Bilateral, interstitial cell, adenoma	6 (60%)	3 (30%)		
Interstitial cell, adenoma	3 (30%)	6 (60%)		
Integumentary System				
Skin	(10)	(10)		
Subcutaneous tissue, lipoma		1 (10%)		
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE E1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols				
Alimentary System				
Intestine large, colon	(51)	(49)	(49)	(47)
Chordoma, metastatic, bone			1 (2%)	
Intestine large, cecum	(51)	(50)	(49)	(49)
Intestine small, duodenum	(50)	(50)	(49)	(49)
Intestine small, jejunum	(51)	(50)	(49)	(48)
Intestine small, ileum	(50)	(50)	(49)	(49)
Adenoma	1 (2%)			
Liver	(51)	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)	1 (2%)
Hepatocellular carcinoma				1 (2%)
Hepatocellular adenoma	1 (2%)	1 (2%)	3 (6%)	
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Mesentery	(20)	(7)	(14)	(10)
Osteosarcoma, metastatic, bone			1 (7%)	
Pancreas	(51)	(50)	(49)	(48)
Histiocytic sarcoma, metastatic, spleen				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Acinar cell, adenoma	5 (10%)	1 (2%)	2 (4%)	4 (8%)
Pharynx	(1)		(1)	
Squamous cell papilloma	1 (100%)		1 (100%)	
Salivary glands			(49)	(49)
Parotid gland, fibrosarcoma				1 (2%)
Stomach, forestomach	(51)	(50)	(49)	(50)
Squamous cell papilloma	1 (2%)		1 (2%)	
Stomach, glandular			(49)	(50)
Tongue	(2)			(1)
Squamous cell carcinoma	1 (50%)			
Squamous cell papilloma	1 (50%)			1 (100%)
Cardiovascular System				
Heart	(51)	(50)	(49)	(49)
Schwannoma malignant	1 (2%)	3 (6%)	1 (2%)	
Endocrine System				
Adrenal cortex	(51)	(50)	(49)	(50)
Adenoma	1 (2%)		1 (2%)	
Adrenal medulla	(51)	(50)	(48)	(50)
Pheochromocytoma malignant	2 (4%)		1 (2%)	1 (2%)
Pheochromocytoma benign	5 (10%)	1 (2%)	10 (21%)	6 (12%)
Bilateral, pheochromocytoma benign	3 (6%)		4 (8%)	2 (4%)
Islets, pancreatic	(51)	(50)	(49)	(48)
Adenoma	1 (2%)	1 (2%)	4 (8%)	4 (8%)
Carcinoma			5 (10%)	2 (4%)

TABLE E1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Endocrine System (continued)				
Pituitary gland	(51)	(49)	(49)	(49)
Pars distalis, adenoma	13 (25%)	14 (29%)	14 (29%)	12 (24%)
Thyroid gland	(50)	(50)	(49)	(49)
Bilateral, C-cell, carcinoma				1 (2%)
C-cell, adenoma	4 (8%)	5 (10%)	6 (12%)	5 (10%)
C-cell, carcinoma		1 (2%)	1 (2%)	1 (2%)
Follicular cell, adenoma			1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Epididymis	(51)	(50)	(49)	(49)
Preputial gland	(51)	(50)	(49)	(49)
Adenoma	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Carcinoma		2 (4%)	4 (8%)	1 (2%)
Prostate	(51)	(50)	(49)	(49)
Seminal vesicle	(51)	(50)	(49)	(48)
Testes	(51)	(50)	(49)	(49)
Bilateral, interstitial cell, adenoma	39 (76%)	39 (78%)	39 (80%)	37 (76%)
Interstitial cell, adenoma	6 (12%)	6 (12%)	4 (8%)	5 (10%)
Hematopoietic System				
Bone marrow	(51)	(50)	(49)	(50)
Lymph node	(11)	(3)	(20)	(10)
Deep cervical, carcinoma, metastatic, thyroid gland				1 (10%)
Mediastinal, fibrous histiocytoma, metastatic, skin				1 (10%)
Mediastinal, histiocytic sarcoma, metastatic, spleen				1 (10%)
Mediastinal, osteosarcoma, metastatic, bone			1 (5%)	
Renal, fibrous histiocytoma, metastatic, skin				1 (10%)
Renal, histiocytic sarcoma, metastatic, spleen				1 (10%)
Lymph node, mandibular	(51)	(50)	(48)	(49)
Lymph node, mesenteric	(51)	(50)	(49)	(48)
Spleen	(51)	(50)	(49)	(49)
Fibroma		1 (2%)		
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Thymus	(47)	(48)	(44)	(40)

TABLE E1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Integumentary System				
Mammary gland	(50)	(49)	(49)	(47)
Carcinoma				1 (2%)
Fibroadenoma	2 (4%)		2 (4%)	2 (4%)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Skin	(51)	(50)	(49)	(50)
Basal cell adenoma	1 (2%)	1 (2%)		
Basal cell carcinoma			1 (2%)	
Keratoacanthoma	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Squamous cell papilloma			2 (4%)	3 (6%)
Trichoepithelioma	2 (4%)			2 (4%)
Subcutaneous tissue, fibroma	2 (4%)		5 (10%)	5 (10%)
Subcutaneous tissue, fibrosarcoma			3 (6%)	
Subcutaneous tissue, fibrous histiocytoma			1 (2%)	2 (4%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, schwannoma NOS				1 (2%)
Musculoskeletal System				
Bone	(51)	(50)	(49)	(50)
Chordoma			1 (2%)	
Hamartoma		1 (2%)		
Osteosarcoma	1 (2%)		2 (4%)	1 (2%)
Skeletal muscle	(2)		(2)	(2)
Fibrous histiocytoma, metastatic, skin				1 (50%)
Osteosarcoma, metastatic, bone			1 (50%)	
Nervous System				
Brain	(51)	(50)	(49)	(50)
Oligodendroglioma malignant				1 (2%)
Respiratory System				
Lung	(51)	(50)	(49)	(49)
Alveolar/bronchiolar adenoma	2 (4%)		1 (2%)	
Alveolar/bronchiolar carcinoma			2 (4%)	
Carcinoma, metastatic, thyroid gland				1 (2%)
Fibrous histiocytoma, metastatic, skin			1 (2%)	1 (2%)
Histiocytic sarcoma, metastatic, spleen				1 (2%)
Trachea	(51)	(50)	(49)	(49)
Carcinoma, metastatic, thyroid gland				1 (2%)
Special Senses System				
Zymbal's gland	(1)		(2)	
Carcinoma	1 (100%)		1 (50%)	

TABLE E1b
Summary of the Incidence of Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Urinary System				
Kidney	(51)	(50)	(49)	(50)
Lipoma		1 (2%)		
Histiocytic sarcoma, metastatic, spleen				1 (2%)
Renal tubule, adenoma		1 (2%)		
Renal tubule, carcinoma	1 (2%)			
Urinary bladder	(51)	(50)	(49)	(49)
Papilloma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(51)	(50)	(49)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	11 (22%)	2 (4%)	24 (49%)	8 (16%)
Mesothelioma malignant	3 (6%)	1 (2%)	1 (2%)	4 (8%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	10	9		
2-Year and 30-month protocols	49	48	46	48
Total primary neoplasms				
15-Month interim evaluation	10	11		
2-Year and 30-month protocols	116	86	152	119
Total animals with benign neoplasms				
15-Month interim evaluation	10	9		
2-Year and 30-month protocols	49	48	46	46
Total benign neoplasms				
15-Month interim evaluation	10	11		
2-Year and 30-month protocols	95	76	104	92
Total animals with malignant neoplasms				
2-Year and 30-month protocols	18	9	34	23
Total malignant neoplasms				
2-Year and 30-month protocols	21	10	48	26
Total animals with metastatic neoplasms				
30-Month protocol			3	4
Total metastatic neoplasms				
30-Month protocol			9	14
Total animals with uncertain neoplasms-benign or malignant				
30-Month protocol				1
Total uncertain neoplasms				
30-Month protocol				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 E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	337.5 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	337.5 mg/kg × Weight-Matched Control
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	15/50 (30%)	8/49 (16%)	9/50 (18%)	8/49 (16%)
Adjusted rate[b]	38.2%	27.5%	25.6%	27.5%
Terminal rate[c]	11/35 (31%)	4/23 (17%)	6/31 (19%)	4/23 (17%)
First incidence (days)	653	635	591	635
Life table test[d]		P=0.324N		P=0.501
Logistic regression test[d]		P=0.127N		P=0.552N
Fisher exact test[d]		P=0.084N		P=0.518N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	16/50 (32%)	8/49 (16%)	10/50 (20%)	8/49 (16%)
Adjusted rate	39.8%	27.5%	28.6%	27.5%
Terminal rate	11/35 (31%)	4/23 (17%)	7/31 (23%)	4/23 (17%)
First incidence (days)	653	635	591	635
Life table test		P=0.265N		P=0.586
Logistic regression test		P=0.087N		P=0.451N
Fisher exact test		P=0.056N		P=0.416N
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	8.6%	11.4%	3.2%	11.4%
Terminal rate	3/35 (9%)	2/23 (9%)	1/31 (3%)	2/23 (9%)
First incidence (days)	729 (T)	684	729 (T)	684
Life table test		P=0.480		P=0.219
Logistic regression test		P=0.577		P=0.270
Fisher exact test		P=0.661N		P=0.309
Pancreas: Adenoma				
Overall rate	12/50 (24%)	10/50 (20%)	12/50 (24%)	10/50 (20%)
Adjusted rate	31.4%	35.9%	33.0%	35.9%
Terminal rate	9/35 (26%)	6/23 (26%)	8/31 (26%)	6/23 (26%)
First incidence (days)	684	704	591	704
Life table test		P=0.394		P=0.543
Logistic regression test		P=0.590		P=0.468N
Fisher exact test		P=0.405N		P=0.405N
Pancreas: Adenoma or Carcinoma				
Overall rate	13/50 (26%)	10/50 (20%)	12/50 (24%)	10/50 (20%)
Adjusted rate	34.1%	35.9%	33.0%	35.9%
Terminal rate	10/35 (29%)	6/23 (26%)	8/31 (26%)	6/23 (26%)
First incidence (days)	684	704	591	704
Life table test		P=0.469		P=0.543
Logistic regression test		P=0.526N		P=0.468N
Fisher exact test		P=0.318N		P=0.405N

TABLE E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	337.5 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	337.5 mg/kg × Weight-Matched Control
Pancreatic Islets: Adenoma				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	5/50 (10%)
Adjusted rate	5.3%	18.3%	2.9%	18.3%
Terminal rate	1/35 (3%)	3/23 (13%)	0/31 (0%)	3/23 (13%)
First incidence (days)	684	613	703	613
Life table test		P=0.113		P=0.067
Logistic regression test		P=0.190		P=0.093
Fisher exact test		P=0.218		P=0.102
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	2/50 (4%)	5/50 (10%)
Adjusted rate	8.1%	18.3%	6.0%	18.3%
Terminal rate	2/35 (6%)	3/23 (13%)	1/31 (3%)	3/23 (13%)
First incidence (days)	684	613	703	613
Life table test		P=0.198		P=0.143
Logistic regression test		P=0.314		P=0.195
Fisher exact test		P=0.357		P=0.218
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	14/50 (28%)	18/49 (37%)	19/48 (40%)	18/49 (37%)
Adjusted rate	34.3%	50.5%	51.5%	50.5%
Terminal rate	9/35 (26%)	7/22 (32%)	12/29 (41%)	7/22 (32%)
First incidence (days)	473	428	521	428
Life table test		P=0.064		P=0.394
Logistic regression test		P=0.216		P=0.506N
Fisher exact test		P=0.238		P=0.468N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.7%	0.0%		
Terminal rate	1/35 (3%)	0/23 (0%)		
First incidence (days)	684	-[e]		
Life table test		P=0.185N		
Logistic regression test		P=0.133N		
Fisher exact test		P=0.121N		
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	8.6%	6.8%		
Terminal rate	3/35 (9%)	0/23 (0%)		
First incidence (days)	729 (T)	687		
Life table test		P=0.655N		
Logistic regression test		P=0.569N		
Fisher exact test		P=0.500N		

TABLE E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	337.5 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	337.5 mg/kg × Weight-Matched Control
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	4/50 (8%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	11.4%	9.7%	9.3%	9.7%
Terminal rate	4/35 (11%)	0/23 (0%)	2/31 (6%)	0/23 (0%)
First incidence (days)	729 (T)	687	709	687
Life table test		P=0.627		P=0.556
Logistic regression test		P=0.574N		P=0.633
Fisher exact test		P=0.500N		P=0.661N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	6/50 (12%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	16.5%	9.7%	9.3%	9.7%
Terminal rate	5/35 (14%)	0/23 (0%)	2/31 (6%)	0/23 (0%)
First incidence (days)	717	687	709	687
Life table test		P=0.440N		P=0.556
Logistic regression test		P=0.315N		P=0.633
Fisher exact test		P=0.243N		P=0.661N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	5.7%	12.5%	8.0%	12.5%
Terminal rate	2/35 (6%)	2/23 (3%)	1/31 (3%)	2/23 (9%)
First incidence (days)	729 (T)	726	620	726
Life table test		P=0.316		P=0.550
Logistic regression test		P=0.332		P=0.642
Fisher exact test		P=0.500		P=0.661N
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, or Fibrosarcoma				
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted rate	5.7%	17.4%	8.0%	17.4%
Terminal rate	2/35 (6%)	2/23 (9%)	1/31 (3%)	2/23 (9%)
First incidence (days)	729 (T)	645	620	645
Life table test		P=0.108		P=0.266
Logistic regression test		P=0.172		P=0.338
Fisher exact test		P=0.218		P=0.357
Testes: Adenoma				
Overall rate	45/50 (90%)	45/50 (90%)	45/50 (90%)	45/50 (90%)
Adjusted rate	97.8%	100.0%	97.8%	100.0%
Terminal rate	34/35 (97%)	23/23 (100%)	30/31 (97%)	23/23 (100%)
First incidence (days)	477	473	458	473
Life table test		P=0.009		P=0.080
Logistic regression test		P=0.405		P=0.467
Fisher exact test		P=0.630N		P=0.630N

TABLE E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	337.5 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	337.5 mg/kg × Weight-Matched Control
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	6/50 (12%)	6/50 (12%)	6/50 (12%)
Adjusted rate	8.6%	22.9%	18.2%	22.9%
Terminal rate	3/35 (9%)	4/23 (17%)	5/31 (16%)	4/23 (17%)
First incidence (days)	729 (T)	696	646	696
Life table test		P=0.093		P=0.438
Logistic regression test		P=0.145		P=0.556
Fisher exact test		P=0.243		P=0.620N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	7/50 (14%)	6/50 (12%)	7/50 (14%)
Adjusted rate	14.3%	24.9%	18.2%	24.9%
Terminal rate	5/35 (14%)	4/23 (17%)	5/31 (16%)	4/23 (17%)
First incidence (days)	729 (T)	653	646	653
Life table test		P=0.162		P=0.328
Logistic regression test		P=0.278		P=0.446
Fisher exact test		P=0.380		P=0.500
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	4/50 (8%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	11.4%	4.3%		
Terminal rate	4/35 (11%)	1/23 (4%)		
First incidence (days)	729 (T)	729 (T)		
Life table test		P=0.324N		
Logistic regression test		P=0.324N		
Fisher exact test		P=0.181N		
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	14.3%	4.3%		
Terminal rate	5/35 (14%)	1/23 (4%)		
First incidence (days)	729 (T)	729 (T)		
Life table test		P=0.221N		
Logistic regression test		P=0.221N		
Fisher exact test		P=0.102N		
Urinary Bladder: Papilloma				
Overall rate	0/50 (0%)	6/50 (12%)	0/50 (0%)	6/50 (12%)
Adjusted rate	0.0%	22.1%	0.0%	22.1%
Terminal rate	0/35 (0%)	3/23 (13%)	0/31 (0%)	3/23 (13%)
First incidence (days)	-	653	-	653
Life table test		P=0.006		P=0.009
Logistic regression test		P=0.011		P=0.013
Fisher exact test		P=0.013		P=0.013

TABLE E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	337.5 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	337.5 mg/kg × Weight-Matched Control
All Organs: Mononuclear Cell Leukemia				
Overall rate	13/50 (26%)	3/50 (6%)	10/50 (20%)	3/50 (6%)
Adjusted rate	32.0%	6.8%	26.2%	6.8%
Terminal rate	8/35 (23%)	0/23 (0%)	5/31 (16%)	0/23 (0%)
First incidence (days)	477	428	526	428
Life table test		P=0.040N		P=0.076N
Logistic regression test		P=0.007N		P=0.033N
Fisher exact test		P=0.006N		P=0.036N
All Organs: Malignant Mesothelioma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.9%	10.3%	3.2%	10.3%
Terminal rate	1/35 (3%)	1/23 (4%)	1/31 (3%)	1/23 (4%)
First incidence (days)	729 (T)	585	729 (T)	585
Life table test		P=0.207		P=0.236
Logistic regression test		P=0.292		P=0.295
Fisher exact test		P=0.309		P=0.309
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	47/50 (94%)	49/50 (98%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	35/35 (100%)	23/23 (100%)	31/31 (100%)	23/23 (100%)
First incidence (days)	473	428	458	428
Life table test		P=0.025		P=0.144
Logistic regression test		P=0.998N		P=0.970N
Fisher exact test		P=0.309N		P=0.309N
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	9/50 (18%)	16/50 (32%)	9/50 (18%)
Adjusted rate	49.9%	22.8%	39.5%	22.8%
Terminal rate	12/35 (34%)	1/23 (4%)	8/31 (26%)	1/23 (4%)
First incidence (days)	477	428	484	428
Life table test		P=0.049N		P=0.198N
Logistic regression test		P=0.002N		P=0.072N
Fisher exact test		P=0.002N		P=0.083N

TABLE E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	337.5 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	337.5 mg/kg × Weight-Matched Control
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	48/50 (96%)	49/50 (98%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	35/35 (100%)	23/23 (100%)	31/31 (100%)	23/23 (100%)
First incidence (days)	473	428	458	428
Life table test		P=0.018		P=0.113
Logistic regression test		-[f]		-
Fisher exact test		P=0.500N		P=0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the *ad libitum*-fed or weight-matched controls and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the dosed group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	8/51 (16%)	1/50 (2%)	14/48 (29%)	8/50 (16%)
Adjusted rate[b]	22.2%	3.4%	66.7%	31.1%
Terminal rate[c]	6/34 (18%)	1/39 (3%)	4/10 (40%)	7/24 (29%)
First incidence (days)	700	731 (T)	752	812
Life table test[d]		P=0.011N		P=0.002N
Logistic regression test[d]		P=0.014N		P=0.011N
Fisher exact test[d]		P=0.017N		P=0.093N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	9/51 (18%)	1/50 (2%)	15/48 (31%)	8/50 (16%)
Adjusted rate	33.3%	3.4%	72.3%	31.1%
Terminal rate	7/34 (21%)	1/39 (3%)	5/10 (50%)	7/24 (29%)
First incidence (days)	700	731 (T)	752	812
Life table test		P=0.006N		P<0.001N
Logistic regression test		P=0.007N		P=0.005N
Fisher exact test		P=0.009N		P=0.061N
Heart: Malignant Schwannoma				
Overall rate	1/51 (2%)	3/50 (6%)	1/49 (2%)	0/49 (0%)
Adjusted rate	2.9%	10.3%		
Terminal rate	1/34 (3%)	3/39 (8%)		
First incidence (days)	730 (T)	731 (T)		
Life table test		P=0.355		
Logistic regression test		P=0.355		
Fisher exact test		P=0.301		
Liver: Hepatocellular Adenoma				
Overall rate	1/51 (2%)	1/50 (2%)	3/49 (6%)	0/50 (0%)
Adjusted rate			16.9%	0.0%
Terminal rate			0/10 (0%)	0/24 (0%)
First incidence (days)			816	-[e]
Life table test				P=0.047N
Logistic regression test				P=0.082N
Fisher exact test				P=0.117N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/51 (2%)	1/50 (2%)	3/49 (6%)	1/50 (2%)
Adjusted rate			16.9%	3.3%
Terminal rate			0/10 (0%)	0/24 (0%)
First incidence (days)			816	854
Life table test				P=0.146N
Logistic regression test				P=0.232N
Fisher exact test				P=0.301N

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/51 (4%)	0/50 (0%)	3/49 (6%)	0/49 (0%)
Adjusted rate			21.8%	0.0%
Terminal rate			1/10 (10%)	0/24 (0%)
First incidence (days)			869	-
Life table test				P=0.035N
Logistic regression test				P=0.049N
Fisher exact test				P=0.121N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	2/51 (4%)	0/50 (0%)	2/49 (4%)	3/50 (6%)
Adjusted rate			13.8%	12.5%
Terminal rate			1/10 (10%)	3/24 (13%)
First incidence (days)			816	910 (T)
Life table test				P=0.533N
Logistic regression test				P=0.669N
Fisher exact test				P=0.510
Oral Cavity (Tongue and Pharynx): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	3/51 (6%)	0/50 (0%)	1/49 (2%)	1/50 (2%)
Adjusted rate	6.6%	0.0%		
Terminal rate	0/34 (0%)	0/39 (0%)		
First incidence (days)	627	-		
Life table test		P=0.132N		
Logistic regression test		P=0.102N		
Fisher exact test		P=0.125N		
Pancreas: Adenoma				
Overall rate	5/51 (10%)	1/50 (2%)	2/49 (4%)	4/48 (8%)
Adjusted rate	23.5%	2.4%	20.0%	14.9%
Terminal rate	3/34 (9%)	0/39 (0%)	2/10 (20%)	3/24 (13%
First incidence (days)	667	674	910 (T)	795
Life table test		P=0.088N		P=0.645N
Logistic regression test		P=0.111N		P=0.535
Fisher exact test		P=0.107N		P=0.329
Pancreatic Islets: Adenoma				
Overall rate	1/51 (2%)	1/50 (2%)	4/49 (8%)	4/48 (8%)
Adjusted rate			19.4%	16.7%
Terminal rate			1/10 (10%)	4/24 (17%)
First incidence (days)			660	910 (T)
Life table test				P=0.287N
Logistic regression test				P=0.569N
Fisher exact test				P=0.631

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Pancreatic Islets: Carcinoma				
Overall rate	0/51 (0%)	0/50 (0%)	5/49 (10%)	2/48 (4%)
Adjusted rate			23.2%	6.8%
Terminal rate			0/10 (0%)	1/24 (4%)
First incidence (days)			763	812
Life table test				P=0.076N
Logistic regression test				P=0.177N
Fisher exact test				P=0.226N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	1/51 (2%)	1/50 (2%)	8/49 (16%)	6/48 (13%)
Adjusted rate			35.0%	23.0%
Terminal rate			1/10 (10%)	5/24 (21%)
First incidence (days)			660	812
Life table test				P=0.079N
Logistic regression test				P=0.294N
Fisher exact test				P=0.403N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	13/51 (25%)	14/49 (29%)	14/49 (29%)	12/49 (24%)
Adjusted rate	31.1%	40.2%	51.4%	38.8%
Terminal rate	7/34 (21%)	11/38 (29%)	2/10 (20%)	7/23 (30%)
First incidence (days)	520	634	556	573
Life table test		P=0.580N		P=0.081N
Logistic regression test		P=0.428		P=0.390N
Fisher exact test		P=0.451		P=0.410N
Preputial Gland: Adenoma				
Overall rate	3/51 (6%)	1/50 (2%)	2/49 (4%)	1/49 (2%)
Adjusted rate	8.8%	3.4%		
Terminal rate	3/34 (9%)	1/39 (3%)		
First incidence (days)	730 (T)	731 (T)		
Life table test		P=0.257N		
Logistic regression test		P=0.257N		
Fisher exact test		P=0.316N		
Preputial Gland: Carcinoma				
Overall rate	0/51 (0%)	2/50 (4%)	4/49 (8%)	1/49 (2%)
Adjusted rate			23.6%	4.2%
Terminal rate			1/10 (10%)	1/24 (4%)
First incidence (days)			571	910 (T)
Life table test				P=0.053N
Logistic regression test				P=0.152N
Fisher exact test				P=0.181N

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/51 (6%)	3/50 (6%)	6/49 (12%)	2/49 (4%)
Adjusted rate	8.8%	10.3%	36.3%	8.3%
Terminal rate	3/34 (9%)	3/39 (8%)	1/10 (10%)	2/24 (8%)
First incidence (days)	730 (T)	731 (T)	571	910 (T)
Life table test		P=0.599N		P=0.018N
Logistic regression test		P=0.599N		P=0.078N
Fisher exact test		P=0.652		P=0.134N
Skin: Squamous Cell Papilloma				
Overall rate	0/51 (0%)	0/50 (0%)	2/49 (4%)	3/50 (6%)
Adjusted rate			9.0%	12.5%
Terminal rate			0/10 (0%)	3/24 (13%)
First incidence (days)			816	910 (T)
Life table test				P=0.567N
Logistic regression test				P=0.649
Fisher exact test				P=0.510
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	1/51 (2%)	2/50 (4%)	4/49 (8%)	4/50 (8%)
Adjusted rate			27.2%	16.7%
Terminal rate			2/10 (20%)	4/24 (17%)
First incidence (days)			816	910 (T)
Life table test				P=0.223N
Logistic regression test				P=0.391N
Fisher exact test				P=0.631N
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	3/51 (6%)	1/50 (2%)	1/49 (2%)	2/50 (4%)
Adjusted rate	19.3%	3.4%	7.7%	8.0%
Terminal rate	3/34 (9%)	1/39 (3%)	0/10 (0%)	1/24 (4%)
First incidence (days)	730 (T)	731 (T)	897	889
Life table test		P=0.257N		P=0.726N
Logistic regression test		P=0.257N		P=0.691
Fisher exact test		P=0.316N		P=0.508
Skin: Basal Cell Papilloma, Keratocanthoma, Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	4/51 (8%)	3/50 (6%)	5/49 (10%)	6/50 (12%)
Adjusted rate	32.8%	10.3%	32.8%	24.0%
Terminal rate	4/34 (12%)	3/39 (8%)	2/10 (20%)	5/24 (21%)
First incidence (days)	730 (T)	731 (T)	816	889
Life table test		P=0.425N		P=0.256N
Logistic regression test		P=0.425N		P=0.435N
Fisher exact test		P=0.511N		P=0.514

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/51 (4%)	0/50 (0%)	5/49 (10%)	5/50 (10%)
Adjusted rate			33.3%	16.4%
Terminal rate			2/10 (20%)	2/24 (8%)
First incidence (days)			690	737
Life table test				P=0.254N
Logistic regression test				P=0.512N
Fisher exact test				P=0.617N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	0/51 (0%)	0/50 (0%)	3/49 (6%)	0/50 (0%)
Adjusted rate			18.8%	0.0%
Terminal rate			1/10 (10%)	0/24 (0%)
First incidence (days)			816	-
Life table test				P=0.042N
Logistic regression test				P=0.076N
Fisher exact test				P=0.117N
Skin (Subcutaneous Tissue): Fibrous Histiocytoma or Fibrosarcoma				
Overall rate	0/51 (0%)	0/50 (0%)	4/49 (8%)	2/50 (4%)
Adjusted rate			27.8%	5.8%
Terminal rate			2/10 (20%)	0/24 (0%)
First incidence (days)			816	199
Life table test				P=0.134N
Logistic regression test				P=0.334N
Fisher exact test				P=0.329N
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, or Fibrosarcoma				
Overall rate	2/51 (4%)	0/50 (0%)	8/49 (16%)	7/50 (14%)
Adjusted rate			52.1%	21.2%
Terminal rate			4/10 (40%)	2/24 (8%)
First incidence (days)			690	199
Life table test				P=0.116N
Logistic regression test				P=0.441N
Fisher exact test				P=0.483N
Testes: Adenoma				
Overall rate	45/51 (88%)	45/50 (90%)	43/49 (88%)	42/49 (86%)
Adjusted rate	100.0%	97.8%	97.7%	100.0%
Terminal rate	32/34 (94%)	38/39 (97%)	9/10 (90%)	24/24 (100%)
First incidence (days)	520	511	445	430
Life table test		P=0.218N		P=0.001N
Logistic regression test		P=0.255		P=0.431N
Fisher exact test		P=0.514		P=0.500N

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/50 (8%)	5/50 (10%)	6/49 (12%)	5/49 (10%)
Adjusted rate	32.8%	14.8%	28.3%	13.2%
Terminal rate	4/34 (12%)	4/39 (10%)	1/10 (10%)	1/24 (4%)
First incidence (days)	730 (T)	685	594	571
Life table test		P=0.579		P=0.281N
Logistic regression test		P=0.525		P=0.503N
Fisher exact test		P=0.500		P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	6/50 (12%)	7/49 (14%)	6/49 (12%)
Adjusted rate	32.8%	18.1%	31.8%	17.0%
Terminal rate	4/34 (12%)	5/39 (13%)	1/10 (10%)	2/24 (8%)
First incidence (days)	730 (T)	685	594	571
Life table test		P=0.452		P=0.235N
Logistic regression test		P=0.397		P=0.491N
Fisher exact test		P=0.370		P=0.500N
All Organs: Mononuclear Cell Leukemia				
Overall rate	11/51 (22%)	2/50 (4%)	24/49 (49%)	8/50 (16%)
Adjusted rate	43.4%	6.9%	71.3%	23.8%
Terminal rate	3/34 (9%)	2/39 (5%)	3/10 (30%)	3/24 (13%)
First incidence (days)	520	731 (T)	556	430
Life table test		P=0.009N		P<0.001N
Logistic regression test		P=0.010N		P<0.001N
Fisher exact test		P=0.008N		P<0.001N
All Organs: Malignant Mesothelioma				
Overall rate	3/51 (6%)	1/50 (2%)	1/49 (2%)	4/50 (8%)
Adjusted rate	8.2%	3.4%	4.2%	12.3%
Terminal rate	2/34 (6%)	1/39 (3%)	0/10 (0%)	1/24 (4%)
First incidence (days)	682	731 (T)	816	737
Life table test		P=0.269N		P=0.343
Logistic regression test		P=0.309N		P=0.204
Fisher exact test		P=0.316N		P=0.187
All Organs: Benign Neoplasms				
Overall rate	49/51 (96%)	48/50 (96%)	46/49 (94%)	46/50 (92%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	34/34 (100%)	39/39 (100%)	10/10 (100%)	24/24 (100%)
First incidence (days)	520	210	445	430
Life table test		P=0.157N		P=0.002N
Logistic regression test		P=0.112		P=0.654N
Fisher exact test		P=0.684N		P=0.511N

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	18/51 (35%)	9/50 (18%)	34/49 (69%)	23/50 (46%)
Adjusted rate	61.8%	29.3%	85.3%	56.4%
Terminal rate	7/34 (21%)	8/39 (21%)	5/10 (50%)	8/24 (33%)
First incidence (days)	520	674	556	199
Life table test		P=0.031N		P<0.001N
Logistic regression test		P=0.045N		P=0.012N
Fisher exact test		P=0.040N		P=0.015N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/51 (96%)	48/50 (96%)	46/49 (94%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	34/34 (100%)	39/39 (100%)	10/10 (100%)	24/24 (100%)
First incidence (days)	520	210	445	199
Life table test		P=0.157N		P=0.004N
Logistic regression test		P=0.112		P=0.206
Fisher exact test		P=0.684N		P=0.490

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, heart, liver, lung, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in a dosed group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE E3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
Disposition Summary			
Animals initially in study	70[b]	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths	1	2	2
Moribund	13	16	15
Natural deaths	1	1	10
Survivors			
Terminal sacrifice	35	31	23
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Intestine large, colon	(10)	(10)	(10)
Parasite metazoan		1 (10%)	1 (10%)
Intestine large, rectum	(10)	(10)	(10)
Parasite metazoan	1 (10%)	2 (20%)	
Liver	(10)	(10)	(10)
Basophilic focus	2 (20%)	3 (30%)	
Clear cell focus	5 (50%)	2 (20%)	3 (30%)
Eosinophilic focus		1 (10%)	
Granuloma	2 (20%)	3 (30%)	
Hepatodiaphragmatic nodule			1 (10%)
Inflammation, chronic	1 (10%)	1 (10%)	1 (10%)
Mixed cell focus	2 (20%)	2 (20%)	3 (30%)
Bile duct, hyperplasia	8 (80%)	5 (50%)	3 (30%)
Hepatocyte, vacuolization cytoplasmic	8 (80%)	5 (50%)	
Lobules, necrosis			1 (10%)
Mesentery	(2)	(3)	(2)
Fat, hemorrhage	1 (50%)		
Fat, metaplasia, osseous		1 (33%)	
Fat, necrosis	1 (50%)	2 (67%)	2 (100%)
Pancreas	(10)	(10)	(10)
Atrophy	3 (30%)	5 (50%)	5 (50%)
Acinar cell, hyperplasia, focal	2 (20%)	3 (30%)	3 (30%)
Cardiovascular System			
Heart	(10)	(10)	(10)
Cardiomyopathy	6 (60%)	3 (30%)	3 (30%)
Pericardium, fibrosis			1 (10%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Ten control animals were examined at 6 months for comparisons with a stop-exposure group that was not included in the dietary restriction study.

TABLE E3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
15-Month Interim Evaluation (continued)			
Endocrine System			
Adrenal cortex	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)	2 (20%)	5 (50%)
Degeneration, fatty			1 (10%)
Hyperplasia, focal	1 (10%)		
Islets, pancreatic	(10)	(10)	(10)
Hyperplasia		1 (10%)	
Pituitary gland	(10)	(10)	(10)
Pars distalis, angiectasis	1 (10%)		
Pars distalis, cyst	1 (10%)	1 (10%)	4 (40%)
Pars distalis, hyperplasia, focal	3 (30%)		1 (10%)
Thyroid gland	(10)	(10)	(10)
C-cell, hyperplasia			1 (10%)
Follicle, cyst	1 (10%)	1 (10%)	1 (10%)
Follicular cell, hypertrophy			2 (20%)
Genital System			
Epididymis	(10)	(10)	(10)
Atypia cellular		1 (10%)	3 (30%)
Preputial gland	(10)	(10)	(10)
Inflammation, chronic	8 (80%)	8 (80%)	6 (60%)
Inflammation, suppurative	2 (20%)	2 (20%)	
Prostate	(10)	(10)	(10)
Corpora amylacea	2 (20%)	1 (10%)	2 (20%)
Edema			1 (10%)
Inflammation, suppurative	6 (60%)	5 (50%)	3 (30%)
Testes	(10)	(10)	(10)
Interstitial cell, hyperplasia	4 (40%)	4 (40%)	1 (10%)
Hematopoietic System			
Lymph node		(1)	
Mediastinal, hemorrhage		1 (100%)	
Lymph node, mandibular	(10)	(10)	(10)
Hemorrhage	3 (30%)		2 (20%)
Pigmentation	1 (10%)		
Lymph node, mesenteric	(10)	(10)	(10)
Hemorrhage			1 (10%)
Hyperplasia, lymphoid	1 (10%)		
Pigmentation		1 (10%)	
Spleen	(10)	(10)	(10)
Hematopoietic cell proliferation	1 (10%)	3 (30%)	2 (20%)
Pigmentation, hemosiderin	2 (20%)		4 (40%)
Thymus	(9)	(10)	(10)
Hemorrhage	1 (11%)		
Integumentary System			
Mammary gland	(9)	(8)	(10)
Hyperplasia, cystic	1 (11%)	1 (13%)	

TABLE E3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
15-Month Interim Evaluation (continued)			
Respiratory System			
Lung	(10)	(10)	(10)
Hemorrhage		1 (10%)	
Infiltration cellular, histiocyte		2 (20%)	2 (20%)
Inflammation, subacute		5 (50%)	2 (20%)
Alveolar epithelium, hyperplasia		3 (30%)	1 (10%)
Nose	(10)	(10)	(10)
Exudate		2 (20%)	1 (10%)
Foreign body		1 (10%)	
Urinary System			
Kidney	(10)	(10)	(10)
Mineralization		2 (20%)	
Nephropathy	10 (100%)	10 (100%)	10 (100%)
Renal tubule, dilatation	1 (10%)		2 (20%)
Transitional epithelium, hyperplasia			1 (10%)
Systems Examined With No Lesions Observed			
General Body System			
Musculoskeletal System			
Nervous System			
Special Senses System			
2-Year Study			
Alimentary System			
Esophagus	(50)	(49)	(49)
Perforation		1 (2%)	1 (2%)
Intestine large, colon	(49)	(50)	(48)
Inflammation, subacute			1 (2%)
Parasite metazoan	7 (14%)	5 (10%)	5 (10%)
Intestine large, rectum	(50)	(50)	(49)
Parasite metazoan	10 (20%)	6 (12%)	5 (10%)
Ulcer			1 (2%)
Intestine large, cecum	(50)	(50)	(50)
Dilatation			1 (2%)
Edema		2 (4%)	
Inflammation, subacute			1 (2%)
Parasite metazoan			1 (2%)
Ulcer		1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)
Erosion			1 (2%)
Ulcer			1 (2%)
Intestine small, ileum	(49)	(50)	(50)
Inflammation, chronic active	1 (2%)		
Ulcer		2 (4%)	

TABLE E3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study (continued)			
Alimentary System (continued)			
Liver	(50)	(50)	(50)
Basophilic focus	33 (66%)	36 (72%)	20 (40%)
Clear cell focus	32 (64%)	21 (42%)	16 (32%)
Congestion	1 (2%)		
Degeneration, cystic	4 (8%)	2 (4%)	
Developmental malformation			1 (2%)
Eosinophilic focus	7 (14%)	7 (14%)	9 (18%)
Hematopoietic cell proliferation		2 (4%)	1 (2%)
Hepatodiaphragmatic nodule	5 (10%)	3 (6%)	2 (4%)
Inflammation, subacute		2 (4%)	2 (4%)
Mixed cell focus	5 (10%)	11 (22%)	2 (4%)
Bile duct, hyperplasia	45 (90%)	40 (80%)	21 (42%)
Centrilobular, atrophy	3 (6%)	4 (8%)	
Hepatocyte, vacuolization cytoplasmic	2 (4%)	3 (6%)	2 (4%)
Lobules, necrosis			1 (2%)
Mesentery	(17)	(16)	(12)
Accessory spleen		1 (6%)	1 (8%)
Fat, necrosis	14 (82%)	14 (88%)	9 (75%)
Pancreas	(50)	(50)	(50)
Atrophy	18 (36%)	17 (34%)	19 (38%)
Acinar cell, basophilic focus	1 (2%)	3 (6%)	
Acinar cell, cytoplasmic alteration	1 (2%)	2 (4%)	15 (30%)
Acinar cell, hyperplasia, focal	16 (32%)	17 (34%)	8 (16%)
Salivary glands	(50)	(50)	(50)
Atrophy			1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Edema	1 (2%)		4 (8%)
Erosion			2 (4%)
Inflammation, chronic			1 (2%)
Mineralization			1 (2%)
Perforation			1 (2%)
Ulcer	1 (2%)	1 (2%)	7 (14%)
Mucosa, hyperplasia		2 (4%)	9 (18%)
Stomach, glandular	(49)	(50)	(50)
Cyst			1 (2%)
Erosion	1 (2%)		2 (4%)
Ulcer	1 (2%)	1 (2%)	1 (2%)
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Embolus	1 (2%)		
Hypertrophy		1 (2%)	5 (10%)
Inflammation, chronic active		1 (2%)	2 (4%)
Heart	(50)	(50)	(50)
Cardiomyopathy	23 (46%)	30 (60%)	24 (48%)
Foreign body			1 (2%)
Inflammation, subacute			1 (2%)
Mineralization			2 (4%)
Pericardium, fibrosis	1 (2%)		

TABLE E3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study (continued)			
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	19 (38%)	13 (26%)	8 (16%)
Basophilic focus			1 (2%)
Congestion	1 (2%)		
Cyst	1 (2%)		
Degeneration, fatty	8 (16%)	4 (8%)	8 (16%)
Hematopoietic cell proliferation		1 (2%)	2 (4%)
Hemorrhage	2 (4%)		1 (2%)
Hyperplasia, focal	4 (8%)	3 (6%)	3 (6%)
Hypertrophy, focal	5 (10%)	2 (4%)	
Adrenal medulla	(50)	(50)	(49)
Hyperplasia	15 (30%)	14 (28%)	14 (29%)
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia		2 (4%)	1 (2%)
Parathyroid gland	(46)	(50)	(45)
Hyperplasia			1 (2%)
Pituitary gland	(50)	(48)	(49)
Congestion	1 (2%)		
Pars distalis, angiectasis	4 (8%)	4 (8%)	2 (4%)
Pars distalis, cyst	5 (10%)	6 (13%)	5 (10%)
Pars distalis, hyperplasia, focal	15 (30%)	14 (29%)	12 (24%)
Pars intermedia, angiectasis			1 (2%)
Pars intermedia, cyst	2 (4%)	1 (2%)	2 (4%)
Thyroid gland	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)	3 (6%)	1 (2%)
C-cell, hyperplasia	14 (28%)	14 (28%)	11 (22%)
Follicle, cyst	1 (2%)	1 (2%)	
Follicular cell, hyperplasia	1 (2%)		1 (2%)
Follicular cell, hypertrophy	1 (2%)		4 (8%)
General Body System			
None			
Genital System			
Epididymis	(50)	(50)	(50)
Atypia cellular	25 (50%)	32 (64%)	31 (62%)
Hypospermia	40 (80%)	33 (66%)	36 (72%)
Preputial gland	(50)	(50)	(50)
Ectasia	20 (40%)	12 (24%)	14 (28%)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic	24 (48%)	16 (32%)	9 (18%)
Inflammation, suppurative	19 (38%)	14 (28%)	17 (34%)
Prostate	(50)	(50)	(50)
Corpora amylacea	28 (56%)	22 (44%)	11 (22%)
Edema			2 (4%)
Hemorrhage			3 (6%)
Hyperplasia, lymphoid	1 (2%)		
Inflammation, suppurative	17 (34%)	27 (54%)	21 (42%)
Epithelium, hyperplasia	8 (16%)	8 (16%)	3 (6%)

TABLE E3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study (continued)			
Genital System (continued)			
Seminal vesicle	(50)	(50)	(49)
Dilatation	1 (2%)	2 (4%)	4 (8%)
Hemorrhage			2 (4%)
Inflammation, suppurative			4 (8%)
Testes	(50)	(50)	(50)
Granuloma sperm		1 (2%)	
Interstitial cell, hyperplasia	1 (2%)	7 (14%)	1 (2%)
Seminiferous tubule, atrophy		4 (8%)	2 (4%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hypercellularity	3 (6%)	3 (6%)	5 (10%)
Lymph node	(9)	(15)	(10)
Iliac, pigmentation		1 (7%)	
Mediastinal, hemorrhage	6 (67%)	6 (40%)	4 (40%)
Mediastinal, hyperplasia, lymphoid			1 (10%)
Mediastinal, pigmentation	5 (56%)	8 (53%)	5 (50%)
Pancreatic, hemorrhage		1 (7%)	
Pancreatic, hyperplasia, lymphoid		1 (7%)	
Renal, pigmentation		1 (7%)	
Lymph node, mandibular	(50)	(49)	(49)
Congestion		1 (2%)	1 (2%)
Ectasia	5 (10%)	7 (14%)	
Hemorrhage	4 (8%)	4 (8%)	3 (6%)
Hyperplasia, lymphoid	5 (10%)	5 (10%)	7 (14%)
Hyperplasia, plasma cell	1 (2%)	1 (2%)	
Pigmentation		2 (4%)	
Lymph node, mesenteric	(50)	(50)	(49)
Ectasia		2 (4%)	
Hemorrhage	3 (6%)	6 (12%)	4 (8%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Pigmentation		2 (4%)	
Spleen	(50)	(50)	(50)
Fibrosis	8 (16%)	3 (6%)	2 (4%)
Hematopoietic cell proliferation	14 (28%)	9 (18%)	23 (46%)
Hyperplasia, reticulum cell			1 (2%)
Metaplasia		1 (2%)	
Necrosis		1 (2%)	
Pigmentation, hemosiderin	14 (28%)	20 (40%)	30 (60%)
Lymphoid follicle, atrophy		1 (2%)	5 (10%)
Thymus	(47)	(50)	(49)
Hemorrhage		1 (2%)	1 (2%)
Cortex, atrophy			2 (4%)

TABLE E3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study (continued)			
Integumentary System			
Mammary gland	(48)	(50)	(49)
Hyperplasia, cystic	11 (23%)	16 (32%)	10 (20%)
Hyperplasia, lobular	2 (4%)	1 (2%)	6 (12%)
Skin	(50)	(50)	(50)
Acanthosis		2 (4%)	1 (2%)
Cyst epithelial inclusion	2 (4%)	4 (8%)	1 (2%)
Hemorrhage	1 (2%)		
Hyperkeratosis		2 (4%)	
Inflammation, chronic	1 (2%)		
Inflammation, suppurative		1 (2%)	
Musculoskeletal System			
Bone	(50)	(50)	(50)
Calvarium, osteopetrosis		1 (2%)	1 (2%)
Nervous System			
Brain	(50)	(50)	(50)
Atrophy		1 (2%)	
Compression	4 (8%)	7 (14%)	4 (8%)
Hydrocephalus	1 (2%)	5 (10%)	2 (4%)
Mineralization	1 (2%)		
Necrosis	1 (2%)		
Respiratory System			
Lung	(50)	(50)	(50)
Congestion	1 (2%)	2 (4%)	4 (8%)
Edema		2 (4%)	4 (8%)
Fibrosis			1 (2%)
Foreign body		2 (4%)	
Hemorrhage		5 (10%)	1 (2%)
Infiltration cellular, histiocyte	8 (16%)	8 (16%)	12 (24%)
Inflammation, subacute	3 (6%)	3 (6%)	3 (6%)
Inflammation, suppurative		2 (4%)	
Metaplasia, osseous			1 (2%)
Alveolar epithelium, hyperplasia	10 (20%)	7 (14%)	6 (12%)
Fat, mediastinum, necrosis	1 (2%)		
Nose	(50)	(50)	(50)
Exudate	15 (30%)	15 (30%)	14 (28%)
Foreign body	4 (8%)	7 (14%)	2 (4%)
Fungus	6 (12%)	3 (6%)	2 (4%)
Mucosa, hyperplasia	6 (12%)	8 (16%)	6 (12%)
Mucosa, metaplasia, squamous	1 (2%)	3 (6%)	1 (2%)

TABLE E3a
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	337.5 mg/kg
2-Year Study (continued)			
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Concretion			33 (66%)
Cyst	1 (2%)	1 (2%)	
Hemorrhage			1 (2%)
Hydronephrosis			28 (56%)
Infarct			1 (2%)
Inflammation, suppurative	6 (12%)	3 (6%)	6 (12%)
Mineralization	3 (6%)	6 (12%)	13 (26%)
Nephropathy	48 (96%)	50 (100%)	48 (96%)
Papilla, fibrosis			1 (2%)
Papilla, necrosis			4 (8%)
Renal tubule, dilatation		1 (2%)	11 (22%)
Renal tubule, pigmentation	2 (4%)	3 (6%)	3 (6%)
Transitional epithelium, hyperplasia	10 (20%)	5 (10%)	43 (86%)
Transitional epithelium, hyperplasia, atypical			3 (6%)
Transitional epithelium, metaplasia			1 (2%)
Ureter			(13)
Concretion			3 (23%)
Dilatation			2 (15%)
Inflammation, subacute			1 (8%)
Mucosa, hyperplasia			12 (92%)
Urethra		(1)	(5)
Concretion			1 (20%)
Inflammation, subacute			1 (20%)
Bulbourethral gland, ectasia		1 (100%)	
Lumen, concretion			2 (40%)
Mucosa, hyperplasia			1 (20%)
Mucosa, metaplasia, squamous			2 (40%)
Urinary bladder	(50)	(50)	(50)
Concretion			10 (20%)
Congestion			1 (2%)
Dilatation		1 (2%)	7 (14%)
Hemorrhage			4 (8%)
Inflammation, subacute			3 (6%)
Mucosa, hyperplasia			41 (82%)

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols[a]

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
Disposition Summary				
Animals initially in study	61	60	49	50
15-Month interim evaluation	10	10		
Early deaths				
Accidental deaths	2	2	4	2
Moribund	13	6	28	14
Natural deaths	2	3	7	10
Survivors				
Died last week of study				1
Terminal sacrifice	34	39	10	23
Animals examined microscopically	61	60	49	50
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)		
Parasite metazoan	2 (20%)			
Intestine large, rectum	(10)	(10)		
Parasite metazoan	1 (10%)			
Liver	(10)	(10)		
Basophilic focus	1 (10%)			
Clear cell focus	1 (10%)			
Congestion	1 (10%)			
Eosinophilic focus	1 (10%)	3 (30%)		
Hepatodiaphragmatic nodule		2 (20%)		
Mixed cell focus	3 (30%)	3 (30%)		
Bile duct, hyperplasia	3 (30%)			
Hepatocyte, vacuolization cytoplasmic	5 (50%)			
Kupffer cell, pigmentation	1 (10%)			
Lobules, necrosis	1 (10%)			
Mesentery	(1)	(1)		
Fibrosis	1 (100%)			
Fat, necrosis		1 (100%)		
Pancreas	(10)	(10)		
Atrophy	5 (50%)	3 (30%)		
Pigmentation	1 (10%)			
Acinar cell, cytoplasmic alteration		1 (10%)		
Acinar cell, hyperplasia, focal	2 (20%)	1 (10%)		
Stomach, forestomach	(10)	(10)		
Erosion		1 (10%)		
Mineralization		2 (20%)		
Ulcer		2 (20%)		
Mucosa, hyperplasia		1 (10%)		

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

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
15-Month Interim Evaluation (continued)				
Cardiovascular System				
Heart	(10)	(10)		
Cardiomyopathy	4 (40%)	4 (40%)		
Inflammation, subacute	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)		
Accessory adrenal cortical nodule	2 (20%)	1 (10%)		
Hyperplasia, focal		1 (10%)		
Islets, pancreatic	(10)	(10)		
Hyperplasia		1 (10%)		
Pituitary gland	(10)	(10)		
Pars distalis, hyperplasia, focal	2 (20%)	1 (10%)		
Thyroid gland	(10)	(10)		
C-cell, hyperplasia		1 (10%)		
Genital System				
Epididymis	(10)	(10)		
Atypia cellular	4 (40%)	2 (20%)		
Hypospermia	1 (10%)	1 (10%)		
Preputial gland	(10)	(10)		
Inflammation, chronic	7 (70%)	4 (40%)		
Prostate	(10)	(10)		
Corpora amylacea	2 (20%)	2 (20%)		
Inflammation, suppurative	4 (40%)	4 (40%)		
Testes	(10)	(10)		
Interstitial cell, hyperplasia	2 (20%)	6 (60%)		
Seminiferous tubule, atrophy	2 (20%)			
Hematopoietic System				
Lymph node	(2)			
Mediastinal, hemorrhage	2 (100%)			
Lymph node, mandibular	(10)	(10)		
Hemorrhage		1 (10%)		
Lymph node, mesenteric	(10)	(10)		
Hemorrhage	1 (10%)			
Spleen	(10)	(10)		
Pigmentation, hemosiderin	1 (10%)	5 (50%)		
Integumentary System				
Mammary gland	(10)	(9)		
Hyperplasia, cystic	1 (10%)			

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)		
Hemorrhage		1 (10%)		
Infiltration cellular, histiocyte	1 (10%)	1 (10%)		
Inflammation, subacute	1 (10%)			
Alveolar epithelium, hyperplasia	1 (10%)	1 (10%)		
Nose	(10)	(10)		
Exudate	1 (10%)			
Fungus	1 (10%)			
Mucosa, metaplasia, squamous	1 (10%)			
Urinary System				
Kidney	(10)	(10)		
Concretion		3 (30%)		
Nephropathy	10 (100%)	10 (100%)		
Transitional epithelium, hyperplasia		1 (10%)		
Urethra	(1)			
Bulbourethral gland, ectasia	1 (100%)			
Systems Examined With No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year and 30-Month Protocols				
Alimentary System				
Esophagus	(50)	(50)	(49)	(48)
Foreign body		1 (2%)		
Hemorrhage		1 (2%)		1 (2%)
Inflammation, granulomatous				1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)		
Intestine large, colon	(51)	(49)	(49)	(47)
Dilatation	1 (2%)		1 (2%)	
Parasite metazoan	8 (16%)	6 (12%)	2 (4%)	
Intestine large, rectum	(51)	(50)	(49)	(49)
Edema			1 (2%)	
Parasite metazoan	9 (18%)	6 (12%)	7 (14%)	2 (4%)
Ulcer		1 (2%)		

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Alimentary System (continued)				
Intestine large, cecum	(51)	(50)	(49)	(49)
Dilatation	1 (2%)		1 (2%)	
Edema	1 (2%)			1 (2%)
Hemorrhage	1 (2%)			
Parasite metazoan		2 (4%)	1 (2%)	
Ulcer			2 (4%)	
Intestine small, duodenum	(50)	(50)	(49)	(49)
Erosion			1 (2%)	
Liver	(51)	(50)	(49)	(50)
Angiectasis		1 (2%)	2 (4%)	
Basophilic focus	24 (47%)	5 (10%)	16 (33%)	11 (22%)
Clear cell focus	11 (22%)	5 (10%)		1 (2%)
Congestion	1 (2%)	1 (2%)		
Concretion			1 (2%)	
Cyst				1 (2%)
Degeneration, cystic	2 (4%)			
Developmental malformation	1 (2%)			
Eosinophilic focus	9 (18%)	15 (30%)	8 (16%)	6 (12%)
Hematopoietic cell proliferation			1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	1 (2%)	6 (12%)	4 (8%)	1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)	1 (2%)
Inflammation, subacute	1 (2%)			
Mixed cell focus	17 (33%)	1 (2%)	2 (4%)	3 (6%)
Bile duct, hyperplasia	36 (71%)	27 (54%)	35 (71%)	35 (70%)
Centrilobular, atrophy	3 (6%)		12 (24%)	4 (8%)
Centrilobular, necrosis				1 (2%)
Hepatocyte, vacuolization cytoplasmic	2 (4%)		6 (12%)	
Hepatocyte, vacuolization nuclear		1 (2%)		
Kupffer cell, hyperplasia	1 (2%)			
Kupffer cell, pigmentation	2 (4%)		7 (14%)	
Lobules, necrosis	1 (2%)		3 (6%)	1 (2%)
Mesentery	(20)	(7)	(14)	(10)
Accessory spleen		1 (14%)	1 (7%)	1 (10%)
Fat, necrosis	18 (90%)	5 (71%)	9 (64%)	4 (40%)
Pancreas	(51)	(50)	(49)	(48)
Atrophy	19 (37%)	16 (32%)	21 (43%)	17 (35%)
Metaplasia, hepatocyte			1 (2%)	
Necrosis	1 (2%)			
Acinar cell, cytoplasmic alteration	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Acinar cell, hyperplasia			1 (2%)	
Acinar cell, hyperplasia, focal	8 (16%)	3 (6%)	6 (12%)	2 (4%)
Salivary glands	(51)	(50)	(49)	(49)
Atrophy				3 (6%)
Inflammation, chronic	1 (2%)			

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Alimentary System (continued)				
Stomach, forestomach	(51)	(50)	(49)	(50)
Developmental malformation	1 (2%)			
Erosion		1 (2%)		
Inflammation, chronic	1 (2%)			
Inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Mineralization	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Ulcer		1 (2%)		2 (4%)
Mucosa, hyperplasia		4 (8%)	3 (6%)	3 (6%)
Stomach, glandular	(51)	(50)	(49)	(50)
Edema	1 (2%)		1 (2%)	1 (2%)
Erosion			1 (2%)	2 (4%)
Fibrosis			1 (2%)	
Inflammation, suppurative		1 (2%)		
Mineralization	1 (2%)			
Ulcer			1 (2%)	1 (2%)
Cardiovascular System				
Blood vessel	(51)	(50)	(48)	(50)
Hypertrophy	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)	1 (2%)
Aorta, mineralization		1 (2%)		
Heart	(51)	(50)	(49)	(49)
Cardiomyopathy	33 (65%)	23 (46%)	36 (73%)	32 (65%)
Inflammation, subacute	1 (2%)	1 (2%)		
Mineralization		1 (2%)		
Thrombosis			3 (6%)	
Endocardium, hyperplasia				1 (2%)
Endocrine System				
Adrenal cortex	(51)	(50)	(49)	(50)
Accessory adrenal cortical nodule	15 (29%)	12 (24%)	11 (22%)	15 (30%)
Angiectasis	1 (2%)		3 (6%)	3 (6%)
Atrophy			1 (2%)	
Cyst	1 (2%)			2 (4%)
Degeneration, fatty	6 (12%)	3 (6%)	2 (4%)	7 (14%)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia, focal	1 (2%)	1 (2%)	4 (8%)	
Hypertrophy, focal	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Mineralization, focal	1 (2%)			
Necrosis			1 (2%)	
Adrenal medulla	(51)	(50)	(48)	(50)
Hyperplasia	6 (12%)	3 (6%)	11 (23%)	3 (6%)
Islets, pancreatic	(51)	(50)	(49)	(48)
Hyperplasia		2 (4%)		

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Endocrine System (continued)				
Parathyroid gland	(48)	(47)	(49)	(48)
Hyperplasia		1 (2%)		
Pituitary gland	(51)	(49)	(49)	(49)
Pars distalis, angiectasis	4 (8%)	4 (8%)	1 (2%)	3 (6%)
Pars distalis, cyst	7 (14%)	5 (10%)	8 (16%)	3 (6%)
Pars distalis, hyperplasia		1 (2%)		
Pars distalis, hyperplasia, focal	9 (18%)	8 (16%)	8 (16%)	8 (16%)
Pars intermedia, angiectasis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pars intermedia, cyst	1 (2%)	4 (8%)	1 (2%)	
Thyroid gland	(50)	(50)	(49)	(49)
Ultimobranchial cyst		1 (2%)		
C-cell, hyperplasia	10 (20%)	5 (10%)	3 (6%)	9 (18%)
Follicle, cyst	2 (4%)	2 (4%)		4 (8%)
Follicle, mineralization	7 (14%)	38 (76%)		
Follicular cell, hyperplasia	3 (6%)	1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(51)	(50)	(49)	(49)
Atypia cellular	38 (75%)	33 (66%)	24 (49%)	25 (51%)
Hypospermia	35 (69%)	34 (68%)	38 (78%)	37 (76%)
Preputial gland	(51)	(50)	(49)	(49)
Ectasia	10 (20%)	8 (16%)	10 (20%)	10 (20%)
Hyperplasia	2 (4%)	2 (4%)		
Inflammation, chronic	30 (59%)	20 (40%)	18 (37%)	10 (20%)
Inflammation, suppurative	8 (16%)	11 (22%)	8 (16%)	8 (16%)
Prostate	(51)	(50)	(49)	(49)
Corpora amylacea	28 (55%)	25 (50%)	23 (47%)	11 (22%)
Edema		1 (2%)		1 (2%)
Fibrosis				1 (2%)
Hemorrhage		1 (2%)		2 (4%)
Inflammation, suppurative	27 (53%)	20 (40%)	19 (39%)	26 (53%)
Epithelium, hyperplasia	15 (29%)	10 (20%)	13 (27%)	7 (14%)
Seminal vesicle	(51)	(50)	(49)	(48)
Inflammation, suppurative		1 (2%)		3 (6%)
Testes	(51)	(50)	(49)	(49)
Interstitial cell, hyperplasia	7 (14%)	5 (10%)	3 (6%)	3 (6%)
Seminiferous tubule, atrophy	1 (2%)	2 (4%)	1 (2%)	5 (10%)

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Hematopoietic System				
Bone marrow	(51)	(50)	(49)	(50)
Hypercellularity	2 (4%)		2 (4%)	4 (8%)
Myelofibrosis			4 (8%)	1 (2%)
Lymph node	(11)	(3)	(20)	(10)
Axillary, hemorrhage				1 (10%)
Iliac, hemorrhage				1 (10%)
Iliac, hyperplasia, lymphoid				1 (10%)
Iliac, pigmentation				1 (10%)
Inguinal, hemorrhage	1 (9%)	1 (33%)	1 (5%)	
Mediastinal, embolus				1 (10%)
Mediastinal, hemorrhage	2 (18%)	2 (67%)	5 (25%)	1 (10%)
Mediastinal, hyperplasia, lymphoid	1 (9%)		1 (5%)	
Mediastinal, infiltration cellular, mast cell	1 (9%)			
Mediastinal, pigmentation	4 (36%)	1 (33%)	7 (35%)	3 (30%)
Pancreatic, ectasia			1 (5%)	
Pancreatic, hemorrhage				2 (20%)
Pancreatic, pigmentation	2 (18%)			1 (10%)
Lymph node, mandibular	(51)	(50)	(48)	(49)
Congestion				1 (2%)
Ectasia	3 (6%)	2 (4%)	1 (2%)	
Hemorrhage	3 (6%)	9 (18%)	2 (4%)	4 (8%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	7 (15%)	4 (8%)
Pigmentation	7 (14%)	6 (12%)	4 (8%)	2 (4%)
Lymph node, mesenteric	(51)	(50)	(49)	(48)
Ectasia	1 (2%)			
Hemorrhage	4 (8%)	3 (6%)	5 (10%)	7 (15%)
Hyperplasia, lymphoid	2 (4%)			1 (2%)
Pigmentation	4 (8%)		3 (6%)	
Spleen	(51)	(50)	(49)	(49)
Fibrosis	3 (6%)	1 (2%)	13 (27%)	2 (4%)
Hematopoietic cell proliferation	6 (12%)	6 (12%)	9 (18%)	13 (27%)
Hemorrhage			3 (6%)	2 (4%)
Pigmentation, hemosiderin	12 (24%)	35 (70%)	15 (31%)	33 (67%)
Lymphoid follicle, atrophy			1 (2%)	
Thymus	(47)	(48)	(44)	(40)
Cyst			1 (2%)	
Hemorrhage	1 (2%)	2 (4%)		
Cortex, atrophy		1 (2%)		

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Integumentary System				
Mammary gland	(50)	(49)	(49)	(47)
Hyperplasia, cystic	12 (24%)	7 (14%)	19 (39%)	9 (19%)
Hyperplasia, lobular			5 (10%)	4 (9%)
Skin	(51)	(50)	(49)	(50)
Acanthosis	1 (2%)		2 (4%)	5 (10%)
Angiectasis				1 (2%)
Cyst epithelial inclusion	1 (2%)	1 (2%)	1 (2%)	
Hemorrhage		1 (2%)	1 (2%)	
Hyperkeratosis	1 (2%)		4 (8%)	8 (16%)
Inflammation, chronic	1 (2%)			1 (2%)
Inflammation, suppurative				2 (4%)
Subcutaneous tissue, edema		1 (2%)		
Musculoskeletal System				
Bone	(51)	(50)	(49)	(50)
Calvarium, osteopetrosis		1 (2%)		1 (2%)
Femur, osteopetrosis		1 (2%)	2 (4%)	1 (2%)
Skeletal muscle	(2)			
Hemorrhage	1 (50%)			
Inflammation, suppurative	1 (50%)			
Necrosis	1 (50%)			
Nervous System				
Brain	(51)	(50)	(49)	(50)
Compression	5 (10%)	2 (4%)	7 (14%)	5 (10%)
Gliosis				1 (2%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hydrocephalus	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Necrosis	2 (4%)		1 (2%)	1 (2%)
Respiratory System				
Lung	(51)	(50)	(49)	(49)
Congestion	3 (6%)	4 (8%)	4 (8%)	2 (4%)
Edema	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Embolus				1 (2%)
Fibrosis				1 (2%)
Foreign body	4 (8%)	4 (8%)	3 (6%)	1 (2%)
Hemorrhage	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Infiltration cellular, histiocyte	10 (20%)	9 (18%)	11 (22%)	18 (37%)
Inflammation, subacute	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Alveolar epithelium, hyperplasia	5 (10%)	5 (10%)	4 (8%)	3 (6%)

TABLE E3b
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols (continued)

	2-Year Restricted Feed		30-Month Restricted Feed	
	Vehicle Control	337.5 mg/kg	Vehicle Control	337.5 mg/kg
2-Year and 30-Month Protocols (continued)				
Respiratory System (continued)				
Nose	(51)	(50)	(49)	(50)
Exudate	14 (27%)	10 (20%)	8 (16%)	17 (34%)
Foreign body	6 (12%)	2 (4%)	2 (4%)	3 (6%)
Fungus	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Mucosa, hyperplasia	3 (6%)	4 (8%)	1 (2%)	5 (10%)
Mucosa, metaplasia, squamous	2 (4%)	1 (2%)		1 (2%)
Trachea			(49)	(49)
Erosion			1 (2%)	
Special Senses System				
Ear			(1)	(1)
Hyperplasia, focal				1 (100%)
Eye	(1)	(2)	(4)	(2)
Cataract	1 (100%)	1 (50%)	3 (75%)	1 (50%)
Hemorrhage			1 (25%)	
Inflammation, suppurative			1 (25%)	1 (50%)
Phthisis bulbi		1 (50%)		
Retina, atrophy	1 (100%)	1 (50%)	2 (50%)	
Zymbal's gland			(2)	
Cyst			1 (50%)	
Urinary System				
Kidney	(51)	(50)	(49)	(50)
Concretion		22 (44%)		35 (70%)
Cyst		1 (2%)		1 (2%)
Fibrosis	1 (2%)			
Hemorrhage		1 (2%)		
Hydronephrosis		1 (2%)	1 (2%)	2 (4%)
Infarct			1 (2%)	
Inflammation, suppurative				3 (6%)
Mineralization	2 (4%)	11 (22%)	4 (8%)	7 (14%)
Nephropathy	44 (86%)	46 (92%)	39 (80%)	48 (96%)
Papilla, necrosis		1 (2%)		1 (2%)
Renal tubule, cytoplasmic alteration			1 (2%)	1 (2%)
Renal tubule, dilatation		1 (2%)	1 (2%)	3 (6%)
Renal tubule, necrosis	1 (2%)		2 (4%)	
Renal tubule, pigmentation	2 (4%)		2 (4%)	6 (12%)
Transitional epithelium, hyperplasia	3 (6%)	18 (36%)	1 (2%)	37 (74%)
Ureter				(1)
Mucosa, hyperplasia				1 (100%)
Urethra			(2)	(2)
Metaplasia, squamous			1 (50%)	2 (100%)
Urinary bladder	(51)	(50)	(49)	(49)
Concretion				1 (2%)
Dilatation				2 (4%)
Hemorrhage			1 (2%)	2 (4%)
Inflammation, suppurative		1 (2%)		2 (4%)
Mucosa, hyperplasia		7 (14%)		8 (16%)

APPENDIX F
SUMMARY OF LESIONS IN MALE MICE IN THE DIETARY RESTRICTION STUDY OF SALICYLAZOSULFAPYRIDINE

TABLE F1a
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths	2	1	
Moribund	5	3	4
Natural deaths	3	1	
Survivors			
Terminal sacrifice	40	45	46
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Hepatocellular adenoma	2 (20%)	1 (10%)	2 (20%)
Stomach, forestomach	(10)	(10)	(10)
Squamous cell papilloma	1 (10%)		
Respiratory System			
Lung	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)		
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
Endocrine System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Special Senses System			
Urinary System			

TABLE F1a
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocol (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
2-Year Study			
Alimentary System			
Intestine large, cecum	(47)	(50)	(50)
Adenocarcinoma			1 (2%)
Intestine small, jejunum	(47)	(50)	(50)
Intestine small, ileum	(47)		(50)
Liver	(50)	(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma	2 (4%)		
Hepatocellular carcinoma	12 (24%)	6 (12%)	8 (16%)
Hepatocellular carcinoma, multiple	1 (2%)		
Hepatocellular adenoma	12 (24%)	8 (16%)	15 (30%)
Hepatocellular adenoma, multiple	1 (2%)		27 (54%)
Mesentery	(4)	(2)	(1)
Pancreas	(50)	(50)	(50)
Carcinoma, metastatic, lung	1 (2%)		
Acinus, adenoma	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Squamous cell papilloma	3 (6%)	5 (10%)	
Stomach, glandular	(50)	(50)	(50)
Adenoma			1 (2%)
Cardiovascular System			
None			
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Carcinoma, metastatic, lung	1 (2%)		
Capsule, adenoma	1 (2%)		
Adrenal medulla	(50)	(50)	(50)
Carcinoma, metastatic, lung	1 (2%)		
Islets, pancreatic	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)
Pituitary gland	(44)	(46)	(47)
Pars distalis, adenoma	1 (2%)		
Pars intermedia, carcinoma	1 (2%)		
Thyroid gland	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)	2 (4%)	1 (2%)
Follicular cell, carcinoma			1 (2%)
General Body System			
None			
Genital System			
Preputial gland	(49)	(50)	(50)
Adenoma			1 (2%)
Prostate	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)

TABLE F1a
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocol (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
2-Year Study (continued)			
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Lymph node	(3)	(1)	(4)
Lymph node, mandibular	(50)	(49)	(49)
Lymph node, mesenteric	(50)	(48)	(50)
Hemangiosarcoma			1 (2%)
Spleen	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)
Thymus	(45)	(46)	(46)
Carcinoma, metastatic, lung	1 (2%)		
Integumentary System			
Skin	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma		1 (2%)	
Subcutaneous tissue, hemangiosarcoma	1 (2%)		
Subcutaneous tissue, plasma cell tumor benign			1 (2%)
Musculoskeletal System			
Skeletal muscle		(1)	
Hemangiosarcoma		1 (100%)	
Nervous System			
Brain	(50)	(50)	(50)
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	9 (18%)	6 (12%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)		2 (4%)
Alveolar/bronchiolar carcinoma	3 (6%)	4 (8%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)
Carcinoma, metastatic, tissue NOS			1 (2%)
Hepatocellular carcinoma, metastatic, liver	4 (8%)	1 (2%)	
Special Senses System			
Harderian gland	(3)	(3)	(2)
Adenoma	2 (67%)		2 (100%)
Carcinoma	1 (33%)	2 (67%)	
Urinary System			
Kidney	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(50)
Hemangioma			1 (2%)

TABLE F1a
Summmary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocol (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
2-Year Study (continued)			
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Lymphoma malignant	5 (10%)	2 (4%)	1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Neoplasm Summary			
Total animals with primary neoplasms[c]			
15-Month interim evaluation	4	1	2
2-Year study	40	30	45
Total primary neoplasms			
15-Month interim evaluation	4	1	2
2-Year study	62	38	75
Total animals with benign neoplasms			
15-Month interim evaluation	4	1	2
2-Year study	26	19	43
Total benign neoplasms			
15-Month interim evaluation	4	1	2
2-Year study	35	21	56
Total animals with malignant neoplasms			
2-Year study	25	16	14
Total malignant neoplasms			
2-Year study	27	17	19
Total animals with metastatic neoplasms			
2-Year study	5	1	1
Total metastatic neoplasms			
2-Year study	8	1	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 F1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols[a]

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
Disposition summary				
Animals initially in study	62	60	48	50
15-Month interim evaluation	8	9		
Accidental deaths[b]	2	1		
Early deaths				
Moribund	6	5	21	9
Natural deaths	4	1	7	7
Survivors				
Terminal sacrifice	42	44	20	34
Animals examined microscopically	62	60	48	50
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)		
Hemangiosarcoma	1 (10%)			
Hepatocellular adenoma	1 (10%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year and 3-Year Protocols				
Alimentary System				
Esophagus	(52)	(50)	(48)	(50)
Gallbladder	(51)	(50)	(48)	(49)
Leiomyosarcoma, metastatic, stomach, glandular			1 (2%)	
Intestine large, colon	(51)	(50)	(47)	(48)
Intestine large, cecum	(51)	(50)	(47)	(47)
Lymphoid tissue, leiomyoma				1 (2%)
Intestine small, duodenum	(51)	(50)	(47)	(46)
Carcinoma, metastatic, harderian gland	1 (2%)			

TABLE F1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Alimentary System (continued)				
Intestine small, jejunum	(51)	(50)	(47)	(46)
Adenocarcinoma	1 (2%)		1 (2%)	
Carcinoma, metastatic, harderian gland	1 (2%)			
Intestine small, ileum	(51)	(50)	(47)	(47)
Liver	(52)	(50)	(48)	(50)
Carcinoid tumor malignant, metastatic, stomach, glandular			1 (2%)	
Hemangiosarcoma			2 (4%)	
Hepatocellular carcinoma	6 (12%)	1 (2%)	13 (27%)	6 (12%)
Hepatocellular carcinoma, multiple	1 (2%)		3 (6%)	
Hepatocellular adenoma	13 (25%)	9 (18%)	9 (19%)	9 (18%)
Hepatocellular adenoma, multiple			1 (2%)	5 (10%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Mast cell tumor NOS		1 (2%)		
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Mesentery	(6)	(2)	(7)	(2)
Carcinoma, metastatic, kidney			1 (14%)	
Leiomyosarcoma, metastatic, stomach, glandular			1 (14%)	
Fat, hemangioma				1 (50%)
Fat, sarcoma	1 (17%)			
Pancreas	(52)	(50)	(48)	(50)
Carcinoma, metastatic, kidney			1 (2%)	
Leiomyosarcoma, metastatic, stomach, glandular			1 (2%)	
Salivary glands	(52)	(50)	(48)	(49)
Stomach, forestomach	(52)	(50)	(47)	(48)
Mast cell tumor NOS		1 (2%)		
Leiomyosarcoma, metastatic, stomach, glandular			1 (2%)	
Squamous cell papilloma	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Stomach, glandular	(52)	(50)	(47)	(48)
Adenoma			1 (2%)	1 (2%)
Carcinoid tumor malignant			1 (2%)	
Carcinoma			1 (2%)	
Leiomyosarcoma			1 (2%)	
Mast cell tumor NOS		1 (2%)		
Cardiovascular System				
Heart	(52)	(50)	(48)	(50)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			

TABLE F1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Endocrine System				
Adrenal cortex	(52)	(50)	(47)	(50)
Leiomyosarcoma, metastatic, stomach, glandular			1 (2%)	
Spindle cell, adenoma			1 (2%)	
Adrenal medulla	(52)	(50)	(47)	(49)
Pheochromocytoma benign				1 (2%)
Islets, pancreatic	(52)	(50)	(48)	(50)
Adenoma			1 (2%)	1 (2%)
Pituitary gland	(48)	(47)	(44)	(48)
Pars distalis, adenoma			1 (2%)	1 (2%)
Thyroid gland	(52)	(50)	(47)	(49)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(52)	(50)	(48)	(50)
Preputial gland	(51)	(50)	(48)	(50)
Prostate	(52)	(50)	(48)	(50)
Seminal vesicle	(52)	(50)	(48)	(50)
Testes	(52)	(50)	(48)	(50)
Interstitial cell, adenoma			1 (2%)	
Hematopoietic System				
Bone marrow	(52)	(50)	(48)	(50)
Mast cell tumor NOS		1 (2%)		
Lymph node	(4)	(2)	(15)	(17)
Mediastinal, carcinoma, metastatic, kidney			1 (7%)	
Mediastinal, carcinoma, metastatic, harderian gland	1 (25%)			
Renal, leiomyosarcoma, metastatic, stomach, glandular			1 (7%)	
Lymph node, mandibular	(51)	(50)	(47)	(49)
Carcinoma, metastatic, kidney	1 (2%)			
Carcinoma, metastatic, harderian gland			1 (2%)	
Lymph node, mesenteric	(52)	(50)	(48)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Spleen	(52)	(50)	(48)	(50)
Hemangioma				1 (2%)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma		1 (2%)	1 (2%)	
Thymus	(51)	(46)	(41)	(42)
Carcinoma, metastatic, harderian gland	1 (2%)			
Carcinoma, metastatic, kidney			1 (2%)	

TABLE F1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Integumentary System				
Skin	(52)	(50)	(48)	(50)
Subcutaneous tissue, carcinoma, metastatic, harderian gland	1 (2%)			
Subcutaneous tissue, hemangioma			1 (2%)	
Subcutaneous tissue, lipoma			1 (2%)	
Musculoskeletal System				
Bone	(52)	(50)	(48)	(50)
Rib, carcinoma, metastatic, harderian gland	1 (2%)			
Skeletal muscle	(2)		(1)	
Carcinoma, metastatic, harderian gland	1 (50%)			
Hemangiosarcoma			1 (100%)	
Osteosarcoma, metastatic, uncertain primary site	1 (50%)			
Nervous System				
None				
Respiratory System				
Lung	(52)	(50)	(48)	(50)
Alveolar/bronchiolar adenoma	10 (19%)	3 (6%)	8 (17%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)		13 (27%)	6 (12%)
Carcinoma, metastatic, harderian gland			2 (4%)	
Carcinoma, metastatic, kidney			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)		2 (4%)	
Histiocytic sarcoma		1 (2%)	1 (2%)	
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Mediastinum, carcinoma, metastatic, harderian gland	1 (2%)			
Nose	(52)	(50)	(48)	(50)
Glands, carcinoma, metastatic, harderian gland	1 (2%)			
Special Senses System				
Harderian gland	(3)	(3)	(8)	(1)
Adenoma	2 (67%)	3 (100%)	6 (75%)	1 (100%)
Carcinoma	1 (33%)		2 (25%)	
Zymbal's gland			(1)	
Carcinoma			1 (100%)	

TABLE F1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Urinary System				
Kidney	(52)	(50)	(48)	(50)
Leiomyosarcoma, metastatic, stomach, glandular			1 (2%)	
Cortex, adenoma			1 (2%)	
Cortex, carcinoma	1 (2%)	1 (2%)	1 (2%)	
Cortex, carcinoma, metastatic, harderian gland	1 (2%)			
Urinary bladder	(52)	(50)	(48)	(50)
Systemic Lesions				
Multiple organs[c]	(52)	(50)	(48)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymphoma malignant	6 (12%)	3 (6%)	5 (10%)	9 (18%)

TABLE F1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	2			
2-Year and 3-year protocols	37	20	42	34
Total primary neoplasms				
15-Month interim evaluation	2			
2-Year and 3-year protocols	49	28	81	52
Total animals with benign neoplasms				
15-Month interim evaluation	1			
2-Year and 3-year protocols	26	16	27	25
Total benign neoplasms				
15-Month interim evaluation	1			
2-Year and 3-year protocols	29	18	35	31
Total animals with malignant neoplasms				
15-Month interim evaluation	1			
2-Year and 3-year protocols	18	6	36	19
Total malignant neoplasms				
15-Month interim evaluation	1			
2-Year and 3-year protocols	20	6	46	21
Total animals with metastatic neoplasms				
2-Year and 3-year protocols	4		7	
Total metastatic neoplasms				
2-Year and 3-year protocols	16		18	
Total animals with malignant neoplasms of uncertain primary site				
2-Year protocol	1			
Total animals with uncertain neoplasms-benign or malignant				
2-Year protocol		1		
Total uncertain neoplasms				
2-Year protocol		4		

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Three animals that died in dosing accidents before the interim evaluation were included in the interim evaluation data
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE F2a
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	2,700 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	2,700 mg/kg × Weight-Matched Control
Harderian Gland: Adenoma or Carcinoma				
Overall rate[a]	3/50 (6%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate[b]	7.5%	4.3%		
Terminal rate[c]	3/40 (8%)	2/46 (4%)		
First incidence (days)	728 (T)	728 (T)		
Life table test[d]		P=0.436N		
Logistic regression test[d]		P=0.436N		
Fisher exact test[d]		P=0.500N		
Liver: Hepatocellular Adenoma				
Overall rate	13/50 (26%)	42/50 (84%)	8/50 (16%)	42/50 (84%)
Adjusted rate	32.5%	87.5%	17.8%	87.5%
Terminal rate	13/40 (33%)	40/46 (87%)	8/45 (18%)	40/46 (87%)
First incidence (days)	728 (T)	497	728 (T)	497
Life table test		P<0.001		P<0.001
Logistic regression test		P<0.001		P<0.001
Fisher exact test		P<0.001		P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	13/50 (26%)	8/50 (16%)	6/50 (12%)	8/50 (16%)
Adjusted rate	29.2%	17.4%	12.9%	17.4%
Terminal rate	9/40 (23%)	8/46 (17%)	5/45 (11%)	8/46 (17%)
First incidence (days)	420	728 (T)	574	728 (T)
Life table test		P=0.106N		P=0.401
Logistic regression test		P=0.159N		P=0.378
Fisher exact test		P=0.163N		P=0.387
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	24/50 (48%)	44/50 (88%)	14/50 (28%)	44/50 (88%)
Adjusted rate	54.3%	91.7%	30.3%	91.7%
Terminal rate	20/40 (50%)	42/46 (91%)	13/45 (29%)	42/46 (91%)
First incidence (days)	420	497	574	497
Life table test		P=0.001		P<0.001
Logistic regression test		P<0.001		P<0.001
Fisher exact test		P<0.001		P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	11/50 (22%)	6/50 (12%)	6/50 (12%)	6/50 (12%)
Adjusted rate	27.5%	13.0%	12.6%	13.0%
Terminal rate	11/40 (28%)	6/46 (13%)	4/45 (9%)	6/46 (13%)
First incidence (days)	728 (T)	728 (T)	574	728 (T)
Life table test		P=0.081N		P=0.609N
Logistic regression test		P=0.081N		P=0.618
Fisher exact test		P=0.143N		P=0.620N

TABLE F2a
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	2,700 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	2,700 mg/kg × Weight-Matched Control
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	4/50 (8%)	5/50 (10%)
Adjusted rate	7.3%	10.9%	8.9%	10.9%
Terminal rate	2/40 (5%)	5/46 (11%)	4/45 (9%)	5/46 (11%)
First incidence (days)	689	728 (T)	728 (T)	728 (T)
Life table test		P=0.434		P=0.514
Logistic regression test		P=0.392		P=0.514
Fisher exact test		P=0.357		P=0.500
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	14/50 (28%)	11/50 (22%)	9/50 (18%)	11/50 (22%)
Adjusted rate	34.1%	23.9%	19.0%	23.9%
Terminal rate	13/40 (33%)	11/46 (24%)	7/45 (16%)	11/46 (24%)
First incidence (days)	689	728 (T)	574	728 (T)
Life table test		P=0.192N		P=0.419
Logistic regression test		P=0.218N		P=0.391
Fisher exact test		P=0.322N		P=0.402
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	3/50 (6%)	0/50 (0%)	5/50 (10%)	0/50 (0%)
Adjusted rate	7.5%	0.0%	10.8%	0.0%
Terminal rate	3/40 (8%)	0/46 (0%)	4/45 (9%)	0/46 (0%)
First incidence (days)	728 (T)	–[e]	610	–
Life table test		P=0.098N		P=0.033N
Logistic regression test		P=0.098N		P=0.033N
Fisher exact test		P=0.121N		P=0.028N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	7.5%	2.2%		
Terminal rate	3/40 (8%)	1/46 (2%)		
First incidence (days)	728 (T)	728 (T)		
Life table test		P=0.257N		
Logistic regression test		P=0.257N		
Fisher exact test		P=0.309N		
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	10.0%	4.3%		
Terminal rate	4/40 (10%)	2/46 (4%)		
First incidence (days)	728 (T)	728 (T)		
Life table test		P=0.275N		
Logistic regression test		P=0.275N		
Fisher exact test		P=0.339N		

TABLE F2a
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	2,700 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	2,700 mg/kg × Weight-Matched Control
All Organs: Malignant Lymphoma (Lymphocytic or Unspecified)				
Overall rate	5/50 (10%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	12.1%	4.3%		
Terminal rate	4/40 (10%)	2/46 (4%)		
First incidence (days)	666	728 (T)		
Life table test		P=0.169N		
Logistic regression test		P=0.198N		
Fisher exact test		P=0.218N		
All Organs: Benign Neoplasms				
Overall rate	26/50 (52%)	43/50 (86%)	19/50 (38%)	43/50 (86%)
Adjusted rate	65.0%	89.6%	39.5%	89.6%
Terminal rate	26/40 (65%)	41/46 (89%)	16/45 (36%)	41/46 (89%)
First incidence (days)	728 (T)	497	574	497
Life table test		P=0.003		P<0.001
Logistic regression test		P<0.001		P<0.001
Fisher exact test		P<0.001		P<0.001
All Organs: Malignant Neoplasms				
Overall rate	25/50 (50%)	15/50 (30%)	16/50 (32%)	15/50 (30%)
Adjusted rate	53.2%	32.6%	33.3%	32.6%
Terminal rate	18/40 (45%)	15/46 (33%)	13/45 (29%)	15/46 (33%)
First incidence (days)	420	728 (T)	574	728 (T)
Life table test		P=0.014N		P=0.476N
Logistic regression test		P=0.028N		P=0.515N
Fisher exact test		P=0.033N		P=0.500N
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/50 (80%)	45/50 (90%)	30/50 (60%)	45/50 (90%)
Adjusted rate	85.1%	93.8%	61.2%	93.8%
Terminal rate	33/40 (83%)	43/46 (93%)	26/45 (58%)	43/46 (93%)
First incidence (days)	420	497	574	497
Life table test		P=0.543N		P=0.003
Logistic regression test		P=0.137		P<0.001
Fisher exact test		P=0.131		P<0.001

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and stomach; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the *ad libitum*-fed or weight-matched controls and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the dosed group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE F2b
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	2/52 (4%)	3/50 (6%)	6/48 (13%)	1/50 (2%)
Adjusted rate[b]	4.5%	8.6%	28.6%	2.8%
Terminal rate[c]	1/42 (2%)	3/44 (7%)	5/20 (25%)	0/34 (0%)
First incidence (days)	660	730 (T)	1,079	1,076
Life table test[d]		P=0.511		P=0.010N
Logistic regression test[d]		P=0.479		P=0.008N
Fisher exact test[d]		P=0.481		P=0.050N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/52 (6%)	3/50 (6%)	8/48 (17%)	1/50 (2%)
Adjusted rate	6.7%	8.6%	32.3%	2.8%
Terminal rate	1/42 (2%)	3/44 (7%)	5/20 (25%)	0/34 (0%)
First incidence (days)	660	730 (T)	750	1,076
Life table test		P=0.649N		P=0.003N
Logistic regression test		P=0.641		P=0.007N
Fisher exact test		P=0.642		P=0.013N
Liver: Hepatocellular Adenoma				
Overall rate	13/52 (25%)	9/50 (18%)	10/48 (21%)	14/50 (28%)
Adjusted rate	34.6%	22.7%	35.0%	38.6%
Terminal rate	10/42 (24%)	8/44 (18%)	5/20 (25%)	12/34 (35%)
First incidence (days)	616	648	555	933
Life table test		P=0.217N		P=0.468N
Logistic regression test		P=0.274N		P=0.398
Fisher exact test		P=0.269N		P=0.278
Liver: Hepatocellular Carcinoma				
Overall rate	7/52 (13%)	1/50 (2%)	16/48 (33%)	6/50 (12%)
Adjusted rate	14.9%	2.3%	42.2%	15.5%
Terminal rate	4/42 (10%)	1/44 (2%)	3/20 (15%)	3/34 (9%)
First incidence (days)	495	729 (T)	445	726
Life table test		P=0.036N		P=0.003N
Logistic regression test		P=0.025N		P=0.020N
Fisher exact test		P=0.034N		P=0.011N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	18/52 (35%)	9/50 (18%)	21/48 (44%)	18/50 (36%)
Adjusted rate	42.2%	22.7%	55.5%	47.0%
Terminal rate	12/42 (29%)	8/44 (18%)	6/20 (30%)	14/34 (41%)
First incidence (days)	495	648	445	726
Life table test		P=0.040N		P=0.042N
Logistic regression test		P=0.044N		P=0.292N
Fisher exact test		P=0.046N		P=0.282N

TABLE F2b
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	11/52 (21%)	3/50 (6%)	8/48 (17%)	7/50 (14%)
Adjusted rate	53.2%	7.9%	33.1%	18.6%
Terminal rate	9/42 (21%)	3/44 (7%)	5/20 (25%)	5/34 (15%)
First incidence (days)	717	729 (T)	862	719
Life table test		P=0.020N		P=0.171N
Logistic regression test		P=0.023N		P=0.335N
Fisher exact test		P=0.025N		P=0.465N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/52 (4%)	0/50 (0%)	13/48 (27%)	6/50 (12%)
Adjusted rate			38.4%	17.1%
Terminal rate			3/20 (15%)	5/34 (15%)
First incidence (days)			718	1,076
Life table test				P=0.010N
Logistic regression test				P=0.049N
Fisher exact test				P=0.051N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/52 (25%)	3/50 (6%)	18/48 (38%)	12/50 (24%)
Adjusted rate	63.4%	7.9%	55.2%	31.8%
Terminal rate	10/42 (24%)	3/44 (7%)	7/20 (35%)	9/34 (26%)
First incidence (days)	661	729 (T)	718	719
Life table test		P=0.007N		P=0.011N
Logistic regression test		P=0.009N		P=0.075N
Fisher exact test		P=0.008N		P=0.109N
All Organs: Hemangiosarcoma				
Overall rate	1/52 (2%)	0/50 (0%)	3/48 (6%)	0/50 (0%)
Adjusted rate			12.0%	0.0%
Terminal rate			2/20 (10%)	0/34 (0%)
First incidence (days)			569	-
Life table test				P=0.066N
Logistic regression test				P=0.123N
Fisher exact test				P=0.114N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/52 (2%)	0/50 (0%)	4/48 (8%)	2/50 (4%)
Adjusted rate			16.8%	5.3%
Terminal rate			3/20 (15%)	1/34 (3%)
First incidence (days)			569	933
Life table test				P=0.167N
Logistic regression test				P=0.308N
Fisher exact test				P=0.319N

TABLE F2b
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
All Organs: Unspecified Malignant Lymphoma				
Overall rate	6/52 (12%)	3/50 (6%)	5/48 (10%)	9/50 (18%)
Adjusted rate	13.4%	6.9%	20.1%	21.1%
Terminal rate	4/42 (10%)	1/44 (2%)	2/20 (10%)	3/34 (9%)
First incidence (days)	647	214	921	314
Life table test		P=0.245N		P=0.501
Logistic regression test		P=0.183N		P=0.201
Fisher exact test		P=0.264N		P=0.217
All Organs: Benign Neoplasms				
Overall rate	26/52 (50%)	16/50 (32%)	27/48 (56%)	25/50 (50%)
Adjusted rate	81.1%	40.1%	83.2%	65.5%
Terminal rate	22/42 (52%)	15/44 (34%)	15/20 (75%)	21/34 (62%)
First incidence (days)	616	648	555	719
Life table test		P=0.029N		P=0.007N
Logistic regression test		P=0.049N		P=0.110N
Fisher exact test		P=0.050N		P=0.338N
All Organs: Malignant Neoplasms				
Overall rate	19/52 (37%)	6/50 (12%)	36/48 (75%)	19/50 (38%)
Adjusted rate	42.9%	13.5%	79.2%	42.7%
Terminal rate	11/42 (26%)	3/44 (7%)	11/20 (55%)	9/34 (26%)
First incidence (days)	495	214	445	314
Life table test		P=0.006N		P<0.001N
Logistic regression test		P=0.002N		P=0.008N
Fisher exact test		P=0.004N		P<0.001N
All Organs: Benign or Malignant Neoplasms				
Overall rate	37/52 (71%)	20/50 (40%)	42/48 (88%)	34/50 (68%)
Adjusted rate	90.8%	46.2%	93.1%	77.1%
Terminal rate	28/42 (67%)	16/44 (36%)	17/20 (85%)	24/34 (71%)
First incidence (days)	495	214	445	314
Life table test		P=0.002N		P<0.001N
Logistic regression test		P=0.001N		P=0.015N
Fisher exact test		P=0.001N		P=0.018N

(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] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in a dosed group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE F3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths	2	1	
Moribund	5	3	4
Natural deaths	3	1	
Survivors			
Terminal sacrifice	40	45	46
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Clear cell focus	1 (10%)		
Cytologic alterations			10 (100%)
Eosinophilic focus			1 (10%)
Hematopoietic cell proliferation			1 (10%)
Vacuolization cytoplasmic	10 (100%)		
Salivary glands	(10)	(10)	(10)
Vacuolization cytoplasmic			1 (10%)
Submandibular gland, depletion secretory			1 (10%)
Stomach, forestomach	(10)	(10)	(10)
Hyperplasia		3 (30%)	
Inflammation, subacute		2 (20%)	
Stomach, glandular	(10)	(10)	(10)
Erosion	1 (10%)		
Endocrine System			
Adrenal cortex	(10)	(10)	(10)
Hypertrophy	1 (10%)	1 (10%)	1 (10%)
Capsule, hyperplasia			1 (10%)
Parathyroid gland	(10)	(10)	(10)
Cyst			1 (10%)
Thyroid gland	(10)	(10)	(10)
Follicle, degeneration	1 (10%)		1 (10%)
Genital System			
Preputial gland	(10)	(10)	(10)
Duct, cyst	4 (40%)	8 (80%)	7 (70%)

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

TABLE F3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
15-Month Interim Evaluation (continued)			
Hematopoietic System			
Lymph node, mesenteric	(10)	(10)	(10)
Angiectasis			1 (10%)
Spleen	(10)	(10)	(10)
Hematopoietic cell proliferation	2 (20%)		10 (100%)
Pigmentation, hemosiderin			10 (100%)
Thymus	(9)	(10)	(10)
Cyst			1 (10%)
Respiratory System			
Lung	(10)	(10)	(10)
Alveolus, infiltration cellular, histiocyte	1 (10%)	1 (10%)	1 (10%)
Mediastinum, hemorrhage		1 (10%)	
Nose	(10)	(10)	(10)
Olfactory epithelium, degeneration	1 (10%)		2 (20%)
Urinary System			
Kidney	(10)	(10)	(10)
Mineralization	8 (80%)	6 (60%)	2 (20%)
Renal tubule, casts	1 (10%)	2 (20%)	1 (10%)
Renal tubule, regeneration	7 (70%)	5 (50%)	4 (40%)
Systems Examined With No Lesions Observed			
Cardiovascular System			
General Body System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Special Senses System			
2-Year Study			
Alimentary System			
Esophagus	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Intestine large, cecum	(47)	(50)	(50)
Parasite metazoan	1 (2%)		
Intestine small, duodenum	(47)	(50)	(50)
Dilatation			1 (2%)
Intestine small, jejunum	(47)	(50)	(50)
Hyperplasia, glandular		1 (2%)	
Intestine small, ileum	(47)	(50)	(50)
Inflammation, chronic			1 (2%)
Peyer's patch, hyperplasia, lymphoid		1 (2%)	

TABLE F3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
2-Year Study (continued)			
Alimentary System (continued)			
Liver	(50)	(50)	(50)
Angiectasis		1 (2%)	
Basophilic focus	1 (2%)		
Clear cell focus	2 (4%)	2 (4%)	8 (16%)
Clear cell focus, multiple			3 (6%)
Eosinophilic focus	5 (10%)	1 (2%)	13 (26%)
Eosinophilic focus, multiple	1 (2%)		9 (18%)
Fatty change, focal	1 (2%)		
Hemorrhage	1 (2%)		
Inflammation, chronic			1 (2%)
Inflammation, subacute	3 (6%)	1 (2%)	
Mineralization	2 (4%)	1 (2%)	
Mixed cell focus	2 (4%)		2 (4%)
Necrosis	3 (6%)	2 (4%)	3 (6%)
Pigmentation, bile	1 (2%)		
Vacuolization cytoplasmic	3 (6%)	7 (14%)	
Bile duct, cyst	2 (4%)		
Mesentery	(4)	(2)	(1)
Fat, inflammation, subacute		1 (50%)	
Fat, necrosis	3 (75%)	1 (50%)	1 (100%)
Pancreas	(50)	(50)	(50)
Necrosis			1 (2%)
Acinus, atrophy		1 (2%)	
Acinus, depletion secretory	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Diverticulum		1 (2%)	
Edema	1 (2%)		
Hyperplasia	18 (36%)	22 (44%)	10 (20%)
Inflammation, subacute	4 (8%)	11 (22%)	2 (4%)
Ulcer	3 (6%)	2 (4%)	
Stomach, glandular	(50)	(50)	(50)
Erosion		1 (2%)	
Hyperplasia	1 (2%)		1 (2%)
Inflammation, subacute		1 (2%)	
Mineralization	1 (2%)		7 (14%)
Pigmentation	1 (2%)		
Ulcer	1 (2%)		
Cardiovascular System			
Heart	(50)	(50)	(50)
Embolus	1 (2%)		
Mineralization	1 (2%)		

TABLE F3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
2-Year Study (continued)			
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Cyst		1 (2%)	
Embolus	1 (2%)		
Hyperplasia	8 (16%)		6 (12%)
Hypertrophy	11 (22%)	8 (16%)	12 (24%)
Vacuolization cytoplasmic	1 (2%)		
Capsule, hyperplasia	1 (2%)		4 (8%)
Adrenal medulla	(50)		(50)
Embolus	1 (2%)		
Islets, pancreatic	(50)	(50)	(50)
Embolus	1 (2%)		
Hyperplasia	2 (4%)		3 (6%)
Parathyroid gland	(48)	(48)	(49)
Cyst			1 (2%)
Pituitary gland	(44)	(46)	(47)
Pars distalis, cyst		4 (9%)	
Thyroid gland	(50)	(50)	(50)
Follicle, cyst	6 (12%)	4 (8%)	9 (18%)
Follicle, degeneration	3 (6%)	3 (6%)	3 (6%)
Follicular cell, hyperplasia	9 (18%)	1 (2%)	2 (4%)
General Body System			
None			
Genital System			
Coagulating gland	(5)		(1)
Dilatation	5 (100%)		
Inflammation, chronic			1 (100%)
Epididymis	(50)	(50)	(50)
Congestion	1 (2%)		
Granuloma sperm	1 (2%)		
Inflammation, chronic	1 (2%)		
Preputial gland	(49)	(50)	(50)
Congestion	1 (2%)		
Inflammation, subacute	2 (4%)		
Duct, cyst	45 (92%)	42 (84%)	38 (76%)
Prostate	(50)	(50)	(50)
Cyst	1 (2%)		
Hyperplasia	1 (2%)		
Inflammation, suppurative	1 (2%)		
Seminal vesicle	(50)	(50)	(50)
Atrophy	2 (4%)		2 (4%)
Dilatation	14 (28%)	1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)
Testes	(50)	(50)	(50)
Atrophy			1 (2%)
Mineralization	1 (2%)		
Interstitial cell, hyperplasia			1 (2%)

TABLE F3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
2-Year Study (continued)			
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Atrophy		2 (4%)	
Myeloid cell, hyperplasia	2 (4%)		
Lymph node	(3)	(1)	(4)
Inguinal, hyperplasia, lymphoid	1 (33%)		
Inguinal, infiltration cellular, mast cell			1 (25%)
Mediastinal, hyperplasia, lymphoid			1 (25%)
Renal, hyperplasia, lymphoid			1 (25%)
Lymph node, mandibular	(50)	(49)	(49)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Lymph node, mesenteric	(50)	(48)	(50)
Angiectasis	17 (34%)	23 (48%)	12 (24%)
Hyperplasia, lymphoid	4 (8%)	3 (6%)	3 (6%)
Spleen	(50)	(50)	(50)
Atrophy	5 (10%)		
Congestion	1 (2%)		1 (2%)
Hematopoietic cell proliferation	11 (22%)	3 (6%)	13 (26%)
Hyperplasia, lymphoid	5 (10%)	8 (16%)	7 (14%)
Pigmentation, hemosiderin	2 (4%)	1 (2%)	47 (94%)
Thymus	(45)	(46)	(46)
Atrophy	3 (7%)		1 (2%)
Cyst	2 (4%)	1 (2%)	1 (2%)
Mineralization		1 (2%)	
Thymocyte, necrosis	1 (2%)		1 (2%)
Integumentary System			
Skin	(50)	(50)	(50)
Hyperkeratosis		1 (2%)	
Subcutaneous tissue, edema		1 (2%)	
Subcutaneous tissue, inflammation, chronic	1 (2%)		
Subcutaneous tissue, metaplasia, osseous			1 (2%)
Subcutaneous tissue, mineralization	1 (2%)		
Musculoskeletal System			
Bone	(50)	(50)	(50)
Cranium, hyperostosis	2 (4%)	1 (2%)	
Nervous System			
Brain	(50)	(50)	(50)
Compression	1 (2%)		
Embolus	1 (2%)		
Hydrocephalus			1 (2%)
Pigmentation, hemosiderin		1 (2%)	
Vacuolization cytoplasmic		1 (2%)	

TABLE F3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
2-Year Study (continued)			
Respiratory System			
Lung	(50)	(50)	(50)
Congestion			1 (2%)
Hyperplasia, macrophage		1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	4 (8%)	3 (6%)	8 (16%)
Alveolus, foreign body	1 (2%)	1 (2%)	
Alveolus, hemorrhage	1 (2%)	1 (2%)	
Alveolus, infiltration cellular, histiocyte	3 (6%)		1 (2%)
Mediastinum, hemorrhage	1 (2%)		
Nose	(50)	(50)	(50)
Glands, cyst	1 (2%)	1 (2%)	
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Bacterium	1 (2%)		
Fibrosis	1 (2%)		
Glomerulosclerosis	3 (6%)		
Infarct		1 (2%)	1 (2%)
Infiltration cellular, lymphocyte	1 (2%)		
Inflammation, subacute	2 (4%)		
Metaplasia, osseous			2 (4%)
Mineralization	37 (74%)	44 (88%)	33 (66%)
Cortex, cyst	5 (10%)	4 (8%)	1 (2%)
Cortex, medulla, inflammation, suppurative	1 (2%)		
Pelvis, necrosis	1 (2%)		
Renal tubule, casts	13 (26%)	7 (14%)	3 (6%)
Renal tubule, degeneration	3 (6%)		1 (2%)
Renal tubule, regeneration	38 (76%)	41 (82%)	24 (48%)
Transitional epithelium, hyperplasia	1 (2%)		
Urinary bladder	(50)	(50)	(50)
Dilatation	1 (2%)		1 (2%)
Inflammation, subacute	1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)		

TABLE F3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols[a]

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
Disposition Summary				
Animals initially in study	62	60	48	50
15-Month interim evaluation	8	9		
Accidental deaths[b]	2	1		
Early deaths				
Moribund	6	5	21	9
Natural deaths	4	1	7	7
Survivors				
Terminal sacrifice	42	44	20	34
Animals examined microscopically	62	60	48	50
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)		
Inflammation, chronic		1 (10%)		
Liver	(10)	(10)		
Basophilic focus	1 (10%)			
Cytologic alterations		6 (60%)		
Vacuolization cytoplasmic	3 (30%)			
Mesentery	(1)			
Fat, inflammation, granulomatous	1 (100%)			
Salivary glands	(10)	(10)		
Submandibular gland, depletion secretory	1 (10%)	3 (30%)		
Submandibular gland, vacuolization cytoplasmic		4 (40%)		
Stomach, forestomach	(10)	(10)		
Hyperplasia	4 (40%)	2 (20%)		
Inflammation, subacute	4 (40%)			
Stomach, glandular	(10)	(10)		
Mineralization	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)		
Hypertrophy	1 (10%)			
Thyroid gland	(10)	(10)		
Follicle, cyst		1 (10%)		
Follicle, degeneration	1 (10%)			
Genital System				
Preputial gland	(10)	(10)		
Duct, cyst	8 (80%)	4 (40%)		

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Three animals that died in dosing accidents before the interim evaluation were included in the interim evaluation data

TABLE F3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Spleen	(10)	(10)		
Hematopoietic cell proliferation		9 (90%)		
Pigmentation, hemosiderin		10 (100%)		
Integumentary System				
Skin	(10)	(10)		
Epidermis, hyperplasia	1 (10%)			
Respiratory System				
Lung	(10)	(10)		
Hemorrhage		1 (10%)		
Urinary System				
Kidney	(10)	(10)		
Atrophy		1 (10%)		
Metaplasia, osseous	1 (10%)			
Mineralization	5 (50%)			
Cortex, cyst		1 (10%)		
Pelvis, inflammation, subacute		1 (10%)		
Renal tubule, casts	2 (20%)	4 (40%)		
Renal tubule, regeneration	4 (40%)	2 (20%)		
Urinary bladder	(10)	(10)		
Inflammation, subacute		1 (10%)		
Transitional epithelium, hyperplasia		1 (10%)		
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year and 3-Year Protocols				
Alimentary System				
Gallbladder	(51)	(50)	(48)	(49)
Dilatation				1 (2%)
Pigmentation				1 (2%)
Intestine small, jejunum	(51)	(50)	(47)	(46)
Dilatation		1 (2%)		
Peyer's patch, hyperplasia, lymphoid		2 (4%)	1 (2%)	

TABLE F3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocol (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Alimentary System (continued)				
Liver	(52)	(50)	(48)	(50)
Angiectasis	1 (2%)		1 (2%)	1 (2%)
Basophilic focus	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Clear cell focus	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Clear cell focus, multiple			1 (2%)	
Congestion			1 (2%)	
Cytologic alterations		2 (4%)		3 (6%)
Eosinophilic focus	5 (10%)	1 (2%)	4 (8%)	7 (14%)
Fibrosis				1 (2%)
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage	1 (2%)		1 (2%)	1 (2%)
Hepatodiaphragmatic nodule			1 (2%)	
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation, subacute		1 (2%)		1 (2%)
Mixed cell focus		1 (2%)	1 (2%)	
Necrosis	2 (4%)	2 (4%)	4 (8%)	
Pigmentation, bile	1 (2%)			
Pigmentation, hemosiderin		2 (4%)		1 (2%)
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	3 (6%)		1 (2%)	1 (2%)
Bile duct, cyst	1 (2%)		1 (2%)	2 (4%)
Mesentery	(6)	(2)	(7)	(2)
Fat, hemorrhage				1 (50%)
Fat, mineralization	1 (17%)			
Fat, necrosis	4 (67%)	1 (50%)	4 (57%)	
Pancreas	(52)	(50)	(48)	(50)
Cytoplasmic alteration		2 (4%)	1 (2%)	2 (4%)
Inflammation, subacute	1 (2%)			
Artery, inflammation, chronic active			1 (2%)	
Duct, cyst	1 (2%)		1 (2%)	1 (2%)
Salivary glands	(52)	(50)	(48)	(49)
Degeneration			1 (2%)	
Stomach, forestomach	(52)	(50)	(47)	(48)
Foreign body	1 (2%)			
Hyperplasia	27 (52%)	10 (20%)	18 (38%)	14 (29%)
Inflammation, subacute	12 (23%)	4 (8%)	1 (2%)	1 (2%)
Ulcer	2 (4%)	1 (2%)	4 (9%)	1 (2%)
Stomach, glandular	(52)	(50)	(47)	(48)
Cyst			2 (4%)	1 (2%)
Erosion	1 (2%)		4 (9%)	1 (2%)
Hyperplasia			1 (2%)	
Metaplasia, hepatocyte				1 (2%)
Mineralization			2 (4%)	
Necrosis				1 (2%)
Pigmentation				1 (2%)
Tongue			(1)	
Hyperplasia, squamous			1 (100%)	
Tooth	(1)		(8)	(3)
Developmental malformation	1 (100%)		8 (100%)	3 (100%)
Inflammation, subacute			1 (13%)	

TABLE F3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Cardiovascular System				
Blood vessel	(52)	(50)	(48)	(50)
Polyarteritis	1 (2%)			
Heart	(52)	(50)	(48)	(50)
Cardiomyopathy			1 (2%)	
Fibrosis				1 (2%)
Mineralization				2 (4%)
Endocrine System				
Adrenal cortex	(52)	(50)	(47)	(50)
Accessory adrenal cortical nodule	1 (2%)			1 (2%)
Hyperplasia			5 (11%)	2 (4%)
Hypertrophy	8 (15%)	5 (10%)	9 (19%)	8 (16%)
Spindle cell, hyperplasia	1 (2%)		2 (4%)	3 (6%)
Adrenal medulla	(52)	(50)	(47)	(49)
Hyperplasia			1 (2%)	1 (2%)
Pigmentation		1 (2%)		
Islets, pancreatic	(52)	(50)	(48)	(50)
Hyperplasia	3 (6%)	1 (2%)	1 (2%)	
Parathyroid gland	(48)	(46)	(47)	(47)
Cyst	2 (4%)	1 (2%)		
Infiltration cellular, lymphocyte			1 (2%)	
Pituitary gland	(48)	(47)	(44)	(48)
Pars distalis, cyst	1 (2%)	1 (2%)	4 (9%)	
Pars distalis, hyperplasia	2 (4%)			1 (2%)
Thyroid gland	(52)	(50)	(47)	(49)
Follicle, cyst	2 (4%)		8 (17%)	4 (8%)
Follicle, degeneration	5 (10%)	2 (4%)	13 (28%)	16 (33%)
Follicular cell, hyperplasia			7 (15%)	
General Body System				
None				
Genital System				
Epididymis	(52)	(50)	(48)	(50)
Granuloma sperm			1 (2%)	
Hemorrhage			1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	
Mineralization	1 (2%)		2 (4%)	
Penis				(1)
Inflammation, subacute				1 (100%)
Preputial gland	(51)	(50)	(48)	(50)
Inflammation, subacute	1 (2%)	2 (4%)	21 (44%)	11 (22%)
Necrosis			1 (2%)	
Duct, cyst	44 (86%)	20 (40%)	43 (90%)	32 (64%)

TABLE F3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Genital System (continued)				
Prostate	(52)	(50)	(48)	(50)
Inflammation, subacute			1 (2%)	
Seminal vesicle	(52)	(50)	(48)	(50)
Atrophy			1 (2%)	5 (10%)
Dilatation	1 (2%)		9 (19%)	
Infiltration cellular, mast cell	1 (2%)			
Testes	(52)	(50)	(48)	(50)
Atrophy			1 (2%)	1 (2%)
Mineralization			2 (4%)	
Hematopoietic System				
Lymph node	(4)	(2)	(15)	(17)
Axillary, hyperplasia, lymphoid				1 (6%)
Axillary, pigmentation, hemosiderin				1 (6%)
Bronchial, hyperplasia, lymphoid	1 (25%)			
Inguinal, hyperplasia, lymphoid			5 (33%)	1 (6%)
Inguinal, infiltration cellular, mast cell			1 (7%)	
Inguinal, pigmentation			4 (27%)	10 (59%)
Mediastinal, hemorrhage			1 (7%)	
Mediastinal, hyperplasia, lymphoid				1 (6%)
Lymph node, mandibular	(51)	(50)	(47)	(49)
Pigmentation, hemosiderin			3 (6%)	
Lymph node, mesenteric	(52)	(50)	(48)	(50)
Angiectasis	20 (38%)	2 (4%)	24 (50%)	14 (28%)
Edema	1 (2%)			
Hemorrhage			1 (2%)	
Hyperplasia, lymphoid	5 (10%)	2 (4%)		3 (6%)
Inflammation, subacute			1 (2%)	
Necrosis	1 (2%)			
Spleen	(52)	(50)	(48)	(50)
Angiectasis	1 (2%)			1 (2%)
Atrophy	2 (4%)	3 (6%)	2 (4%)	5 (10%)
Congestion	1 (2%)	1 (2%)		
Depletion cellular	1 (2%)			
Hematopoietic cell proliferation	6 (12%)	5 (10%)	12 (25%)	7 (14%)
Hyperplasia, lymphoid	9 (17%)	3 (6%)	1 (2%)	1 (2%)
Pigmentation, hemosiderin		39 (78%)		37 (74%)
Capsule, fibrosis				1 (2%)
Thymus	(51)	(46)	(41)	(42)
Atrophy	2 (4%)	2 (4%)	4 (10%)	2 (5%)
Cyst	1 (2%)		2 (5%)	1 (2%)
Mineralization		1 (2%)		
Necrosis	1 (2%)			

TABLE F3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Integumentary System				
Skin	(52)	(50)	(48)	(50)
Edema			1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, subacute		2 (4%)	1 (2%)	1 (2%)
Ulcer				1 (2%)
Epidermis, cyst			1 (2%)	
Musculoskeletal System				
Bone	(52)	(50)	(48)	(50)
Hyperostosis			1 (2%)	
Sternum, developmental malformation		1 (2%)		
Nervous System				
Brain	(52)	(50)	(48)	(50)
Atrophy				1 (2%)
Hemorrhage				1 (2%)
Vacuolization cytoplasmic			6 (13%)	10 (20%)
Respiratory System				
Lung	(52)	(50)	(48)	(50)
Congestion				1 (2%)
Hemorrhage		1 (2%)	3 (6%)	2 (4%)
Infiltration cellular, histiocyte			1 (2%)	
Pigmentation			2 (4%)	
Alveolar epithelium, hyperplasia	3 (6%)	2 (4%)	3 (6%)	9 (18%)
Nose	(52)	(50)	(48)	(50)
Glands, cyst		1 (2%)		
Glands, mineralization	3 (6%)			
Inflammation, subacute				3 (6%)
Lumen, inflammation, suppurative		1 (2%)		
Respiratory epithelium, mineralization		1 (2%)		
Special Senses System				
Ear	(1)	(1)		
External ear, inflammation, granulomatous	1 (100%)			
Eye			(1)	
Inflammation, suppurative			1 (100%)	

TABLE F3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	2,700 mg/kg	Vehicle Control	2,700 mg/kg
2-Year and 3-Year Protocols (continued)				
Urinary System				
Kidney	(52)	(50)	(48)	(50)
Fibrosis			1 (2%)	1 (2%)
Glomerulosclerosis			7 (15%)	4 (8%)
Infarct	5 (10%)	2 (4%)	1 (2%)	3 (6%)
Infiltration cellular, lymphocyte				1 (2%)
Inflammation, chronic	1 (2%)			
Inflammation, subacute	1 (2%)		1 (2%)	
Inflammation, suppurative		1 (2%)		
Metaplasia, osseous		1 (2%)	1 (2%)	1 (2%)
Mineralization	49 (94%)	38 (76%)	41 (85%)	41 (82%)
Artery, inflammation, chronic active			1 (2%)	
Cortex, cyst	1 (2%)	4 (8%)	15 (31%)	5 (10%)
Renal tubule, casts	13 (25%)	20 (40%)	29 (60%)	26 (52%)
Renal tubule, degeneration	1 (2%)		4 (8%)	7 (14%)
Renal tubule, dilation				1 (2%)
Renal tubule, pigmentation			1 (2%)	
Renal tubule, regeneration	36 (69%)	23 (46%)	27 (56%)	31 (62%)
Urinary bladder	(52)	(50)	(48)	(50)
Inflammation, subacute			1 (2%)	
Transitional epithelium, hyperplasia			1 (2%)	1 (2%)
Transitional epithelium, pigmentation			1 (2%)	1 (2%)

APPENDIX G
SUMMARY OF LESIONS IN MALE MICE IN THE DIETARY RESTRICTION STUDY OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

TABLE G1a
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Disposition Summary			
Animals initially in study	70[b]	60	70[b]
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths		1	2
Moribund	4	2	7
Natural deaths	6	6	2
Survivors			
Terminal sacrifice	40	41	39
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Hepatocellular carcinoma			1 (10%)
Hepatocellular adenoma	1 (10%)	1 (10%)	
Hepatocellular adenoma, multiple	1 (10%)		
Respiratory System			
Lung	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	2 (20%)	1 (10%)	1 (10%)
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
Endocrine System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Special Senses System			
Urinary System			

TABLE G1a
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study			
Alimentary System			
Intestine small, duodenum	(50)	(50)	(50)
Adenoma	1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)
Intestine small, ileum	(49)	(50)	(48)
Liver	(50)	(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma, metastatic, skin	1 (2%)		
Hemangiosarcoma, metastatic, spleen		1 (2%)	
Hepatocellular carcinoma	6 (12%)	4 (8%)	7 (14%)
Hepatocellular carcinoma, multiple		1 (2%)	
Hepatocellular adenoma	10 (20%)	4 (8%)	8 (16%)
Hepatocellular adenoma, multiple	16 (32%)	1 (2%)	
Hepatocholangiocarcinoma		1 (2%)	
Histiocytic sarcoma	3 (6%)		1 (2%)
Ito cell tumor NOS, multiple	1 (2%)		
Mesentery	(4)	(1)	(2)
Histiocytic sarcoma			1 (50%)
Pancreas	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)
Mast cell tumor benign		1 (2%)	
Squamous cell papilloma		2 (4%)	
Tooth	(14)		(2)
Odontoma	1 (7%)		1 (50%)
Cardiovascular System			
None			
Endocrine System			
Islets, pancreatic	(50)	(50)	(50)
Adenoma	3 (6%)		1 (2%)
Pituitary gland	(48)	(48)	(44)
Pars distalis, adenoma			1 (2%)
Pars intermedia, adenoma	1 (2%)	1 (2%)	
Thyroid gland	(50)	(50)	(50)
Follicular cell, adenoma		1 (2%)	1 (2%)
General Body System			
None			
Genital System			
Epididymis	(50)	(50)	(50)
Hemangiosarcoma, metastatic, bone marrow		1 (2%)	
Preputial gland	(50)	(50)	(50)
Sarcoma			1 (2%)

TABLE G1a
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
Hemangiosarcoma, metastatic, skin	1 (2%)		
Hemangiosarcoma, metastatic, spleen		1 (2%)	
Lymph node	(2)	(1)	(3)
Mediastinal, histiocytic sarcoma			1 (33%)
Lymph node, mandibular	(49)	(49)	(46)
Lymph node, mesenteric	(48)	(43)	(47)
Histiocytic sarcoma	3 (6%)		1 (2%)
Spleen	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
Hemangiosarcoma, metastatic, skin	1 (2%)		
Histiocytic sarcoma	2 (4%)		1 (2%)
Thymus	(42)	(45)	(40)
Mediastinum, hemangioma		1 (2%)	
Integumentary System			
Skin	(50)	(50)	(50)
Mast cell tumor malignant			
Subcutaneous tissue, hemangiosarcoma	1 (2%)		
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	11 (22%)	9 (18%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	2 (4%)	3 (6%)
Histiocytic sarcoma	1 (2%)		1 (2%)
Nose	(50)	(50)	(50)
Mast cell tumor malignant			1 (2%)
Special Senses System			
Harderian gland	(16)	(15)	(13)
Adenoma	3 (19%)	1 (7%)	2 (15%)
Carcinoma			1 (8%)

TABLE G1a
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Urinary System			
Kidney	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Artery, hepatocellular carcinoma, metastatic, liver			1 (2%)
Renal tubule, carcinoma	2 (4%)		
Urinary bladder	(50)	(50)	(49)
Systemic Lesions			
Multiple organs[c]	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)		1 (2%)
Leukemia lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		3 (6%)
Lymphoma malignant mixed	3 (6%)	3 (6%)	
Neoplasm Summary			
Total animals with primary neoplasms[d]			
15-Month interim evaluation	4	2	2
2-Year study	43	24	29
Total primary neoplasms			
15-Month interim evaluation	4	2	2
2-Year study	69	34	37
Total animals with benign neoplasms			
15-Month interim evaluation	4	2	1
2-Year study	36	18	18
Total benign neoplasms			
15-Month interim evaluation	4	2	1
2-Year study	48	22	20
Total animals with malignant neoplasms			
15-Month interim evaluation			1
2-Year study	17	11	15
Total malignant neoplasms			
15-Month interim evaluation			1
2-Year study	20	12	17
Total animals with metastatic neoplasms			
2-Year study	4	4	3
Total metastatic neoplasms			
2-Year study	6	5	4
Total animals with uncertain neoplasms–benign or malignant			
2-Year study	1		
Total uncertain neoplasms			
2-Year study	1		

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Ten animals were removed for supplemental evaluations that were not included in the dietary restriction study.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE G1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols[a]

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Disposition Summary				
Animals initially in study	60	60	50	50
15-Month interim evaluation	10	10		
Early deaths				
Moribund			11	5
Natural deaths	1	2	11	8
Survivors				
Terminal sacrifice	49	48	28	37
Animals examined microscopically	60	60	50	50
15-Month Interim Evaluation				
Endocrine System				
Thyroid gland	(10)	(10)		
Follicular cell, adenoma		1 (10%)		
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year and 3-Year Protocols				
Alimentary System				
Intestine small, duodenum	(50)	(49)	(50)	(50)
Carcinoma				1 (2%)
Intestine small, jejunum	(50)	(50)	(50)	(49)
Carcinoma				1 (2%)
Hemangiosarcoma			2 (4%)	
Intestine small, ileum	(49)	(50)	(50)	(49)
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, stomach, glandular				1 (2%)
Hemangiosarcoma			1 (2%)	
Hepatocellular carcinoma	2 (4%)		7 (14%)	4 (8%)
Hepatocellular carcinoma, multiple		1 (2%)		1 (2%)

TABLE G1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Alimentary System (continued)				
Liver (continued)	(50)	(50)	(50)	(50)
Hepatocellular adenoma	3 (6%)		7 (14%)	7 (14%)
Hepatocellular adenoma, multiple				1 (2%)
Histiocytic sarcoma			2 (4%)	1 (2%)
Mesentery	(1)		(5)	(1)
Pancreas	(50)	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma		2 (4%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoma			1 (2%)	1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, lung			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Capsule, adenoma				1 (2%)
Adrenal medulla	(50)	(49)		
Pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(50)	(49)	(50)	(50)
Adenoma			1 (2%)	1 (2%)
Pituitary gland	(48)	(30)	(47)	(47)
Pars distalis, adenoma				3 (6%)
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma		1 (2%)	1 (2%)	
General Body System				
Tissue NOS				(1)
Sarcoma				1 (100%)
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Prostate	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	2 (4%)			
Histiocytic sarcoma				1 (2%)

TABLE G1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Histiocytic sarcoma			1 (2%)	1 (2%)
Lymph node			(4)	(4)
Hepatocellular carcinoma, metastatic, liver			1 (25%)	
Lymph node, mandibular	(50)	(49)	(48)	(47)
Lymph node, mesenteric	(50)	(49)	(49)	(46)
Carcinoma, metastatic, stomach, glandular				1 (2%)
Lymph node, mediastinal	(1)		(7)	(3)
Carcinoma, metastatic, lung			1 (14%)	
Spleen	(50)	(50)	(50)	(50)
Hemangioma			1 (2%)	
Hemangiosarcoma	1 (2%)		2 (4%)	1 (2%)
Histiocytic sarcoma			1 (2%)	
Thymus	(45)	(45)	(34)	(38)
Integumentary System				
Skin	(50)	(50)	(48)	(50)
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle				(1)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, lung			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	8 (16%)	7 (14%)	7 (14%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple			3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)		7 (14%)	7 (14%)
Alveolar/bronchiolar carcinoma, multiple				1 (2%)
Carcinoma, metastatic, harderian gland			1 (2%)	
Hepatocellular carcinoma, metastatic, liver		1 (2%)	2 (4%)	1 (2%)
Special Senses System				
Ear			(2)	
Histiocytic sarcoma			1 (50%)	
Harderian gland	(22)	(24)	(24)	(23)
Adenoma	2 (9%)		2 (8%)	4 (17%)
Carcinoma			1 (4%)	

TABLE G1b
Summary of the Incidence of Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Carcinoma, metastatic, lung			1 (2%)	
Renal tubule, adenoma				1 (2%)
Urinary bladder	(50)	(49)	(50)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			3 (6%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	5 (10%)	4 (8%)
Lymphoma malignant, mixed			5 (10%)	8 (16%)
Lymphoma malignant, undifferentiated cell			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation		1		
2-Year and 3-year protocols	19	11	38	40
Total primary neoplasms				
15-Month interim evaluation		1		
2-Year and 3-year protocols	23	12	59	61
Total animals with benign neoplasms				
15-Month interim evaluation		1		
2-Year and 3-year protocols	14	9	21	24
Total benign neoplasms				
15-Month interim evaluation		1		
2-Year and 3-year protocols	16	10	24	30
Total animals with malignant neoplasms				
2-Year and 3-year protocols	6	2	30	29
Total malignant neoplasms				
2-Year and 3-year protocols	7	2	35	31
Total animals with metastatic neoplasms				
2-Year and 3-year protocols		1	6	2
Total metastatic neoplasms				
2-Year and 3-year protocols		1	9	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 G2a
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	25 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	25 mg/kg × Weight-Matched Control
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Adjusted rate[b]	7.0%	4.6%		
Terminal rate[c]	2/40 (5%)	1/39 (3%)		
First incidence (days)	540	405		
Life table test[d]		P=0.511N		
Logistic regression test[d]		P=0.441N		
Fisher exact test[d]		P=0.500N		
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	7.0%	7.1%	2.4%	7.1%
Terminal rate	2/40 (5%)	2/39 (5%)	1/41 (2%)	2/39 (5%)
First incidence (days)	540	405	726 (T)	405
Life table test		P=0.649		P=0.303
Logistic regression test		P=0.619N		P=0.292
Fisher exact test		P=0.661N		P=0.309
Liver: Hepatocellular Adenoma				
Overall rate	26/50 (52%)	8/50 (16%)	5/50 (10%)	8/50 (16%)
Adjusted rate	59.0%	19.1%	11.9%	19.1%
Terminal rate	22/40 (55%)	6/39 (15%)	4/41 (10%)	6/39 (15%)
First incidence (days)	680	587	721	587
Life table test		P<0.001N		P=0.259
Logistic regression test		P<0.001N		P=0.308
Fisher exact test		P<0.001N		P=0.277
Liver: Hepatocellular Carcinoma				
Overall rate	6/50 (12%)	7/50 (14%)	5/50 (10%)	7/50 (14%)
Adjusted rate	14.2%	17.3%	11.8%	17.3%
Terminal rate	4/40 (10%)	6/39 (15%)	4/41 (10%)	6/39 (15%)
First incidence (days)	700	622	532	622
Life table test		P=0.476		P=0.357
Logistic regression test		P=0.468		P=0.413
Fisher exact test		P=0.500		P=0.380
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	30/50 (60%)	15/50 (30%)	10/50 (20%)	15/50 (30%)
Adjusted rate	65.2%	35.3%	23.2%	35.3%
Terminal rate	24/40 (60%)	12/39 (31%)	8/41 (20%)	12/39 (31%)
First incidence (days)	680	587	532	587
Life table test		P=0.007N		P=0.162
Logistic regression test		P=0.004N		P=0.217
Fisher exact test		P=0.002N		P=0.178

TABLE G2a
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	25 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	25 mg/kg × Weight-Matched Control
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/50 (24%)	6/50 (12%)	10/50 (20%)	6/50 (12%)
Adjusted rate	28.3%	15.4%	24.4%	15.4%
Terminal rate	10/40 (25%)	6/39 (15%)	10/41 (24%)	6/39 (15%)
First incidence (days)	683	726 (T)	726 (T)	726 (T)
Life table test		P=0.110N		P=0.235N
Logistic regression test		P=0.120N		P=0.235N
Fisher exact test		P=0.096N		P=0.207N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Adjusted rate	6.8%	5.1%		
Terminal rate	1/40 (3%)	2/39 (5%)		
First incidence (days)	680	726 (T)		
Life table test		P=0.519N		
Logistic regression test		P=0.516N		
Fisher exact test		P=0.500N		
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/50 (30%)	8/50 (16%)	11/50 (22%)	8/50 (16%)
Adjusted rate	33.8%	20.5%	26.8%	20.5%
Terminal rate	11/40 (28%)	8/39 (21%)	11/41 (27%)	8/39 (21%)
First incidence (days)	680	726 (T)	726 (T)	726 (T)
Life table test		P=0.096N		P=0.345N
Logistic regression test		P=0.098N		P=0.345N
Fisher exact test		P=0.077N		P=0.306N
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	7.0%	2.6%		
Terminal rate	2/40 (5%)	1/39 (3%)		
First incidence (days)	647	726 (T)		
Life table test		P=0.324N		
Logistic regression test		P=0.313N		
Fisher exact test		P=0.309N		
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate			7.3%	0.0%
Terminal rate			3/41 (7%)	0/39 (0%)
First incidence (days)			726 (T)	-
Life table test				P=0.130N
Logistic regression test				P=0.130N
Fisher exact test				P=0.121N

TABLE G2a
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	25 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	25 mg/kg × Weight-Matched Control
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.9%	2.5%		
Terminal rate	2/40 (5%)	0/39 (0%)		
First incidence (days)	447	707		
Life table test		P=0.322N		
Logistic regression test		P=0.275N		
Fisher exact test		P=0.309N		
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	4/50 (8%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	9.5%	7.4%	7.3%	7.4%
Terminal rate	3/40 (8%)	2/39 (5%)	3/41 (7%)	2/39 (5%)
First incidence (days)	680	705	726 (T)	705
Life table test		P=0.519N		P=0.641
Logistic regression test		P=0.526N		P=0.661N
Fisher exact test		P=0.500N		P=0.661N
All Organs: Benign Neoplasms				
Overall rate	36/50 (72%)	18/50 (36%)	18/50 (36%)	18/50 (36%)
Adjusted rate	78.2%	42.3%	42.9%	42.3%
Terminal rate	30/40 (75%)	15/39 (38%)	17/41 (41%)	15/39 (38%)
First incidence (days)	540	405	721	405
Life table test		P=0.001N		P=0.522
Logistic regression test		P<0.001N		P=0.504N
Fisher exact test		P<0.001N		P=0.582N
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	15/50 (30%)	11/50 (22%)	15/50 (30%)
Adjusted rate	36.8%	34.6%	26.1%	34.6%
Terminal rate	11/40 (28%)	11/39 (28%)	10/41 (24%)	11/39 (28%)
First incidence (days)	447	405	532	405
Life table test		P=0.464N		P=0.223
Logistic regression test		P=0.423N		P=0.295
Fisher exact test		P=0.415N		P=0.247

TABLE G2a
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	25 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	25 mg/kg × Weight-Matched Control
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	29/50 (58%)	24/50 (48%)	29/50 (58%)
Adjusted rate	87.8%	62.8%	55.8%	62.8%
Terminal rate	34/40 (85%)	22/39 (56%)	22/41 (54%)	22/39 (56%)
First incidence (days)	447	405	532	405
Life table test		P=0.018N		P=0.178
Logistic regression test		P=0.002N		P=0.304
Fisher exact test		P=0.002N		P=0.212

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pancreatic islets; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the *ad libitum*-fed or weight-matched controls and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the dosed group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE G2b
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	2/50 (4%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate[b]			5.7%	10.8%
Terminal rate[c]			1/28 (4%)	4/37 (11%)
First incidence (days)			799	1086 (T)
Life table test[d]				P=0.452
Logistic regression test[d]				P=0.348
Fisher exact test[d]				P=0.339
Harderian Gland: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	4/50 (8%)
Adjusted rate			8.3%	10.8%
Terminal rate			1/28 (4%)	4/37 (11%)
First incidence (days)			799	1086 (T)
Life table test				P=0.613
Logistic regression test				P=0.512
Fisher exact test				P=0.500
Liver: Hepatocellular Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	7/50 (14%)	8/50 (16%)
Adjusted rate	6.1%	0.0%	19.7%	21.6%
Terminal rate	3/49 (6%)	0/48 (0%)	3/28 (11%)	8/37 (22%)
First incidence (days)	722 (T)	-	762	1086 (T)
Life table test		P=0.125N		P=0.541N
Logistic regression test		P=0.125N		P=0.531
Fisher exact test		P=0.121N		P=0.500
Liver: Hepatocellular Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	7/50 (14%)	5/50 (10%)
Adjusted rate			18.3%	11.2%
Terminal rate			2/28 (7%)	1/37 (3%)
First incidence (days)			784	784
Life table test				P=0.320N
Logistic regression test				P=0.413N
Fisher exact test				P=0.380N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	5/50 (10%)	1/50 (2%)	13/50 (26%)	13/50 (26%)
Adjusted rate	10.2%	2.1%	33.4%	30.9%
Terminal rate	5/49 (10%)	1/48 (2%)	5/28 (18%)	9/37 (24%)
First incidence (days)	722 (T)	722 (T)	762	784
Life table test		P=0.109N		P=0.397N
Logistic regression test		P=0.109N		P=0.582
Fisher exact test		P=0.102N		P=0.590N

TABLE G2b
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	8/50 (16%)	7/50 (14%)	10/50 (20%)	11/50 (22%)
Adjusted rate	16.3%	14.6%	28.0%	28.9%
Terminal rate	8/49 (16%)	7/48 (15%)	5/28 (18%)	10/37 (27%)
First incidence (days)	722 (T)	722 (T)	620	1036
Life table test		P=0.517N		P=0.475N
Logistic regression test		P=0.517N		P=0.534
Fisher exact test		P=0.500N		P=0.500
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	7/50 (14%)	8/50 (16%)
Adjusted rate			22.0%	19.3%
Terminal rate			5/28 (18%)	5/37 (14%)
First incidence (days)			941	819
Life table test				P=0.561N
Logistic regression test				P=0.515
Fisher exact test				P=0.500
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	10/50 (20%)	7/50 (14%)	17/50 (34%)	18/50 (36%)
Adjusted rate	20.4%	14.6%	46.5%	43.5%
Terminal rate	10/49 (20%)	7/48 (15%)	10/28 (36%)	14/37 (38%)
First incidence (days)	722 (T)	722 (T)	620	819
Life table test		P=0.314N		P=0.379N
Logistic regression test		P=0.314N		P=0.535
Fisher exact test		P=0.298N		P=0.500
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	0/48 (0%)	0/30 (0%)	0/47 (0%)	3/47 (6%)
Adjusted rate			0.0%	8.8%
Terminal rate			0/27 (0%)	3/34 (9%)
First incidence (days)			-	1086 (T)
Life table test				P=0.164
Logistic regression test				P=0.164
Fisher exact test				P=0.121
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate			12.7%	2.7%
Terminal rate			3/28 (11%)	1/37 (3%)
First incidence (days)			859	1,086 (T)
Life table test				P=0.118N
Logistic regression test				P=0.170N
Fisher exact test				P=0.181N

TABLE G2b
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
All Organs: Histiocytic Sarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate			8.8%	2.2%
Terminal rate			0/28 (0%)	0/37 (0%)
First incidence (days)			1,016	898
Life table test				P=0.272N
Logistic regression test				P=0.310N
Fisher exact test				P=0.309N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	1/50 (2%)	1/50 (2%)	11/50 (22%)	12/50 (24%)
Adjusted rate			29.0%	28.1%
Terminal rate			4/28 (14%)	7/37 (19%)
First incidence (days)			784	880
Life table test				P=0.509N
Logistic regression test				P=0.497
Fisher exact test				P=0.500
All Organs: Benign Neoplasms				
Overall rate	14/50 (28%)	9/50 (18%)	21/50 (42%)	24/50 (48%)
Adjusted rate	28.6%	18.8%	56.6%	61.4%
Terminal rate	14/49 (29%)	9/48 (19%)	13/28 (46%)	22/37 (59%)
First incidence (days)	722 (T)	722 (T)	620	892
Life table test		P=0.186N		P=0.405N
Logistic regression test		P=0.186N		P=0.407
Fisher exact test		P=0.171N		P=0.344
All Organs: Malignant Neoplasms				
Overall rate	6/50 (12%)	2/50 (4%)	30/50 (60%)	29/50 (58%)
Adjusted rate	12.0%	4.1%	66.3%	59.2%
Terminal rate	5/49 (10%)	1/48 (2%)	13/28 (46%)	17/37 (46%)
First incidence (days)	515	502	784	784
Life table test		P=0.147N		P=0.230N
Logistic regression test		P=0.093N		P=0.501
Fisher exact test		P=0.134N		P=0.500N

TABLE G2b
Statistical Analysis of Primary Neoplasms in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	19/50 (38%)	11/50 (22%)	38/50 (76%)	40/50 (80%)
Adjusted rate	38.0%	22.4%	80.6%	81.6%
Terminal rate	18/49 (37%)	10/48 (21%)	19/28 (68%)	28/37 (76%)
First incidence (days)	515	502	620	784
Life table test		P=0.078N		P=0.257N
Logistic regression test		P=0.059N		P=0.428
Fisher exact test		P=0.063N		P=0.405

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pituitary gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in a dosed group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE G3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Disposition Summary			
Animals initially in study	70[b]	60	70[b]
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths		1	2
Moribund	4	2	7
Natural deaths	6	6	2
Survivors			
Terminal sacrifice	40	41	39
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Esophagus	(10)	(10)	(10)
Periesophageal tissue, inflammation, suppurative		1 (10%)	
Intestine small, jejunum	(10)	(10)	(10)
Hyperplasia, lymphoid		1 (10%)	
Liver	(10)	(10)	(10)
Basophilic focus		1 (10%)	
Clear cell focus	1 (10%)		
Eosinophilic focus	1 (10%)		
Fatty change	2 (20%)		
Mixed cell focus	1 (10%)		
Bile duct, hyperplasia	1 (10%)		
Hepatocyte, hypertrophy			
Mesentery	(1)		
Fat, inflammation, chronic active	1 (100%)		
Pancreas	(10)	(10)	(10)
Atrophy			1 (10%)
Atypia cellular		1 (10%)	
Stomach, forestomach	(10)	(10)	(10)
Hyperplasia, focal		1 (10%)	2 (20%)
Endocrine System			
Adrenal cortex	(10)	(10)	(10)
Hyperplasia	4 (40%)	2 (20%)	2 (20%)
Capsule, hyperplasia, adenomatous	1 (10%)	1 (10%)	3 (30%)
Islets, pancreatic	(10)	(10)	(10)
Hyperplasia	3 (30%)	1 (10%)	
Pituitary gland	(10)		(9)
Cyst	1 (10%)		

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Ten animals were removed for supplemental evaluations that were not included in the dietary restriction study.

TABLE G3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
15-Month Interim Evaluation (continued)			
Genital System			
Preputial gland	(10)	(10)	(10)
Duct, ectasia	10 (100%)	9 (90%)	9 (90%)
Respiratory System			
Lung	(10)	(10)	(10)
Granuloma		1 (10%)	
Alveolar epithelium, hyperplasia			1 (10%)
Special Senses System			
Eye			(1)
Degeneration			1 (100%)
Harderian gland	(4)	(3)	(3)
Inflammation, chronic active			2 (67%)
Urinary System			
Kidney	(10)	(10)	(10)
Developmental malformation		1 (10%)	
Nephropathy	10 (100%)	7 (70%)	6 (60%)
Systems Examined With No Lesions Observed			
Cardiovascular System			
General Body System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
2-Year Study			
Alimentary System			
Esophagus	(50)	(50)	(50)
Cyst	1 (2%)		
Periesophageal tissue, inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)
Intestine small, jejunum	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
Ulcer			1 (2%)
Intestine small, ileum	(49)	(50)	(48)
Amyloid deposition			1 (2%)

TABLE G3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Alimentary System (continued)			
Liver	(50)	(50)	(50)
Amyloid deposition			1 (2%)
Basophilic focus	3 (6%)		
Clear cell focus	12 (24%)	2 (4%)	
Eosinophilic focus	21 (42%)		2 (4%)
Fatty change	1 (2%)		
Hematopoietic cell proliferation	2 (4%)		2 (4%)
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)
Mixed cell focus	5 (10%)	2 (4%)	1 (2%)
Necrosis	1 (2%)	1 (2%)	3 (6%)
Bile duct, cyst		1 (2%)	
Mesentery	(4)	(1)	(2)
Fat, inflammation, chronic active		1 (100%)	1 (50%)
Fat, necrosis	2 (50%)		
Pancreas	(50)	(50)	(50)
Atrophy	2 (4%)		1 (2%)
Artery, inflammation, chronic active		1 (2%)	
Duct, cyst			2 (4%)
Salivary glands	(50)	(50)	(50)
Atrophy		1 (2%)	
Stomach, forestomach	(50)	(50)	(50)
Hyperplasia, focal	3 (6%)	16 (32%)	6 (12%)
Infiltration cellular, mast cell		1 (2%)	
Stomach, glandular	(50)	(50)	(50)
Dysplasia		1 (2%)	
Erosion		5 (10%)	
Tooth	(14)		(2)
Dysplasia	13 (93%)		1 (50%)
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Aorta, inflammation, chronic active			1 (2%)
Heart	(50)	(50)	(50)
Mineralization	2 (4%)		
Artery, inflammation, chronic active			1 (2%)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)	1 (2%)	1 (2%)
Hyperplasia	23 (46%)	10 (20%)	25 (50%)
Capsule, hyperplasia, adenomatous	7 (14%)	6 (12%)	3 (6%)
Adrenal medulla	(49)	(50)	(50)
Inflammation, chronic active	1 (2%)		
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia	29 (58%)	2 (4%)	2 (4%)

TABLE G3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Endocrine System (continued)			
Pituitary gland	(48)	(48)	(44)
Pars distalis, hyperplasia	1 (2%)		
Pars intermedia, hyperplasia			1 (2%)
Thyroid gland	(50)	(50)	(50)
Follicular cell, hyperplasia	13 (26%)	1 (2%)	5 (10%)
General Body System			
None			
Genital System			
Epididymis	(50)	(50)	(50)
Granuloma sperm	1 (2%)		
Inflammation, chronic active		1 (2%)	1 (2%)
Preputial gland	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)	3 (6%)
Duct, ectasia	47 (94%)	47 (94%)	45 (90%)
Prostate	(49)	(50)	(50)
Inflammation, chronic active			2 (4%)
Seminal vesicle	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)		
Testes	(50)	(50)	(50)
Atrophy	2 (4%)		
Hypoplasia		1 (2%)	
Interstitial cell, hyperplasia			1 (2%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Thrombosis			1 (2%)
Erythroid cell, hyperplasia		5 (10%)	2 (4%)
Myeloid cell, hyperplasia	1 (2%)	1 (2%)	5 (10%)
Lymph node	(2)	(1)	(3)
Lumbar, hyperplasia, lymphoid			1 (33%)
Mediastinal, hyperplasia, lymphoid	1 (50%)		
Lymph node, mandibular	(49)	(49)	(46)
Hyperplasia, lymphoid			1 (2%)
Lymph node, mesenteric	(48)	(43)	(47)
Hematopoietic cell proliferation	2 (4%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)		
Hyperplasia, plasma cell			1 (2%)

TABLE G3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Hematopoietic System (continued)			
Spleen	(50)	(50)	(50)
Amyloid deposition			1 (2%)
Angiectasis	1 (2%)	1 (2%)	
Depletion lymphoid		5 (10%)	3 (6%)
Hematopoietic cell proliferation	8 (16%)	7 (14%)	12 (24%)
Hyperplasia, lymphoid	1 (2%)		
Thymus	(42)	(45)	(40)
Atrophy	6 (14%)	5 (11%)	7 (18%)
Epithelial cell, hyperplasia		1 (2%)	
Integumentary System			
Skin	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)
Ulcer			1 (2%)
Subcutaneous tissue, lymphangiectasis	1 (2%)		
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(50)	(50)
Neuron, necrosis	1 (2%)	1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Embolus	1 (2%)		
Inflammation, chronic active			1 (2%)
Inflammation, suppurative	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	8 (16%)	5 (10%)	1 (2%)
Nose	(50)	(50)	(50)
Inflammation, suppurative			2 (4%)
Special Senses System			
Eye			(2)
Cornea, inflammation, chronic active			1 (50%)
Harderian gland	(16)	(15)	(13)
Hyperplasia	1 (6%)		

TABLE G3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Urinary System			
Kidney	(50)	(50)	(50)
Cyst	6 (12%)	3 (6%)	3 (6%)
Hydronephrosis			1 (2%)
Inflammation, chronic active	2 (4%)		2 (4%)
Necrosis			1 (2%)
Nephropathy	48 (96%)	42 (84%)	37 (74%)
Glomerulus, amyloid deposition			1 (2%)
Urinary bladder	(50)	(50)	(49)
Inflammation, chronic active	2 (4%)		3 (6%)

TABLE G3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols[a]

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Disposition Summary				
Animals initially in study	60	60	50	50
15-Month interim evaluation	10	10		
Early deaths				
Moribund			11	5
Natural deaths	1	2	11	8
Survivors				
Terminal sacrifice	49	48	28	37
Animals examined microscopically	60	60	50	50
15-Month Interim Evaluation				
Alimentary System				
Stomach, forestomach	(10)	(10)		
Hyperplasia, focal	6 (60%)	6 (60%)		
Stomach, glandular	(10)	(10)		
Dysplasia		1 (10%)		
Cardiovascular System				
Heart	(10)	(10)		
Inflammation, chronic active	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)		
Accessory adrenal cortical nodule	2 (20%)			
Pituitary gland	(10)	(8)		
Cyst		1 (13%)		
Hematopoietic System				
Bone marrow	(10)	(10)		
Hyperplasia, mast cell	1 (10%)			
Special Senses System				
Harderian gland	(4)	(2)		
Inflammation, chronic active	2 (50%)	2 (100%)		
Urinary System				
Kidney	(10)	(10)		
Hyperplasia, mast cell	1 (10%)			
Nephropathy	9 (90%)	5 (50%)		

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

TABLE G3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
15-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
2-Year and 3-Year Protocols				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Periesophageal tissue, inflammation, suppurative	1 (2%)			
Gallbladder	(50)	(49)	(50)	(49)
Inflammation, acute				1 (2%)
Intestine small, jejunum	(50)	(50)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	5 (10%)
Inflammation, chronic active			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus			1 (2%)	1 (2%)
Clear cell focus	1 (2%)			
Eosinophilic focus	1 (2%)		1 (2%)	1 (2%)
Hematopoietic cell proliferation			1 (2%)	
Hepatodiaphragmatic nodule			1 (2%)	
Hyperplasia, lymphoid			2 (4%)	
Mixed cell focus		1 (2%)	2 (4%)	
Necrosis	1 (2%)	1 (2%)	1 (2%)	
Bile duct, cyst				2 (4%)
Bile duct, hyperplasia, cystic	1 (2%)			
Mesentery	(1)		(5)	(1)
Fibrosis	1 (100%)			
Artery, inflammation, chronic, active				1 (100%)
Fat, inflammation, chronic active			3 (60%)	
Fat, necrosis			2 (40%)	
Pancreas	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	
Acinus, atrophy		1 (2%)	2 (4%)	
Acinus, hyperplasia, focal				1 (2%)
Artery, inflammation, chronic active			2 (4%)	
Duct, ectasia			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Cyst				2 (4%)
Hyperplasia, focal	38 (76%)	32 (64%)	25 (50%)	33 (66%)
Hyperplasia, mast cell				3 (6%)

TABLE G3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Alimentary System (continued)				
Stomach, glandular	(50)	(50)	(50)	(50)
Dysplasia	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Hyperplasia			1 (2%)	
Tongue	(1)			(1)
Mineralization	1 (100%)			
Tooth	(2)		(3)	(7)
Dysplasia	2 (100%)		3 (100%)	6 (86%)
Inflammation, chronic active				1 (14%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Degeneration			1 (2%)	
Mineralization			1 (2%)	1 (2%)
Atrium, thrombosis				1 (2%)
Valve, inflammation, chronic active				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	2 (4%)		1 (2%)	1 (2%)
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage			1 (2%)	
Hyperplasia	14 (28%)	6 (12%)	6 (12%)	12 (24%)
Capsule, hyperplasia			3 (6%)	1 (2%)
Capsule, hyperplasia, adenomatous	6 (12%)			
Adrenal medulla	(50)	(49)	(50)	(50)
Hyperplasia			3 (6%)	1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(50)
Hyperplasia	1 (2%)		3 (6%)	
Parathyroid gland	(42)	(44)	(50)	(47)
Cyst				1 (2%)
Hyperplasia, focal				1 (2%)
Pituitary gland	(48)	(30)	(47)	(47)
Pars distalis, cyst			3 (6%)	1 (2%)
Pars distalis, hyperplasia			2 (4%)	3 (6%)
Thyroid gland	(50)	(50)	(50)	(50)
Inflammation			1 (2%)	
Inflammation, chronic active				1 (2%)
Follicular cell, hyperplasia	1 (2%)		6 (12%)	2 (4%)
General Body System				
None				

TABLE G3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm			7 (14%)	6 (12%)
Inflammation, chronic active			1 (2%)	
Spermatocele				1 (2%)
Preputial gland	(50)	(49)	(50)	(50)
Degeneration				1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	7 (14%)	6 (12%)
Duct, ectasia	24 (48%)	10 (20%)	24 (48%)	15 (30%)
Testes	(50)	(50)	(50)	(50)
Atrophy	1 (2%)		9 (18%)	7 (14%)
Hypoplasia	1 (2%)			
Interstitial cell, hyperplasia			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myelofibrosis			2 (4%)	
Erythroid cell, hyperplasia				3 (6%)
Myeloid cell, hyperplasia			6 (12%)	1 (2%)
Lymph node, mandibular	(50)	(49)	(48)	(47)
Hyperplasia, lymphoid				1 (2%)
Lymph node, mesenteric	(50)	(49)	(49)	(46)
Angiectasis			5 (10%)	5 (11%)
Hyperplasia, lymphoid				2 (4%)
Hyperplasia, plasma cell				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Depletion lymphoid		1 (2%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	15 (30%)	11 (22%)
Hyperplasia, lymphoid			1 (2%)	1 (2%)
Hyperplasia, plasma cell				1 (2%)
Thrombosis			1 (2%)	
Thymus	(45)	(45)	(34)	(38)
Atrophy		1 (2%)	13 (38%)	9 (24%)
Integumentary System				
Skin	(50)	(50)	(48)	(50)
Subcutaneous tissue, inflammation, chronic active			2 (4%)	
Musculoskeletal System				
None				

TABLE G3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Infiltration cellular, lymphocyte		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Bronchiectasis, focal	1 (2%)			
Inflammation			1 (2%)	
Alveolar epithelium, hyperplasia	5 (10%)	1 (2%)	4 (8%)	7 (14%)
Bronchiole, hyperplasia		1 (2%)	1 (2%)	
Nose	(50)	(50)	(50)	(50)
Respiratory epithelium, inflammation, chronic active	1 (2%)			
Special Senses System				
Eye			(1)	(3)
Lens, cataract			1 (100%)	2 (67%)
Harderian gland	(22)	(24)	(24)	(23)
Hyperplasia	1 (5%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst			3 (6%)	1 (2%)
Necrosis, focal			1 (2%)	
Nephropathy	47 (94%)	45 (90%)	40 (80%)	40 (80%)
Renal tubule, hyperplasia	1 (2%)			1 (2%)

APPENDIX H
SUMMARY OF LESIONS IN FEMALE MICE IN THE DIETARY RESTRICTION STUDY OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

TABLE H1a
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Disposition Summary			
Animals initially in study	70[b]	60	70[b]
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths	2	1	
Moribund	9	10	7
Natural deaths	7	3	6
Survivors			
Terminal sacrifice	33	36	38
Animals examined microscopically	61	60	61
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Hepatocellular adenoma	1 (10%)		
Endocrine System			
Thyroid gland	(10)	(10)	(10)
Follicular cell, adenoma			1 (10%)
Genital System			
Ovary	(10)	(10)	(10)
Cystadenoma	1 (10%)		
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
General Body System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			

TABLE H1a
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study			
Alimentary System			
Gallbladder	(51)	(50)	(51)
Intestine small, jejunum	(51)	(49)	(50)
Carcinoma	1 (2%)		
Liver	(51)	(50)	(51)
Hemangiosarcoma, multiple	1 (2%)		
Hepatocellular carcinoma	7 (14%)	2 (4%)	4 (8%)
Hepatocellular carcinoma, multiple	1 (2%)		
Hepatocellular adenoma	10 (20%)	7 (14%)	4 (8%)
Hepatocellular adenoma, multiple	5 (10%)		2 (4%)
Hepatocholangiocarcinoma	1 (2%)		
Histiocytic sarcoma	1 (2%)	3 (6%)	1 (2%)
Bile duct, carcinoma	1 (2%)		
Mesentery	(7)	(5)	(5)
Carcinoma, metastatic, liver	1 (14%)		
Histiocytic sarcoma		1 (20%)	1 (20%)
Lipoma		1 (20%)	
Pancreas	(51)	(50)	(51)
Carcinoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma			1 (2%)
Salivary glands	(51)	(50)	(51)
Stomach, forestomach	(51)	(50)	(51)
Squamous cell papilloma		1 (2%)	2 (4%)
Stomach, glandular	(51)	(50)	(51)
Tongue		(1)	
Squamous cell carcinoma		1 (100%)	
Cardiovascular System			
Heart	(51)	(50)	(51)
Carcinoma, metastatic, liver	1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		
Endocrine System			
Adrenal cortex	(51)	(50)	(51)
Adrenal medulla	(51)	(49)	(50)
Pheochromocytoma malignant	1 (2%)		
Pituitary gland	(50)	(48)	(46)
Pars distalis, adenoma	4 (8%)	1 (2%)	3 (7%)
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(51)	(50)	(51)
Follicular cell, adenoma	3 (6%)	1 (2%)	2 (4%)
General Body System			
None			

TABLE H1a
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Genital System			
Ovary	(51)	(49)	(51)
Cystadenoma	3 (6%)		1 (2%)
Hemangiosarcoma	1 (2%)		
Histiocytic sarcoma		2 (4%)	
Luteoma			1 (2%)
Uterus	(51)	(50)	(51)
Adenoma	1 (2%)		
Hemangiosarcoma	1 (2%)	1 (2%)	
Hemangiosarcoma, metastatic, ovary	1 (2%)		
Histiocytic sarcoma		2 (4%)	
Neoplasm NOS		1 (2%)	
Polyp stromal	1 (2%)	1 (2%)	
Sarcoma stromal	1 (2%)		
Hematopoietic System			
Bone marrow	(51)	(50)	(51)
Hemangiosarcoma			1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)	
Lymph node	(6)	(3)	(3)
Bronchial, carcinoma, metastatic, liver	1 (17%)		
Bronchial, hepatocholangiocarcinoma, metastatic, liver	1 (17%)		
Bronchial, histiocytic sarcoma		1 (33%)	
Mediastinal, carcinoma, metastatic, liver	1 (17%)		
Mediastinal, hepatocholangiocarcinoma, metastatic, liver	1 (17%)		
Mediastinal, histiocytic sarcoma	1 (17%)	1 (33%)	1 (33%)
Lymph node, mandibular	(50)	(48)	(51)
Histiocytic sarcoma		1 (2%)	
Lymph node, mesenteric	(50)	(48)	(48)
Histiocytic sarcoma		1 (2%)	
Spleen	(51)	(50)	(51)
Hemangiosarcoma	1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)
Thymus	(48)	(43)	(45)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma	1 (2%)	1 (2%)	
Mast cell tumor malignant			1 (2%)
Integumentary System			
Skin	(51)	(50)	(51)
Squamous cell carcinoma			1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		

TABLE H1a
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Musculoskeletal System			
Bone	(51)	(50)	(51)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		
Skeletal muscle	(1)		
Hepatocholangiocarcinoma, metastatic, liver	1 (100%)		
Rhabdomyosarcoma			
Nervous System			
Brain		(50)	(51)
Respiratory System			
Lung	(51)	(50)	(51)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)		
Carcinoma, metastatic, liver	1 (2%)		
Hemangiosarcoma, metastatic, ovary	1 (2%)		
Hepatocellular carcinoma, metastatic, liver	1 (2%)		1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma	1 (2%)	2 (4%)	
Mediastinum, hemangiosarcoma		1 (2%)	
Nose	(51)	(50)	(51)
Histiocytic sarcoma		1 (2%)	
Special Senses System			
Harderian gland	(17)	(10)	(13)
Adenoma	1 (6%)	3 (30%)	1 (8%)
Carcinoma	2 (12%)		
Urinary System			
Kidney	(51)	(50)	(51)
Carcinoma, metastatic, liver	1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma		1 (2%)	
Urinary bladder	(50)	(50)	(51)
Systemic Lesions			
Multiple organs[c]	(51)	(50)	(51)
Histiocytic sarcoma	1 (2%)	4 (8%)	1 (2%)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	4 (8%)
Lymphoma malignant mixed	7 (14%)	5 (10%)	3 (6%)

TABLE H1a
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Neoplasm Summary			
Total animals with primary neoplasms[d]			
15-Month interim evaluation	1		1
2-Year study	40	28	29
Total primary neoplasms			
15-Month interim evaluation	2		1
2-Year study	62	35	35
Total animals with benign neoplasms			
15-Month interim evaluation	1		1
2-Year study	24	14	18
Total benign neoplasms			
15-Month interim evaluation	2		1
2-Year study	31	17	19
Total animals with malignant neoplasms			
2-Year study	26	16	14
Total malignant neoplasms			
2-Year study	31	17	16
Total animals with metastatic neoplasms			
2-Year study	5		1
Total metastatic neoplasms			
2-Year study	19		1
Total animals with uncertain neoplasms-benign or malignant			
2-Year study		1	
Total uncertain neoplasms			
2-Year study		1	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Nine animals were removed for supplemental evaluations that were not included in the dietary restriction study.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE H1b
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols[a]

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Disposition Summary				
Animals initially in study	60	60	50	50
15-Month interim evaluation	10	10		
Early deaths				
Accidental deaths		1		1
Moribund	2	2	18	16
Natural deaths	1	3	12	14
Survivors				
Terminal sacrifice	47	44	20	19
Animals examined microscopically	60	60	50	50
Systems Examined At 15 Months With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year and 3-Year Protocols				
Alimentary System				
Gallbladder	(50)	(50)	(50)	(49)
Intestine large, cecum	(50)	(50)	(49)	(48)
Intestine small, jejunum	(50)	(50)	(50)	(49)
Histiocytic sarcoma			2 (4%)	
Sarcoma, metastatic, skin				1 (2%)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma			3 (6%)	4 (8%)
Hepatocellular carcinoma, multiple			1 (2%)	
Hepatocellular adenoma	3 (6%)	3 (6%)	11 (22%)	7 (14%)
Hepatocellular adenoma, multiple			1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)	3 (6%)	4 (8%)	5 (10%)
Osteosarcoma, metastatic, bone		1 (2%)		
Mesentery	(2)		(6)	(6)
Hemangiosarcoma			1 (17%)	
Histiocytic sarcoma	1 (50%)		2 (33%)	2 (33%)
Sarcoma, metastatic, skin			2 (33%)	2 (33%)
Pancreas	(50)	(50)	(49)	(50)
Sarcoma, metastatic, skin				1 (2%)

TABLE H1b
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Alimentary System (continued)				
Salivary glands	(50)	(50)	(49)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Tooth			(2)	(2)
Histiocytic sarcoma				1 (50%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Pericardium, osteosarcoma, metastatic, bone		1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Adrenal medulla	(49)	(50)	(49)	(50)
Pheochromocytoma benign	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma			1 (2%)	2 (4%)
Carcinoma			2 (4%)	
Pituitary gland	(46)	(46)	(42)	(49)
Histiocytic sarcoma				1 (2%)
Pars distalis, adenoma		1 (2%)	3 (7%)	2 (4%)
Pars intermedia, adenoma	1 (2%)		4 (10%)	2 (4%)
Thyroid gland	(50)	(49)	(50)	(50)
Bilateral, follicular cell, adenoma				1 (2%)
Follicular cell, adenoma	1 (2%)		1 (2%)	
Follicular cell, carcinoma				1 (2%)
General Body System				
None				
Genital System				
Ovary	(50)	(50)	(49)	(49)
Adenoma				1 (2%)
Adenoma, tubular				1 (2%)
Cystadenoma			1 (2%)	2 (4%)
Granulosa cell tumor benign			1 (2%)	
Histiocytic sarcoma	1 (2%)		3 (6%)	2 (4%)
Sarcoma, metastatic, skin				1 (2%)
Uterus	(50)	(50)	(49)	(49)
Histiocytic sarcoma	2 (4%)	1 (2%)	4 (8%)	3 (6%)
Polyp stromal		2 (4%)	1 (2%)	2 (4%)

TABLE H1b
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Hematopoietic System				
Blood				(1)
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma			2 (4%)	1 (2%)
Hemangiosarcoma, multiple			1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Lymph node			(13)	(8)
Hepatocellular carcinoma, metastatic, liver			1 (8%)	
Histiocytic sarcoma			2 (15%)	
Axillary, sarcoma, metastatic, skin			1 (8%)	
Pancreatic, sarcoma, metastatic, skin			1 (8%)	
Lymph node, bronchial		(1)		(1)
Lymph node, mandibular	(50)	(48)	(45)	(47)
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)
Mast cell tumor NOS			1 (2%)	
Lymph node, mesenteric	(44)	(50)	(43)	(48)
Histiocytic sarcoma	1 (2%)	2 (4%)	2 (5%)	3 (6%)
Lymph node, mediastinal	(2)	(4)	(12)	(11)
Histiocytic sarcoma	1 (50%)	2 (50%)	1 (8%)	2 (18%)
Sarcoma, metastatic, skin			1 (8%)	
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)	3 (6%)
Histiocytic sarcoma		2 (4%)	1 (2%)	
Thymus	(45)	(49)	(37)	(42)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Histiocytic sarcoma			2 (5%)	
Osteosarcoma, metastatic, bone		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(49)	(49)
Carcinoma	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)		
Squamous cell carcinoma				1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, sarcoma			4 (8%)	5 (10%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)
Vertebra, osteosarcoma		1 (2%)		

TABLE H1b
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Histiocytic sarcoma				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	2 (4%)	4 (8%)
Alveolar/bronchiolar carcinoma	1 (2%)		3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)			
Hepatocellular carcinoma, metastatic, liver			2 (4%)	
Histiocytic sarcoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)		
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Nose	(50)	(49)	(50)	(50)
Special Senses System				
Harderian gland	(24)	(23)	(22)	(25)
Adenoma	3 (13%)			2 (8%)
Bilateral, adenoma				1 (4%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		2 (4%)	1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Urinary bladder	(50)	(50)	(49)	(49)
Histiocytic sarcoma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	3 (6%)	5 (10%)	5 (10%)
Lymphoma malignant lymphocytic			5 (10%)	4 (8%)
Lymphoma malignant mixed	2 (4%)	3 (6%)	9 (18%)	9 (18%)

TABLE H1b
Summary of the Incidence of Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]				
2-Year and 3-year protocols	19	16	42	41
Total primary neoplasms				
2-Year and 3-year protocols	20	17	68	65
Total animals with benign neoplasms				
2-Year and 3-year protocols	12	10	22	18
Total benign neoplasms				
2-Year and 3-year protocols	12	10	28	29
Total animals with malignant neoplasms				
2-Year and 3-year protocols	8	7	35	31
Total malignant neoplasms				
2-Year and 3-year protocols	8	7	39	36
Total animals with metastatic neoplasms				
2-Year and 3-year protocols	1	1	4	3
Total metastatic neoplasms				
2-Year and 3-year protocols	2	4	8	6
Total animals with uncertain neoplasms–benign or malignant				
3-Year protocol			1	
Total uncertain neoplasms				
3-Year protocol			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 H2a
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

	Ad Libitum-Fed Control	25 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	25 mg/kg × Weight-Matched Control
Harderian Gland: Adenoma				
Overall rate[a]	1/51 (2%)	1/51 (2%)	3/50 (6%)	1/51 (2%)
Adjusted rate[b]			7.7%	2.6%
Terminal rate[c]			1/36 (3%)	1/38 (3%)
First incidence (days)			707	726 (T)
Life table test[d]				P=0.305N
Logistic regression test[d]				P=0.316N
Fisher exact test[d]				P=0.301N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/51 (6%)	1/51 (2%)	3/50 (6%)	1/51 (2%)
Adjusted rate	7.2%	2.6%	7.7%	2.6%
Terminal rate	1/33 (3%)	1/38 (3%)	1/36 (3%)	1/38 (3%)
First incidence (days)	511	726 (T)	707	726 (T)
Life table test		P=0.285N		P=0.305N
Logistic regression test		P=0.320N		P=0.316N
Fisher exact test		P=0.309N		P=0.301N
Liver: Hepatocellular Adenoma				
Overall rate	15/51 (29%)	6/51 (12%)	7/50 (14%)	6/51 (12%)
Adjusted rate	42.3%	15.4%	18.9%	15.4%
Terminal rate	13/33 (39%)	5/38 (13%)	6/36 (17%)	5/38 (13%)
First incidence (days)	604	694	721	694
Life table test		P=0.011N		P=0.469N
Logistic regression test		P=0.017N		P=0.526N
Fisher exact test		P=0.024N		P=0.485N
Liver: Hepatocellular Carcinoma				
Overall rate	8/51 (16%)	4/51 (8%)	2/50 (4%)	4/51 (8%)
Adjusted rate	21.1%	10.3%	4.8%	10.3%
Terminal rate	5/33 (15%)	3/38 (8%)	1/36 (3%)	3/38 (8%)
First incidence (days)	594	694	611	694
Life table test		P=0.139N		P=0.345
Logistic regression test		P=0.170N		P=0.339
Fisher exact test		P=0.179N		P=0.348
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	22/51 (43%)	9/51 (18%)	9/50 (18%)	9/51 (18%)
Adjusted rate	57.1%	23.1%	23.2%	23.1%
Terminal rate	17/33 (52%)	8/38 (21%)	7/36 (19%)	8/38 (21%)
First incidence (days)	594	694	611	694
Life table test		P=0.002N		P=0.568N
Logistic regression test		P=0.003N		P=0.578
Fisher exact test		P=0.005N		P=0.584N

TABLE H2a
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	25 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	25 mg/kg × Weight-Matched Control
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/51 (6%)	2/51 (4%)	2/50 (4%)	2/51 (4%)
Adjusted rate	8.0%	5.3%		
Terminal rate	1/33 (3%)	2/38 (5%)		
First incidence (days)	618	726 (T)		
Life table test		P=0.453N		
Logistic regression test		P=0.493N		
Fisher exact test		P=0.500N		
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/51 (8%)	3/51 (6%)	3/50 (6%)	3/51 (6%)
Adjusted rate	10.8%	7.4%	7.8%	7.4%
Terminal rate	2/33 (6%)	2/38 (5%)	2/36 (6%)	2/38 (5%)
First incidence (days)	618	604	707	604
Life table test		P=0.450N		P=0.655N
Logistic regression test		P=0.496N		P=0.661N
Fisher exact test		P=0.500N		P=0.652N
Ovary: Cystadenoma				
Overall rate	3/51 (6%)	1/51 (2%)	0/49 (0%)	1/51 (2%)
Adjusted rate	7.1%	2.6%		
Terminal rate	0/33 (0%)	1/38 (3%)		
First incidence (days)	511	726 (T)		
Life table test		P=0.289N		
Logistic regression test		P=0.316N		
Fisher exact test		P=0.309N		
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/50 (8%)	3/46 (7%)	1/48 (2%)	3/46 (7%)
Adjusted rate	11.8%	8.2%	2.2%	8.2%
Terminal rate	3/33 (9%)	2/33 (6%)	0/34 (0%)	2/33 (6%)
First incidence (days)	720	670	617	670
Life table test		P=0.484N		P=0.299
Logistic regression test		P=0.543N		P=0.290
Fisher exact test		P=0.547N		P=0.292
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/51 (6%)	2/51 (4%)	1/50 (2%)	2/51 (4%)
Adjusted rate	9.1%	4.9%		
Terminal rate	3/33 (9%)	1/38 (3%)		
First incidence (days)	726 (T)	677		
Life table test		P=0.442N		
Logistic regression test		P=0.483N		
Fisher exact test		P=0.500N		

TABLE H2a
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	25 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	25 mg/kg × Weight-Matched Control
All Organs: Hemangiosarcoma				
Overall rate	4/51 (8%)	1/51 (2%)	3/50 (6%)	1/51 (2%)
Adjusted rate	11.3%	2.6%	8.0%	2.6%
Terminal rate	2/33 (6%)	1/38 (3%)	2/36 (6%)	1/38 (3%)
First incidence (days)	709	726 (T)	721	726 (T)
Life table test		P=0.151N		P=0.292N
Logistic regression test		P=0.162N		P=0.316N
Fisher exact test		P=0.181N		P=0.301N
All Organs: Histiocytic Sarcoma				
Overall rate	1/51 (2%)	1/51 (2%)	4/50 (8%)	1/51 (2%)
Adjusted rate			8.8%	2.5%
Terminal rate			0/36 (0%)	0/38 (0%)
First incidence (days)			589	691
Life table test				P=0.206N
Logistic regression test				P=0.172N
Fisher exact test				P=0.175N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	9/51 (18%)	7/51 (14%)	6/50 (12%)	7/51 (14%)
Adjusted rate	23.0%	16.2%	15.6%	16.2%
Terminal rate	5/33 (15%)	3/38 (8%)	5/36 (14%)	3/38 (8%)
First incidence (days)	581	551	464	551
Life table test		P=0.332N		P=0.517
Logistic regression test		P=0.393N		P=0.519
Fisher exact test		P=0.393N		P=0.515
All Organs: Benign Neoplasms				
Overall rate	24/51 (47%)	18/51 (35%)	14/50 (28%)	18/51 (35%)
Adjusted rate	60.9%	43.8%	34.7%	43.8%
Terminal rate	18/33 (55%)	15/38 (39%)	10/36 (28%)	15/38 (39%)
First incidence (days)	511	670	617	670
Life table test		P=0.072N		P=0.309
Logistic regression test		P=0.129N		P=0.225
Fisher exact test		P=0.157N		P=0.283
All Organs: Malignant Neoplasms				
Overall rate	26/51 (51%)	14/51 (27%)	16/50 (32%)	14/51 (27%)
Adjusted rate	54.8%	31.6%	36.2%	31.6%
Terminal rate	12/33 (36%)	8/38 (21%)	9/36 (25%)	8/38 (21%)
First incidence (days)	492	551	464	551
Life table test		P=0.016N		P=0.410N
Logistic regression test		P=0.025N		P=0.405N
Fisher exact test		P=0.013N		P=0.389N

TABLE H2a
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	25 mg/kg × *Ad Libitum*-Fed Control	Weight-Matched Control	25 mg/kg × Weight-Matched Control
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/51 (78%)	29/51 (57%)	28/50 (56%)	29/51 (57%)
Adjusted rate	83.2%	64.3%	60.5%	64.3%
Terminal rate	25/33 (76%)	22/38 (58%)	18/36 (50%)	22/38 (58%)
First incidence (days)	492	551	464	551
Life table test		P=0.013N		P=0.551
Logistic regression test		P=0.029N		P=0.467
Fisher exact test		P=0.017N		P=0.545

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the *ad libitum* or weight-matched controls and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE H2b
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Bone Marrow: Hemangiosarcoma				
Overall rate[a]	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate[b]			7.1%	5.3%
Terminal rate[c]			0/20 (0%)	1/19 (5%)
First incidence (days)			611	1,087 (T)
Life table test[d]				P=0.318N
Logistic regression test[d]				P=0.281N
Fisher exact test[d]				P=0.309N
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	6.4%	0.0%	0.0%	11.5%
Terminal rate	3/47 (6%)	0/44 (0%)	0/20 (0%)	1/19 (5%)
First incidence (days)	723 (T)	-	-	972
Life table test		P=0.133N		P=0.140
Logistic regression test		P=0.133N		P=0.121
Fisher exact test		P=0.121N		P=0.121
Liver: Hepatocellular Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	12/50 (24%)	8/50 (16%)
Adjusted rate	6.4%	6.8%	47.5%	31.8%
Terminal rate	3/47 (6%)	3/44 (7%)	8/20 (40%)	3/19 (16%)
First incidence (days)	723 (T)	723 (T)	771	987
Life table test		P=0.632		P=0.241N
Logistic regression test		P=0.632		P=0.207N
Fisher exact test		P=0.661N		P=0.227N
Liver: Hepatocellular Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adjusted rate			13.4%	15.6%
Terminal rate			1/20 (5%)	2/19 (11%)
First incidence (days)			901	848
Life table test				P=0.639N
Logistic regression test				P=0.643
Fisher exact test				P=0.643N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	15/50 (30%)	11/50 (22%)
Adjusted rate	6.4%	6.8%	54.8%	39.6%
Terminal rate	3/47 (6%)	3/44 (7%)	9/20 (45%)	4/19 (21%)
First incidence (days)	723 (T)	723 (T)	771	848
Life table test		P=0.632		P=0.266N
Logistic regression test		P=0.632		P=0.232N
Fisher exact test		P=0.661N		P=0.247N

TABLE H2b
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rate	6.4%	4.4%	6.9%	15.4%
Terminal rate	3/47 (6%)	1/44 (2%)	1/20 (5%)	1/19 (5%)
First incidence (days)	723 (T)	666	555	848
Life table test		P=0.528N		P=0.332
Logistic regression test		P=0.508N		P=0.338
Fisher exact test		P=0.500N		P=0.339
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rate	6.3%	0.0%	8.9%	10.5%
Terminal rate	2/47 (4%)	0/44 (0%)	0/20 (0%)	2/19 (11%)
First incidence (days)	628	–	860	1,087 (T)
Life table test		P=0.134N		P=0.528N
Logistic regression test		P=0.107N		P=0.500N
Fisher exact test		P=0.121N		P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/50 (12%)	2/50 (4%)	5/50 (10%)	6/50 (12%)
Adjusted rate	12.5%	4.4%	15.2%	24.8%
Terminal rate	5/47 (11%)	1/44 (2%)	1/20 (5%)	3/19 (16%)
First incidence (days)	628	666	555	848
Life table test		P=0.159N		P=0.474
Logistic regression test		P=0.129N		P=0.499
Fisher exact test		P=0.134N		P=0.500
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/49 (6%)	2/50 (4%)
Adjusted rate			11.5%	6.6%
Terminal rate			1/20 (5%)	0/19 (0%)
First incidence (days)			898	703
Life table test				P=0.504N
Logistic regression test				P=0.491N
Fisher exact test				P=0.490N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	0/46 (0%)	1/46 (2%)	3/42 (7%)	2/49 (4%)
Adjusted rate			16.7%	8.0%
Terminal rate			3/18 (17%)	0/19 (0%)
First incidence (days)			1,087 (T)	987
Life table test				P=0.471N
Logistic regression test				P=0.425N
Fisher exact test				P=0.427N

TABLE H2b
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Pituitary Gland (Pars Intermedia): Adenoma				
Overall rate	1/46 (2%)	0/46 (0%)	4/42 (10%)	2/49 (4%)
Adjusted rate			16.5%	7.3%
Terminal rate			1/18 (6%)	0/19 (0%)
First incidence (days)			946	980
Life table test				P=0.315N
Logistic regression test				P=0.086N
Fisher exact test				P=0.268N
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	5/50 (10%)
Adjusted rate			11.0%	13.5%
Terminal rate			0/20 (0%)	0/19 (0%)
First incidence (days)			537	737
Life table test				P=0.502
Logistic regression test				P=0.537
Fisher exact test				P=0.500
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	5/50 (10%)
Adjusted rate			14.4%	13.5%
Terminal rate			0/20 (0%)	0/19 (0%)
First incidence (days)			537	737
Life table test				P=0.615N
Logistic regression test				P=0.603N
Fisher exact test				P=0.630N
Spleen: Hemangiosarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate			2.1%	13.2%
Terminal rate			0/20 (0%)	2/19 (11%)
First incidence (days)			611	952
Life table test				P=0.318
Logistic regression test				P=0.306
Fisher exact test				P=0.309
All Organs: Hemangiosarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rate			7.1%	13.2%
Terminal rate			0/20 (0%)	2/19 (11%)
First incidence (days)			611	952
Life table test				P=0.656N
Logistic regression test				P=0.656N
Fisher exact test				P=0.661N

TABLE H2b
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
All Organs: Histiocytic Sarcoma				
Overall rate	2/50 (4%)	3/50 (6%)	5/50 (10%)	5/50 (10%
Adjusted rate	4.1%	6.4%	13.9%	16.0%
Terminal rate	1/47 (2%)	1/44 (2%)	1/20 (5%)	1/19 (5%)
First incidence (days)	492	597	555	679
Life table test		P=0.481		P=0.615N
Logistic regression test		P=0.532		P=0.609N
Fisher exact test		P=0.500		P=0.630N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	2/50 (4%)	3/50 (6%)	14/50 (28%)	13/50 (26%)
Adjusted rate	4.3%	6.8%	47.0%	35.1%
Terminal rate	2/47 (4%)	3/44 (7%)	6/20 (30%)	1/19 (5%)
First incidence (days)	723 (T)	723 (T)	771	561
Life table test		P=0.470		P=0.518N
Logistic regression test		P=0.470		P=0.499N
Fisher exact test		P=0.500		P=0.500N
All Organs: Benign Neoplasms				
Overall rate	12/50 (24%)	10/50 (20%)	22/50 (44%)	18/50 (36%)
Adjusted rate	25.5%	22.2%	71.2%	60.2%
Terminal rate	12/47 (26%)	9/44 (20%)	12/20 (60%)	8/19 (42%)
First incidence (days)	723 (T)	666	555	703
Life table test		P=0.473N		P=0.301N
Logistic regression test		P=0.452N		P=0.259N
Fisher exact test		P=0.405N		P=0.270N
All Organs: Malignant Neoplasms				
Overall rate	8/50 (16%)	7/50 (14%)	35/50 (70%)	31/50 (62%)
Adjusted rate	16.0%	14.8%	75.2%	71.4%
Terminal rate	5/47 (11%)	4/44 (9%)	9/20 (45%)	8/19 (42%)
First incidence (days)	492	538	537	561
Life table test		P=0.541N		P=0.364N
Logistic regression test		P=0.429N		P=0.261N
Fisher exact test		P=0.500N		P=0.263N

TABLE H2b
Statistical Analysis of Primary Neoplasms in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	19/50 (38%)	16/50 (32%)	42/50 (84%)	41/50 (82%)
Adjusted rate	38.0%	33.3%	87.2%	88.9%
Terminal rate	16/47 (34%)	12/44 (27%)	14/20 (70%)	14/19 (74%)
First incidence (days)	492	538	537	561
Life table test		P=0.426N		P=0.518N
Logistic regression test		P=0.285N		P=0.600N
Fisher exact test		P=0.338N		P=0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for bone marrow, liver, lung, pancreatic islets, pituitary gland, and spleen; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE H3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Disposition Summary			
Animals initially in study	70[b]	60	70[b]
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths	2	1	
Moribund	9	10	7
Natural deaths	7	3	6
Survivors			
Terminal sacrifice	33	36	38
Animals examined microscopically	61	60	61
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Basophilic focus		1 (10%)	
Inflammation			1 (10%)
Mixed cell focus	1 (10%)		
Necrosis			1 (10%)
Pancreas	(10)	(10)	(10)
Atrophy	1 (10%)		
Stomach, forestomach	(10)	(10)	(10)
Hyperplasia, focal	2 (20%)	1 (10%)	2 (20%)
Endocrine System			
Adrenal cortex	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)		
Parathyroid gland	(10)	(10)	(8)
Cyst	1 (10%)		
Pituitary gland	(10)	(10)	(10)
Pars distalis, hyperplasia	3 (30%)		1 (10%)
Thyroid gland	(10)	(10)	(10)
Follicular cell, hyperplasia	2 (20%)		
Inflammation, chronic active		1 (10%)	
Genital System			
Ovary	(10)	(10)	(10)
Cyst	1 (10%)	1 (10%)	2 (20%)
Uterus	(10)	(10)	(10)
Hyperplasia, cystic	5 (50%)	1 (10%)	4 (40%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Nine animals were removed for supplemental evaluations that were not included in the dietary restriction study.

TABLE H3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
15-Month Interim Evaluation (continued)			
Hematopoietic System			
Bone marrow	(10)	(10)	(10)
Myelofibrosis	1 (10%)	1 (10%)	
Thymus	(9)	(10)	(10)
Inflammation, chronic active			1 (10%)
Mineralization	1 (11%)		
Respiratory System			
Lung	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)		
Alveolar epithelium, hyperplasia	1 (10%)		
Urinary System			
Kidney	(10)	(10)	(10)
Nephropathy	5 (50%)	2 (20%)	2 (20%)
Systems Examined With No Lesions Observed			
Cardiovascular System			
General Body System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Special Senses System			
2-Year Study			
Alimentary System			
Esophagus	(51)	(50)	(50)
Perforation	1 (2%)	1 (2%)	
Periesophageal tissue, inflammation, suppurative	3 (6%)	1 (2%)	
Intestine large, rectum	(51)	(50)	(50)
Inflammation, chronic active			1 (2%)
Intestine small, jejunum	(51)	(49)	(50)
Hyperplasia, lymphoid	2 (4%)	2 (4%)	3 (6%)
Inflammation, chronic active		1 (2%)	
Liver	(51)	(50)	(51)
Angiectasis	1 (2%)	2 (4%)	1 (2%)
Basophilic focus	1 (2%)		3 (6%)
Clear cell focus		1 (2%)	
Ectopic tissue		1 (2%)	
Eosinophilic focus	17 (33%)	4 (8%)	9 (18%)
Fatty change		1 (2%)	
Hematopoietic cell proliferation		1 (2%)	1 (2%)

TABLE H3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Alimentary System (continued)			
Liver (continued)	(51)	(50)	(51)
Inflammation, chronic active	1 (2%)		
Mixed cell focus	6 (12%)	1 (2%)	3 (6%)
Necrosis		3 (6%)	1 (2%)
Mesentery	(7)	(5)	(5)
Inflammation, suppurative		2 (40%)	
Fat, necrosis	6 (86%)	1 (20%)	2 (40%)
Pancreas	(51)	(50)	(51)
Atrophy	5 (10%)	4 (8%)	
Hypertrophy	1 (2%)		
Duct, cyst	2 (4%)	3 (6%)	
Salivary glands	(51)	(50)	(51)
Atrophy		1 (2%)	
Duct, hyperplasia	1 (2%)		
Stomach, forestomach	(51)	(50)	(51)
Cyst		1 (2%)	
Diverticulum			1 (2%)
Hyperplasia, focal	6 (12%)	16 (32%)	12 (24%)
Stomach, glandular	(51)	(50)	(51)
Erosion	2 (4%)	2 (4%)	
Mineralization		1 (2%)	
Cardiovascular System			
Blood vessel	(51)	(50)	(51)
Aorta, inflammation, chronic active	1 (2%)		
Mineralization		1 (2%)	
Heart	(51)	(50)	(51)
Inflammation, chronic active	1 (2%)		
Mineralization	2 (4%)	1 (2%)	
Artery, inflammation, chronic active			2 (4%)
Endocrine System			
Adrenal cortex	(51)	(50)	(51)
Accessory adrenal cortical nodule		2 (4%)	1 (2%)
Hyperplasia	1 (2%)		1 (2%)
Adrenal medulla	(51)	(49)	(50)
Hyperplasia	3 (6%)	1 (2%)	
Islets, pancreatic	(51)	(50)	(51)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)
Parathyroid gland	(48)	(38)	(45)
Cytoplasmic alteration, focal		1 (3%)	
Pituitary gland	(50)	(48)	(46)
Pars distalis, hyperplasia	24 (48%)	11 (23%)	13 (28%)
Pars intermedia, hyperplasia			1 (2%)
Thyroid gland	(51)	(50)	(51)
Inflammation, chronic active	1 (2%)		1 (2%)
Follicular cell, hyperplasia	16 (31%)	5 (10%)	8 (16%)

TABLE H3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
General Body System			
None			
Genital System			
Clitoral gland	(48)	(50)	(48)
Duct, ectasia		1 (2%)	1 (2%)
Ovary	(51)	(49)	(51)
Cyst	16 (31%)	9 (18%)	12 (24%)
Inflammation, suppurative		2 (4%)	1 (2%)
Uterus	(51)	(50)	(51)
Hyperplasia, cystic	38 (75%)	28 (56%)	23 (45%)
Inflammation, chronic active	1 (2%)	1 (2%)	
Thrombosis		1 (2%)	
Hematopoietic System			
Bone marrow	(51)	(50)	(51)
Myelofibrosis	22 (43%)	17 (34%)	13 (25%)
Erythroid cell, hyperplasia	3 (6%)	2 (4%)	
Myeloid cell, hyperplasia	9 (18%)	7 (14%)	3 (6%)
Lymph node	(6)	(3)	(3)
Bronchial, inflammation, chronic active		1 (33%)	
Lymph node, mandibular	(50)	(48)	(51)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
Lymph node, mesenteric	(50)	(48)	(48)
Hyperplasia, lymphoid		1 (2%)	2 (4%)
Inflammation, chronic active		1 (2%)	
Spleen	(51)	(50)	(51)
Depletion lymphoid	2 (4%)	1 (2%)	
Hematopoietic cell proliferation	17 (33%)	11 (22%)	7 (14%)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	2 (4%)
Hyperplasia, plasma cell	1 (2%)		
Thymus	(48)	(43)	(45)
Atrophy	3 (6%)	2 (5%)	3 (7%)
Integumentary System			
Mammary gland	(51)	(50)	(51)
Hyperplasia	1 (2%)		4 (8%)
Skin	(51)	(50)	(51)
Cyst epithelial inclusion			1 (2%)
Inflammation, chronic active	1 (2%)		
Ulcer	1 (2%)		

TABLE H3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
2-Year Study (continued)			
Musculoskeletal System			
None			
Nervous System			
Brain	(51)	(50)	(51)
Infarct	1 (2%)		
Neuron, necrosis	1 (2%)	4 (8%)	2 (4%)
Peripheral nerve	(2)	(2)	
Degeneration	2 (100%)	1 (50%)	
Respiratory System			
Lung	(51)	(50)	(51)
Inflammation, chronic active	1 (2%)		
Special Senses System			
Eye	(2)		
Cornea, inflammation, chronic active	2 (100%)		
Ear		(1)	
Internal ear, inflammation, chronic active		1 (100%)	
Urinary System			
Kidney	(51)	(50)	(51)
Cyst	1 (2%)		
Infarct	1 (2%)		
Inflammation, chronic active			1 (2%)
Mineralization		1 (2%)	
Nephropathy	23 (45%)	23 (46%)	10 (20%)
Artery, inflammation, chronic active			1 (2%)
Renal tubule, necrosis, acute	1 (2%)		
Urinary bladder	(50)	(50)	(51)
Inflammation, chronic active			1 (2%)
Artery, inflammation, chronic active			1 (2%)

TABLE H3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols[a]

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
Disposition Summary				
Animals initially in study	60	60	50	50
15-Month interim evaluation	10	10		
Early deaths				
Accidental deaths		1		1
Moribund	2	2	18	16
Natural deaths	1	3	12	14
Survivors				
Terminal sacrifice	47	44	20	19
Animals examined microscopically	60	60	50	50
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)		
Basophilic focus		1 (10%)		
Stomach, forestomach	(10)	(10)		
Hyperplasia, focal	7 (70%)	6 (60%)		
Cardiovascular System				
Heart	(10)	(10)		
Inflammation, chronic active	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)		
Accessory adrenal cortical nodule	1 (10%)			
Parathyroid gland	(8)	(8)		
Cyst		1 (13%)		
Pituitary gland	(10)	(10)		
Pars distalis, hyperplasia	1 (10%)			
Genital System				
Ovary	(10)	(10)		
Cyst	1 (10%)			
Uterus	(10)	(10)		
Hyperplasia, cystic		2 (20%)		
Respiratory System				
Lung	(10)	(10)		
Inflammation, chronic active		1 (10%)		

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

TABLE H3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
15-Month Interim Evaluation (continued)				
Special Senses System				
Harderian gland		(3)		
Inflammation, chronic active		1 (33%)		
Systems Examined With No Lesions Observed				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Urinary System				
2-Year and 3-Year Protocols				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Periesophageal tissue, degeneration		1 (2%)		
Periesophageal tissue, hemorrhage				1 (2%)
Gallbladder	(50)	(50)	(50)	(49)
Inflammation, chronic active			1 (2%)	1 (2%)
Intestine small, jejunum	(50)	(50)	(50)	(49)
Hemorrhage				1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			1 (2%)
Basophilic focus	1 (2%)	1 (2%)		3 (6%)
Clear cell focus				2 (4%)
Eosinophilic focus		1 (2%)	4 (8%)	
Hematopoietic cell proliferation			1 (2%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, focal			1 (2%)	
Mixed cell focus	2 (4%)			1 (2%)
Necrosis		1 (2%)	2 (4%)	1 (2%)
Bile duct, cyst				2 (4%)
Bile duct, hyperplasia		1 (2%)		
Centrilobular, necrosis	1 (2%)			
Serosa, pigmentation, hemosiderin	1 (2%)			
Pancreas	(50)	(50)	(49)	(50)
Acinus, atrophy		3 (6%)	4 (8%)	3 (6%)
Acinus, hyperplasia, focal	3 (6%)			
Artery, inflammation, chronic active			2 (4%)	
Duct, ectasia		1 (2%)	1 (2%)	2 (4%)

TABLE H3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Cyst			1 (2%)	
Erosion	1 (2%)			
Hyperplasia, focal	29 (58%)	31 (62%)	23 (46%)	29 (58%)
Infiltration cellular, mast cell	1 (2%)			
Mineralization				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Dysplasia				1 (2%)
Erosion				1 (2%)
Mineralization				1 (2%)
Tooth			(2)	(2)
Dysplasia			2 (100%)	1 (50%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)		
Aorta, inflammation			1 (2%)	
Aorta, thrombosis			2 (4%)	
Heart	(50)	(50)	(50)	(50)
Degeneration				1 (2%)
Mineralization	2 (4%)		1 (2%)	
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Accessory adrenal cortical nodule		1 (2%)		1 (2%)
Angiectasis			1 (2%)	2 (4%)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Hypertrophy	1 (2%)			
Capsule, hyperplasia			1 (2%)	
Adrenal medulla	(49)	(50)	(49)	(50)
Hyperplasia				1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia			1 (2%)	
Parathyroid gland	(44)	(41)	(45)	(46)
Cyst		1 (2%)		1 (2%)
Pituitary gland	(46)	(46)	(42)	(49)
Pars distalis, hyperplasia	1 (2%)	4 (9%)	8 (19%)	1 (2%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(49)	(50)	(50)
Inflammation, chronic active	1 (2%)			
Follicular cell, hyperplasia	2 (4%)		9 (18%)	2 (4%)
General Body System				
None				

TABLE H3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Genital System				
Clitoral gland	(49)	(49)	(50)	(48)
Inflammation, chronic active			1 (2%)	1 (2%)
Duct, ectasia			2 (4%)	
Ovary	(50)	(50)	(49)	(49)
Angiectasis		1 (2%)	2 (4%)	1 (2%)
Atrophy	1 (2%)			
Cyst	13 (26%)	9 (18%)	18 (37%)	19 (39%)
Hemorrhage	1 (2%)			
Inflammation, chronic active			2 (4%)	
Thrombosis			1 (2%)	1 (2%)
Corpus luteum, hyperplasia			1 (2%)	
Uterus	(50)	(50)	(49)	(49)
Hemorrhage			1 (2%)	
Hyperplasia, cystic	16 (32%)	15 (30%)	9 (18%)	11 (22%)
Inflammation, suppurative	1 (2%)			
Thrombosis			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Myelofibrosis	7 (14%)	13 (26%)	19 (38%)	13 (26%)
Erythroid cell, hyperplasia		1 (2%)	4 (8%)	1 (2%)
Myeloid cell, hyperplasia	1 (2%)	1 (2%)	9 (18%)	7 (14%)
Lymph node			(13)	(8)
Hematopoietic cell proliferation				1 (13%)
Hyperplasia, lymphoid			1 (8%)	
Lymph node, mandibular	(50)	(48)	(45)	(47)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	
Lymph node, mesenteric	(44)	(50)	(43)	(48)
Angiectasis			3 (7%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Depletion lymphoid				1 (2%)
Hematopoietic cell proliferation	3 (6%)	7 (14%)	21 (42%)	17 (34%)
Hyperplasia, lymphoid	1 (2%)		2 (4%)	
Thymus	(45)	(49)	(37)	(42)
Atrophy	1 (2%)	1 (2%)	9 (24%)	5 (12%)
Hyperplasia, lymphoid		2 (4%)		
Integumentary System				
Mammary gland			(49)	(49)
Hyperplasia	(50)	(50)	1 (2%)	
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, inflammation, chronic active			1 (2%)	1 (2%)

TABLE H3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

	2-Year Restricted Feed		3-Year Restricted Feed	
	Vehicle Control	25 mg/kg	Vehicle Control	25 mg/kg
2-Year and 3-Year Protocols (continued)				
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Granuloma, focal				1 (2%)
Neuron, necrosis			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Infiltration cellular, histiocyte	2 (4%)			
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, chronic active				1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	4 (8%)		4 (8%)
Nose	(50)	(49)	(50)	(50)
Infiltration cellular, mast cell			1 (2%)	
Special Senses System				
Eye			(1)	(3)
Lens, cataract			1 (100%)	3 (100%)
Harderian gland	(24)	(23)	(22)	(25)
Hyperplasia				1 (4%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cytoplasmic alteration		1 (2%)	1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	
Nephropathy	16 (32%)	6 (12%)	19 (38%)	13 (26%)
Pelvis, inflammation, chronic active				1 (2%)
Renal tubule, necrosis	1 (2%)			
Urinary bladder	(50)	(50)	(49)	(49)
Inflammation, chronic active			1 (2%)	1 (2%)

APPENDIX I
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE I1a
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	12,000 ppm
Male			
n	10	10	10
Necropsy body wt	458 ± 10	397 ± 9	416 ± 8**▲▲
Epididymis			
Absolute	0.428 ± 0.016	0.451 ± 0.032	0.433 ± 0.009
Relative	0.93 ± 0.02	1.14 ± 0.08	1.04 ± 0.02**
R. Kidney			
Absolute	1.608 ± 0.045	1.425 ± 0.043	1.706 ± 0.048▲▲
Relative	3.52 ± 0.10	3.58 ± 0.03	4.10 ± 0.08**▲▲
Liver			
Absolute	15.463 ± 0.524	12.350 ± 0.429	15.761 ± 0.483▲▲
Relative	33.75 ± 0.92	31.08 ± 0.64	37.82 ± 0.78**▲▲
R. Testis			
Absolute	1.638 ± 0.122	1.640 ± 0.177	1.771 ± 0.165
Relative	3.62 ± 0.36	4.15 ± 0.46	4.27 ± 0.42

	Ad Libitum-Fed Control	Weight-Matched Control	24,000 ppm
Female			
n	10	10	10
Necropsy body wt	279 ± 7	198 ± 2	215 ± 4**▲▲
R. Kidney			
Absolute	0.931 ± 0.022	0.674 ± 0.017	0.878 ± 0.018▲▲
Relative	3.34 ± 0.07	3.40 ± 0.06	4.09 ± 0.12**▲▲
Liver			
Absolute	8.629 ± 0.189	5.122 ± 0.123	8.377 ± 0.153▲▲
Relative	31.01 ± 0.81	25.87 ± 0.52	38.96 ± 0.57**▲▲

** Significantly different ($P \leq 0.01$) from the *ad libitum*-fed control group by Student's *t*-test
▲▲ Significantly different ($P \leq 0.01$) from the weight-matched control group by Student's *t*-test
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE I1b
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and 30-Month Restricted Feed Protocols[a]

	0 ppm	12,000 ppm
Male		
n	10	10
Necropsy body wt	381 ± 5	365 ± 7
Epididymis		
Absolute	0.464 ± 0.007	0.458 ± 0.016
Relative	1.22 ± 0.03	1.26 ± 0.06
R. Kidney		
Absolute	1.329 ± 0.027	1.488 ± 0.020**
Relative	3.49 ± 0.07	4.08 ± 0.05**
Liver		
Absolute	11.546 ± 0.248	12.229 ± 0.317
Relative	30.26 ± 0.47	33.51 ± 0.67**
R. Testis		
Absolute	1.552 ± 0.017	1.552 ± 0.166
Relative	4.07 ± 0.07	4.25 ± 0.44
	0 ppm	**24,000 ppm**
Female		
n	10	10
Necropsy body wt	235 ± 3	195 ± 4**
R. Kidney		
Absolute	0.838 ± 0.012	0.808 ± 0.014
Relative	3.57 ± 0.06	4.15 ± 0.07**
Liver		
Absolute	7.241 ± 0.149	7.191 ± 0.162
Relative	30.82 ± 0.57	36.85 ± 0.45**

** Significantly different ($P \leq 0.01$) from the control group by Student's *t*-test
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE I2a
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 3-Month Interim Evaluation in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	5,000 ppm
n	10	10	10
Male			
Necropsy body wt	355 ± 7	329 ± 3	341 ± 6
Epididymis			
Absolute	0.472 ± 0.020	0.454 ± 0.009	0.479 ± 0.014
Relative	1.33 ± 0.07	1.38 ± 0.03	1.41 ± 0.04
R. Kidney			
Absolute	1.389 ± 0.038	1.261 ± 0.021	1.385 ± 0.052▲
Relative	3.91 ± 0.06	3.84 ± 0.05	4.06 ± 0.10
Liver			
Absolute	13.467 ± 0.435	12.424 ± 0.592	14.420 ± 0.451▲
Relative	37.88 ± 0.62	37.81 ± 1.77	42.26 ± 0.86**▲
R. Testis			
Absolute	1.489 ± 0.022	1.451 ± 0.015	1.485 ± 0.022
Relative	4.21 ± 0.11	4.42 ± 0.04	4.36 ± 0.07
Female			
Necropsy body wt	199 ± 2	180 ± 2	181 ± 2**
R. Kidney			
Absolute	0.749 ± 0.013	0.684 ± 0.006	0.675 ± 0.015**
Relative	3.76 ± 0.07	3.80 ± 0.04	3.73 ± 0.07
Liver			
Absolute	6.310 ± 0.150	5.589 ± 0.085	6.255 ± 0.096▲▲
Relative	31.70 ± 0.80	31.07 ± 0.47	34.61 ± 0.37**▲▲

** Significantly different ($P \leq 0.01$) from the *ad libitum*-fed control group by Student's *t*-test
▲ Significantly different ($P \leq 0.05$) from the weight-matched control group by Student's *t*-test
▲▲ $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE I2b
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 3-Month Interim Evaluation in the Dietary Restriction Study of *t*-Butylhydroquinone: Restricted Feed Protocol[a]

	0 ppm	5,000 ppm
n	10	10
Male		
Necropsy body wt	303 ± 4	297 ± 4
Epididymis		
Absolute	0.461 ± 0.010	0.464 ± 0.012
Relative	1.52 ± 0.02	1.56 ± 0.03
R. Kidney		
Absolute	1.195 ± 0.025	1.269 ± 0.029
Relative	3.95 ± 0.07	4.28 ± 0.08**
Liver		
Absolute	10.851 ± 0.323	12.871 ± 0.145**
Relative	35.79 ± 0.75	43.44 ± 0.70**
R. Testis		
Absolute	1.494 ± 0.018	1.460 ± 0.031
Relative	4.94 ± 0.07	4.92 ± 0.08
Female		
Necropsy body wt	174 ± 3	162 ± 2**
R. Kidney		
Absolute	0.645 ± 0.014	0.624 ± 0.018
Relative	3.70 ± 0.04	3.84 ± 0.10
Liver		
Absolute	5.577 ± 0.528	6.004 ± 0.511
Relative	31.80 ± 2.46	37.00 ± 3.19

** Significantly different ($P \leq 0.01$) from the control group by Student's *t*-test
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE I3a
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 15-Month Interim Evaluation in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	377.5 mg/kg
n	10	10	10
Necropsy body wt	491 ± 8	477 ± 8	459 ± 8*
R. Kidney			
Absolute	1.639 ± 0.061	1.569 ± 0.043	1.590 ± 0.029
Relative	3.33 ± 0.10	3.29 ± 0.07	3.47 ± 0.05
Liver			
Absolute	16.660 ± 0.544	15.768 ± 0.431	15.713 ± 0.370
Relative	33.89 ± 0.92	33.06 ± 0.85	34.24 ± 0.69
Spleen			
Absolute	0.803 ± 0.026	0.738 ± 0.034	0.727 ± 0.015*
Relative	1.63 ± 0.04	1.64 ± 0.07	1.58 ± 0.02
L. Testis			
Absolute	1.641 ± 0.055	1.783 ± 0.111	1.842 ± 0.167
Relative	3.34 ± 0.08	3.65 ± 0.25	4.01 ± 0.35
R. Testis			
Absolute	1.559 ± 0.040	1.512 ± 0.047	1.743 ± 0.157
Relative	3.17 ± 0.06	3.18 ± 0.13	3.79 ± 0.32
Thyroid gland			
Absolute	0.025 ± 0.003	0.020 ± 0.003	0.022 ± 0.002
Relative	0.05 ± 0.01	0.04 ± 0.01	0.05 ± 0.00

* Significantly different ($P \leq 0.05$) from the *ad libitum*-fed control group by Student's *t*-test
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE I3b
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 15-Month Interim Evaluation in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols[a]

	Vehicle Control	337.5 mg/kg
n	10	10
Necropsy body wt	419 ± 11	396 ± 8
R. Kidney		
Absolute	1.404 ± 0.037	1.394 ± 0.042
Relative	3.36 ± 0.07	3.51 ± 0.05
Liver		
Absolute	13.635 ± 0.331	13.083 ± 0.498[b]
Relative	32.67 ± 0.79	32.59 ± 1.06[b]
Spleen		
Absolute	0.734 ± 0.038	0.653 ± 0.014
Relative	1.76 ± 0.10	1.65 ± 0.04
L. Testis		
Absolute	1.699 ± 0.068	1.801 ± 0.129
Relative	4.06 ± 0.11	4.59 ± 0.41
R. Testis		
Absolute	1.443 ± 0.205	1.576 ± 0.085
Relative	3.41 ± 0.48	3.97 ± 0.21
Thyroid gland		
Absolute	0.017 ± 0.001	0.017 ± 0.001
Relative	0.04 ± 0.00	0.04 ± 0.00

[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE I4a
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Mice at the 15-Month Interim Evaluation in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	2,700 mg/kg
n	10	10	10
Necropsy body wt	53.9 ± 1.1	45.7 ± 1.4	44.9 ± 1.3**
R. Kidney			
Absolute	0.424 ± 0.018	0.353 ± 0.010	0.359 ± 0.011**
Relative	7.87 ± 0.30	7.76 ± 0.22	8.05 ± 0.30
Liver			
Absolute	2.328 ± 0.106	1.610 ± 0.112	2.305 ± 0.062▲▲
Relative	43.02 ± 1.15	35.01 ± 1.59	51.55 ± 1.19**▲▲
Spleen			
Absolute	0.100 ± 0.008	0.073 ± 0.005	0.119 ± 0.006▲▲
Relative	1.86 ± 0.17	1.61 ± 0.12	2.67 ± 0.15**▲▲
R. Testis			
Absolute	0.113 ± 0.004[b]	0.117 ± 0.003	0.108 ± 0.005
Relative	2.11 ± 0.08[b]	2.57 ± 0.07	2.44 ± 0.14
Thyroid gland			
Absolute	0.003 ± 0.000	0.004 ± 0.000	0.004 ± 0.000
Relative	0.06 ± 0.01	0.08 ± 0.01	0.08 ± 0.01

** Significantly different ($P \leq 0.01$) from the *ad libitum*-fed control group by Student's *t*-test
▲▲ Significantly different ($P \leq 0.01$) from the weight-matched control group by Student's *t*-test
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE I4b
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Mice at the 15-Month Interim Evaluation in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols[a]

	Vehicle Control	2,700 mg/kg
n	10	10
Necropsy body wt	47.7 ± 1.7	34.4 ± 0.6**
R. Kidney		
Absolute	0.325 ± 0.013	0.279 ± 0.011*
Relative	6.85 ± 0.28	8.14 ± 0.38*
Liver		
Absolute	1.758 ± 0.097	1.757 ± 0.034
Relative	36.75 ± 1.26	51.18 ± 1.10**
Spleen		
Absolute	0.073 ± 0.004	0.124 ± 0.007**
Relative	1.53 ± 0.07	3.62 ± 0.23**
R. Testis		
Absolute	0.122 ± 0.004	0.112 ± 0.002*
Relative	2.58 ± 0.11	3.27 ± 0.10**
Thyroid gland		
Absolute	0.003 ± 0.000	0.003 ± 0.000
Relative	0.06 ± 0.01	0.08 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Student's *t*-test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE I5a
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

	Ad Libitum-Fed Control	Weight-Matched Control	25 mg/kg
Male			
n	9	10	10
Necropsy body wt	50.2 ± 0.6	39.3 ± 1.3	39.0 ± 0.6**
R. Epididymis			
Absolute	0.062 ± 0.003	0.057 ± 0.003	0.057 ± 0.003
Relative	1.23 ± 0.05	1.47 ± 0.08	1.45 ± 0.06*
R. Kidney			
Absolute	0.376 ± 0.015	0.303 ± 0.010	0.325 ± 0.006**
Relative	7.47 ± 0.22	7.73 ± 0.22	8.32 ± 0.09**▲
Liver			
Absolute	2.336 ± 0.122	1.300 ± 0.051	2.152 ± 0.353▲
Relative	46.54 ± 2.34	33.09 ± 0.91	55.43 ± 9.41▲
R. Testis			
Absolute	0.119 ± 0.003	0.116 ± 0.004	0.117 ± 0.003
Relative	2.37 ± 0.05	2.98 ± 0.16	2.99 ± 0.04**
Female			
n	10	10	10
Necropsy body wt	53.2 ± 1.9	41.4 ± 1.2	40.7 ± 1.7**
R. Kidney			
Absolute	0.256 ± 0.005	0.233 ± 0.004	0.237 ± 0.008
Relative	4.83 ± 0.10	5.68 ± 0.21	5.87 ± 0.16**
Liver			
Absolute	1.915 ± 0.058	1.613 ± 0.023	1.820 ± 0.051▲▲
Relative	36.09 ± 0.58	39.27 ± 1.19	45.15 ± 1.50**▲▲

* Significantly different ($P \leq 0.05$) from the *ad libitum*-fed control group by Student's *t*-test
** $P \leq 0.01$
▲ Significantly different ($P \leq 0.05$) from the weight-matched control group by Student's *t*-test
▲▲ $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE I5b
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols[a]

	Vehicle Control	25 mg/kg
n	10	10
Male		
Necropsy body wt	38.2 ± 0.5	36.6 ± 0.6*
R. Epididymis		
Absolute	0.055 ± 0.002	0.053 ± 0.003
Relative	1.43 ± 0.04	1.46 ± 0.07
R. Kidney		
Absolute	0.340 ± 0.006	0.314 ± 0.004**
Relative	8.91 ± 0.18	8.60 ± 0.09
Liver		
Absolute	1.766 ± 0.016	1.714 ± 0.023
Relative	46.25 ± 0.52	46.94 ± 0.81
R. Testis		
Absolute	0.120 ± 0.002	0.117 ± 0.003
Relative	3.13 ± 0.06	3.19 ± 0.06
Female		
Necropsy body wt	35.8 ± 0.8	34.4 ± 0.6
R. Kidney		
Absolute	0.238 ± 0.003	0.243 ± 0.007
Relative	6.68 ± 0.15	7.06 ± 0.23
Liver		
Absolute	1.630 ± 0.031	1.619 ± 0.025
Relative	45.64 ± 1.14	47.14 ± 0.89

* Significantly different ($P \leq 0.05$) from the control group by Student's *t*-test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX J
MEAN BODY WEIGHT AND SURVIVAL RESULTS

TABLE J1a
Mean Body Weights and Survival of Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Weeks on Study	*Ad Libitum*-Fed Control		Weight-Matched Control		12,000 ppm			
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of *ad libitum*-fed controls)	Wt. (% of weight-matched controls)	No. of Survivors
Male								
1	113	60	110	60	108	96	98	60
2	149	60	146	60	141	95	97	60
3	183	60	181	60	180	98	99	60
4	205	60	210	60	208	101	99	60
5	233	60	234	60	226	97	97	60
6	253	60	252	60	243	96	97	60
7	266	60			255	96	100	60
8	286	60	282	60	272	95	96	60
9	298	60	297	60	284	95	96	60
10	310	60	306	60	291	94	95	60
11	319	60	319	60	301	94	94	60
12	326	60	325	60	312	96	96	60
13	339	60	335	60	315	93	94	60
17	370	60	365	60	338	91	93	60
21	391	60	352	60	351	90	100	60
25	391	60	364	60	362	93	100	60
29	416	60	381	60	377	91	99	59
33	423	60	399	60	382	90	96	59
37	429	60	395	60	389	91	98	59
41	437	58	378	60	394	90	104	59
45	443	58	391	60	405	92	104	58
49	449	58	365	60	413	92	113	58
53	451	58	400	59	414	92	104	58
57	450	58	391	59	412	92	105	58
61	451	58	413	59	413	92	100	58
65	451	57	412	58	420	93	102	58
69[a]	446	46	422	47	419	94	99	46
73	448	45	427	45	427	95	100	45
77	446	45	427	45	428	96	100	45
81	440	42	432	45	422	96	98	44
85	440	40	433	44	418	95	97	44
89	439	36	438	43	413	94	94	42
93	440	33	438	42	422	96	96	39
97	433	32	434	38	411	95	95	35
101	426	31	433	36	402	94	93	29
Mean for weeks								
1-13	252		250		241	96	96	
14-52	417		377		379	91	101	
53-101	443		423		417	94	99	

TABLE J1a
Mean Body Weights and Survival of Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

Weeks on Study	*Ad Libitum*-Fed Control		Weight-Matched Control		24,000 ppm			
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of *ad libitum*-fed controls)	Wt. (% of weight-matched controls)	No. of Survivors
Female								
1	99	60	97	60	92	93	95	60
2	121	60	120	60	114	94	95	60
3	135	60	134	60	127	94	95	60
4	142	60	142	60	137	97	96	60
5	153	60	151	60	142	93	94	60
6	159	59	159	60	151	95	95	60
7	167	59	166	60	157	94	95	60
8	171	59	170	60	160	94	95	60
9	175	59	174	60	166	95	96	60
10	178	59	180	60	171	96	95	60
11	180	59	183	60	170	95	93	60
12	186	59	186	60	175	94	94	60
13	185	59	184	60	176	95	96	60
17	198	59	193	60	183	93	95	60
21	204	59	203	60	187	92	92	60
25	213	59	209	60	193	91	92	60
29	218	59	221	60	197	91	89	60
33	223	59	211	59	199	89	94	60
37	231	59	204	59	203	88	99	60
41	238	59	198	59	206	87	104	60
45	240	59	196	59	207	86	106	60
49	258	59	194	59	212	82	109	60
53	269	59	199	59	214	80	108	60
57	276	58	200	59	214	78	107	60
61	281	58	202	59	216	77	107	59
65	286	58	203	59	220	77	109	59
69[a]	296	48	216	49	222	75	103	46
73	298	48	208	48	226	76	109	44
77	300	47	228	48	230	77	101	44
81	300	47	228	47	222	74	97	43
85	312	45	239	46	231	74	97	43
89	321	44	245	46	237	74	97	39
93	320	44	238	46	236	74	99	39
97	319	42	247	46	233	73	94	39
101	318	36	254	46	232	73	92	32
105			236	42	247		105	29
Mean for weeks								
1-13	158		157		149	94	95	
14-52	225		203		199	88	98	
53-105	300		225		227	76	101	

[a] Interim evaluation occurred during week 66.

TABLE J1b
Mean Body Weights and Survival of Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and Long-Term Restricted Feed Protocols

Weeks on Study	2-Year Protocol					30-Month Protocol				
	0 ppm		12,000 ppm			0 ppm		12,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
Male										
1	103	60	101	98	60	103	50	101	98	50
2	140	60	138	99	60	139	50	138	99	50
3	146	60	143	98	60	146	50	143	98	50
4	156	60	155	99	60	155	50	154	100	50
5	176	60	168	95	60	182	50	167	92	50
6	200	60	180	90	60	204	50	179	89	50
7	208	60	199	96	60	210	50	204	97	50
8	227	60	216	95	60	233	50	217	94	50
9	246	60	234	95	60	246	50	244	99	49
10	260	60	248	95	60	262	50	254	97	49
11	258	60	249	97	60	261	50	258	99	49
12	261	60	251	96	60	263	50	256	97	49
13	285	60	274	96	60	287	50	280	97	49
17	301	60	294	98	60	307	50	303	99	48
21	339	60	324	96	60	349	50	323	93	48
25	358	60	339	95	60	363	50	342	94	48
29	349	60	340	98	60	356	50	344	97	48
33	362	60	347	96	60	376	50	351	93	48
37	366	60	344	94	60	378	50	346	92	48
41	383	60	349	91	60	390	50	351	90	48
45	372	60	345	93	60	376	50	357	95	48
49	366	60	343	94	60	371	50	344	93	48
53	368	60	351	95	59	376	50	357	95	48
57	378	60	370	98	59	398	50	373	94	48
61	399	60	375	94	59	404	50	378	94	48
65	388	59	374	96	59	405	50	379	94	48
69[a]	406	48	377	93	49	408	50	381	94	48
73	403	48	378	94	49	410	50	374	91	46
77	377	47	354	94	48	376	49	347	92	44
81	395	46	372	94	48	389	49	364	93	42
85	398	45	362	91	48	399	48	364	91	41
89	371	44	342	92	45	371	46	345	93	40
93	365	42	362	99	41	378	44	367	97	37
97	371	41	341	92	39	386	40	348	90	36
101	354	38	340	96	35	370	37	342	93	33
105						360	32	334	93	30
109						359	26	327	91	26
113						359	20	332	93	24
117						332	16	314	94	19
121						324	12	304	94	18
125						329	11	307	93	14
Mean for weeks										
1-13	205		197	96		207		200	97	
14-52	355		336	95		363		340	94	
53-101	383		361	94		390		363	93	
102-125						344		320	93	

TABLE J1b
Mean Body Weights and Survival of Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and Long-Term Restricted Feed Protocols (continued)

Weeks on Study	2-Year Protocol					32-Month Protocol				
	0 ppm		24,000 ppm			0 ppm		24,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
Female										
1	94	60	88	93	60	95	50	87	91	50
2	116	60	107	92	60	118	50	105	89	50
3	128	60	118	92	60	128	50	116	91	50
4	131	60	124	95	60	131	50	122	93	50
5	133	60	127	96	60	134	50	127	95	50
6	146	60	134	92	60	146	50	133	91	50
7	141	60	130	92	60	142	50	130	91	50
8	141	60	141	100	60	141	50	139	98	50
9	159	60	148	93	60	158	50	147	93	50
10	155	60	145	94	60	155	50	145	93	50
11	157	60	146	93	60	157	50	146	93	50
12	160	60	152	95	60	161	50	151	94	50
13	162	60	155	96	60	163	50	151	92	50
17	170	60	164	97	60	170	50	164	96	50
21	176	60	164	93	60	180	50	164	91	50
25	189	60	178	94	60	188	50	176	93	50
29	193	60	180	93	60	194	50	180	93	50
33	194	60	175	90	60	195	50	173	89	50
37	182	60	176	97	60	183	50	180	99	50
41	191	60	175	92	60	199	50	173	87	50
45	190	60	180	95	60	192	50	178	93	50
49	198	59	184	93	60	200	50	184	92	50
53	206	58	191	93	60	209	49	191	91	50
57	217	58	194	90	60	221	49	191	87	50
61	222	58	198	89	60	227	49	196	86	50
65	228	58	197	87	59	232	49	197	85	50
69[a]	233	48	202	87	49	238	48	199	84	50
73	244	48	208	85	48	247	46	203	82	50
77	254	48	208	82	48	257	46	207	81	49
81	263	46	210	80	48	269	46	205	76	49
85	273	46	211	77	48	280	45	206	73	49
89	276	44	212	77	46	284	45	207	73	49
93	282	42	212	75	46	289	45	210	73	47
97	284	41	211	74	43	294	43	210	72	47
101	276	37	213	77	41	293	37	209	71	44
105						288	34	210	73	39
109						290	28	211	73	36
113						283	28	211	75	34
117						283	26	210	74	31
121						282	23	208	74	27
125						291	19	206	71	22
Mean for weeks										
1-13	140		132	94		141		131	93	
14-52	187		175	94		189		175	93	
53-101	251		205	82		257		202	79	
102-125						286		209	73	

[a] Interim evaluation occurred during week 66 of the 2-year protocol.

TABLE J2a
Mean Body Weights and Survival of Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Weeks on Study	*Ad Libitum*-Fed Control		Weight-Matched Control		5,000 ppm			
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of *ad libitum*-fed controls)	Wt. (% of weight-matched controls)	No. of Survivors
Male								
1	99	70	97	70	91	92	94	70
2	141	70	139	70	127	90	91	70
3	175	70	161	70	157	90	98	70
4	209	70	188	70	188	90	100	70
5	233	70	189	70	217	93	115	70
6	267	70	215	70	244	91	113	70
7	283	70	247	70	261	92	106	70
8	299	70	250	70	275	92	110	70
9	313	70	260	70	287	92	110	70
10	316	70	273	70	299	95	109	70
11	324	70	296	70	304	94	103	70
12	344	70	314	70	318	92	101	70
13	356	70	323	70	320	90	99	70
17[a]	379	60	364	60	346	91	95	60
21	400	60	336	60	358	89	106	60
25	413	60	348	60	376	91	108	60
29	419	60	384	60	386	92	100	60
33	428	60	380	60	392	92	103	60
37	437	60	389	60	402	92	103	60
41	450	60	393	60	416	92	106	60
45	452	60	406	60	415	92	102	60
49	444	60	398	60	415	94	104	60
53	468	60	417	60	431	92	103	60
57	468	59	415	59	435	93	105	60
61	467	59	419	59	440	94	105	60
65	470	59	429	59	440	94	103	59
69	468	59	428	59	437	93	102	59
73	472	56	423	59	433	92	102	57
77	463	55	435	59	438	95	101	55
81	464	52	432	59	436	94	101	53
85	462	51	428	58	429	93	100	52
89	455	51	431	54	425	93	99	51
93	458	46	429	51	419	92	98	44
97	455	39	434	45	421	92	97	39
101	447	35	430	41	421	94	98	34
105	440	28	426	35	409	93	96	30
109	420	21	416	30	412	98	99	25
113	429	13	419	27	395	92	95	19
117	428	10	399	23	397	93	99	15
121	417	8	406	14	386	93	95	14
Mean for weeks								
1-13	258		227		238	92	105	
14-52	425		378		390	92	103	
53-121	453		423		422	93	100	

TABLE J2a
Mean Body Weights and Survival of Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

Weeks on Study	*Ad Libitum*-Fed Control		Weight-Matched Control		5,000 ppm			
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of *ad libitum*-fed controls)	Wt. (% of weight-matched controls)	No. of Survivors
Female								
1	92	70	92	70	83	91	91	70
2	121	70	121	70	110	91	91	70
3	135	70	126	70	125	92	99	70
4	147	70	130	70	134	92	104	70
5	159	70	123	70	146	92	119	70
6	171	70	129	70	154	90	120	70
7	177	70	155	70	161	91	104	70
8	181	70	161	70	165	92	103	70
9	186	70	149	70	173	93	116	70
10	176	70	150	70	176	100	118	70
11	193	70	168	70	181	94	108	70
12	196	70	175	70	181	92	103	70
13	198	70	180	70	184	93	102	70
17[a]	203	60	192	60	188	93	98	60
21	224	60	192	60	200	89	104	60
25	222	60	207	60	203	91	98	60
29	229	60	213	60	210	91	98	60
33	231	60	210	60	210	91	100	60
37	232	60	219	60	213	92	97	60
41	240	60	227	60	219	92	97	60
45	248	58	225	60	227	91	101	60
49	257	58	231	60	232	90	100	60
53	264	58	227	59	236	90	104	60
57	279	57	236	59	246	88	104	60
61	285	55	240	58	257	90	107	60
65	292	55	243	58	263	90	108	60
69	301	55	245	58	265	88	108	60
73	309	54	250	58	270	87	108	59
77	315	54	259	56	274	87	106	59
81	323	51	257	56	278	86	108	59
85	327	49	266	56	282	87	106	57
89	333	48	272	54	287	86	106	54
93	342	43	274	51	290	85	106	50
97	348	42	270	50	299	86	111	46
101	347	39	282	50	301	87	107	43
105	345	35	285	46	303	88	106	42
109	341	31	287	42	300	88	104	40
113	337	24	295	39	301	89	102	37
117	348	18	295	35	309	89	105	33
121	341	16	294	31	315	92	107	27
Mean for weeks								
1-13	164		143		152	93	106	
14-52	232		213		211	91	99	
53-121	321		265		282	88	106	

[a] Interim evaluation occurred during week 14.

TABLE J2b
Mean Body Weights and Survival of Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: 30-Month Restricted Feed Protocol

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm Number of Survivors	5,000 ppm Av. Wt. (g)	5,000 ppm Wt. (% of controls)	5,000 ppm Number of Survivors
Male					
1	107	70	94	88	70
2	151	70	139	92	70
3	185	70	167	90	70
4	185	70	163	89	70
5	195	70	179	92	70
6	208	70	195	94	70
7	231	70	216	94	70
8	246	70	229	93	70
9	255	70	240	94	70
10	266	70	250	94	70
11	274	70	260	95	70
12	289	70	276	96	70
13	291	70	281	97	70
17[a]	314	60	309	98	60
21	351	60	341	97	60
25	343	60	342	100	60
29	348	60	344	99	60
33	358	60	362	101	60
37	371	60	370	100	60
41	390	60	387	99	60
45	404	60	397	99	60
49	403	60	393	98	60
53	386	60	391	101	60
57	392	60	394	100	60
61	395	60	391	99	60
65	398	60	396	100	60
69	399	60	395	99	60
73	395	59	389	99	60
77	382	59	378	99	60
81	393	58	393	100	60
85	395	55	390	99	60
89	401	51	397	99	59
93	400	46	391	98	57
97	403	43	389	97	56
101	401	39	387	97	53
105	369	35	364	99	50
109	383	30	372	97	41
113	370	26	367	99	39
117	364	18	348	96	34
121	360	13	348	97	29
125	350	13	343	98	26
129	324	11	315	97	24
Mean for weeks					
1-13	222		207	93	
14-52	365		361	99	
53-129	383		377	98	

TABLE J2b
Mean Body Weights and Survival of Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: 30-Month Restricted Feed Protocol (continued)

Weeks on Study	0 ppm		5,000 ppm		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
Female					
1	92	70	82	89	70
2	128	70	120	94	70
3	129	70	120	93	70
4	128	70	120	94	70
5	132	70	124	94	70
6	134	70	129	97	70
7	141	70	135	96	70
8	146	70	141	96	70
9	150	70	145	96	70
10	153	70	144	94	70
11	157	70	148	94	70
12	162	70	155	96	70
13	181	70	175	97	70
17[a]	172	60	171	100	60
21	189	60	188	99	60
25	181	60	183	101	60
29	184	60	183	99	60
33	194	60	195	101	60
37	212	60	213	100	60
41	213	60	214	100	60
45	208	60	210	101	60
49	209	60	211	101	60
53	204	60	204	100	60
57	221	60	224	101	60
61	224	60	226	101	59
65	231	60	235	102	59
69	236	60	237	101	59
73	240	59	243	101	58
77	244	59	244	100	58
81	254	58	258	102	57
85	264	57	262	100	57
89	279	56	274	98	55
93	294	53	283	96	55
97	302	52	290	96	52
101	308	49	296	96	50
105	317	44	289	91	49
109	315	43	295	94	47
113	317	38	296	94	42
117	308	35	285	93	40
121	300	27	278	93	35
125	285	20	273	96	27
129	270	18	264	98	25
Mean for weeks					
1-13	141		134	95	
14-52	196		196	100	
53-129	271		263	97	

[a] Interim evaluation occurred during week 14.

TABLE J3a
Mean Body Weights and Survival of Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Weeks on Study	*Ad Libitum*-Fed Control		Weight-Matched Control		337.5 mg/kg			
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of *ad libitum*-fed controls)	Wt. (% of weight-matched controls)	No. of Survivors
1	102	70	103	60	102	100	99	60
2	139	70	136	60	135	97	100	60
3	171	70	174	60	173	101	99	60
4	196	70	200	60	195	100	98	60
5	216	70	220	60	215	100	98	60
6	238	70	243	60	240	101	99	60
7	258	70	259	60	259	100	100	60
8	273	70	273	60	275	101	101	60
9	287	70	286	60	280	97	98	60
10	299	70	298	60	296	99	99	60
11	307	70	305	59	301	98	99	60
12	317	70	316	59	313	99	99	60
13	324	70	324	59	316	97	97	60
14	333	70	337	59	331	100	98	60
18	360	70	364	59	358	99	98	60
21	374	70	371	59	363	97	98	59
25	393	69	394	59	386	98	98	59
29[a]	416	59	410	59	400	96	98	59
33	424	59	425	59	413	97	97	59
37	439	59	431	59	423	96	98	58
41	447	59	437	59	428	96	98	58
45	457	59	451	59	439	96	97	58
49	461	59	459	59	444	96	97	58
53	469	59	463	59	451	96	98	58
57	471	59	467	59	460	98	99	58
61	477	59	468	59	453	95	97	58
65	477	59	474	59	459	96	97	56
69[a]	474	48	471	48	461	97	98	45
73	477	46	470	47	463	97	98	45
77	472	45	469	45	451	96	96	45
81	468	44	468	44	449	96	96	45
85	467	44	458	43	450	96	98	42
89	461	43	460	42	444	96	97	41
93	453	42	449	40	439	97	98	39
97	442	41	437	39	437	99	100	34
101	422	39	426	35	417	99	98	31
Mean for weeks								
1-13	241		241		238	99	99	
14-52	410		408		399	97	98	
53-101	464		460		449	97	98	

[a] Interim evaluation occurred during weeks 27 (*ad libitum*-fed controls only) and 66.

TABLE J3b
Mean Body Weights and Survival of Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols

Weeks on Study	2-Year Protocol					30-Month Protocol				
	Vehicle Control		337.5 mg/kg			Vehicle Control		337.5 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	107	61	108	102	60	109	49	109	100	50
2	140	61	140	100	60	143	49	141	99	50
3	167	61	167	100	60	171	49	168	98	50
4	183	61	181	99	60	183	49	181	99	50
5	205	61	205	100	60	204	49	204	100	50
6	216	61	215	99	60	217	48	217	100	50
7	230	61	230	100	60	232	48	231	100	50
8	241	61	240	99	60	243	48	238	98	50
9	250	61	248	99	60	253	48	245	97	50
10	261	61	255	98	60	261	48	254	97	50
11	270	61	267	99	60	273	48	264	97	50
12	283	61	281	99	60	289	48	277	96	50
14	298	61	296	99	59	302	48	290	96	50
17	306	61	298	97	59	315	48	295	94	50
20	318	61	308	97	59	320	48	306	95	49
24	336	61	324	96	59	339	48	319	94	49
28	345	61	325	94	58	344	48	324	94	49
32	359	61	341	95	57	357	48	339	95	47
37	363	61	343	95	57	363	48	347	96	47
40	370	61	354	96	57	375	48	351	94	47
44	383	61	356	93	57	381	48	357	94	47
48	384	61	359	94	57	387	47	362	93	47
53	383	61	360	94	57	384	47	361	94	47
56	408	61	382	94	57	408	47	385	94	47
60	420	61	387	92	57	422	47	388	92	47
64	425	60	382	90	57	424	46	381	90	46
68[a]	427	50	386	90	47	433	45	386	89	46
72	423	49	378	89	47	425	45	378	89	46
76	409	48	361	88	45	408	45	361	88	46
80	403	48	349	87	45	407	44	348	86	46
84	405	48	345	85	45	401	43	348	87	43
89	402	47	342	85	43	400	42	346	87	43
92	396	44	340	86	42	394	41	341	87	42
96	400	41	339	85	42	398	39	340	85	42
100	400	36	329	82	40	386	38	329	85	41
104	384	34	317	83	40	388	35	327	84	41
108						375	33	311	83	39
112						380	29	304	80	39
116						365	25	295	81	35
120						351	19	282	80	32
124						335	18	273	81	29
128						304	13	255	84	24
Mean for weeks										
1-13	213		211	99		215		211	98	
14-52	346		330	95		348		329	95	
53-104	406		357	88		406		359	88	
105-128						352		287	82	

[a] Interim evaluation occurred during week 66 of the 2-year protocol.

TABLE J4a
Mean Body Weights and Survival of Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Weeks on Study	*Ad Libitum*-Fed Control		Weight-Matched Control		2,700 mg/kg			
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of *ad libitum*-fed controls)	Wt. (% of weight-matched controls)	No. of Survivors
1	23.5	60	23.4	60	23.2	99	99	60
2	25.3	60	24.7	60	25.0	99	101	58
3	25.9	60	26.0	60	26.6	103	102	58
4	27.7	60	27.3	60	27.7	100	102	58
5	28.4	60	28.0	60	28.1	99	100	58
6	29.1	60	28.5	60	28.3	97	99	58
7	30.0	60	29.0	60	29.5	98	102	58
8	31.4	60	30.2	60	30.4	97	101	58
9	31.6	60	31.0	60	30.7	97	99	58
10	32.0	60	31.0	60	30.8	96	99	58
11	32.9	60	31.9	60	31.7	96	99	58
12	33.5	60	32.3	60	31.4	94	97	58
13	34.6	60	33.7	60	32.5	94	96	58
14	35.2	60	33.5	60	32.5	92	97	58
18	38.2	60	36.5	60	34.2	90	94	58
22	40.7	60	40.1	60	37.0	91	92	58
26	44.7	59	42.4	59	37.9	85	89	58
30	45.2	59	37.5	59	39.2	87	105	58
34	47.7	59	35.3	59	39.4	83	112	58
38	48.7	59	39.6	59	40.0	82	101	58
42	49.2	59	41.7	59	40.1	82	96	58
46	49.7	59	45.1	59	41.0	83	91	58
50	50.2	59	42.2	59	41.8	83	99	58
54	51.7	58	43.6	59	43.1	83	99	58
58	52.6	58	45.3	59	44.7	85	99	58
62	52.8	56	47.7	59	45.9	87	96	58
66[a]	53.3	46			46.2	87		48
68[a]			47.1	49				
70	54.0	46	46.8	49	45.2	84	97	48
74	53.6	46	45.1	49	48.2	90	107	47
78	54.4	46	45.3	49	45.8	84	101	47
82	54.3	46	43.8	49	47.2	87	108	47
86	52.7	46	45.4	48	46.2	88	102	47
90	52.9	44	49.0	46	46.8	89	96	47
94	53.4	44	49.5	45	47.2	88	95	46
98	52.3	41	49.9	45	44.8	86	90	46
102	52.0	40	50.5	45	45.7	88	91	46
Mean for weeks								
1-13	29.7		29.0		28.9	97	100	
14-52	45.0		39.4		38.3	85	97	
53-102	53.1		46.8		45.9	86	98	

[a] Interim evaluation occurred during week 66.

TABLE J4b
Mean Body Weights and Survival of Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols

Weeks on Study	2-Year Protocol					3-Year Protocol				
	Vehicle Control		2,700 mg/kg			Vehicle Control		2,700 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.4	62	23.2	99	60	23.7	48	23.5	99	50
2	25.1	62	24.7	98	60	25.3	48	25.3	100	50
3	24.9	62	24.3	98	60	24.9	48	24.7	99	50
4	23.4	62	22.8	97	60	23.3	48	23.1	99	50
5	24.9	62	23.5	94	60	24.7	48	23.9	97	50
6	24.9	62	23.2	93	60	24.7	48	23.4	95	50
7	25.9	62	23.7	92	60	25.6	48	23.9	93	50
8	27.0	62	25.2	93	60	27.0	48	24.9	92	50
9	27.1	62	25.5	94	60	26.8	48	25.8	96	49
10	27.9	62	26.1	94	60	27.9	48	26.5	95	49
11	27.8	62	26.5	95	60	27.7	48	26.7	96	49
12	29.0	62	26.2	90	60	29.0	48	26.4	91	49
13	29.4	62	27.2	93	60	29.3	48	27.4	94	49
17	32.4	62	28.3	87	60	32.0	48	28.5	89	49
18	32.9	62	28.6	87	60	32.4	48	28.7	89	49
22	35.0	62	30.1	86	60	34.4	48	30.3	88	49
26	35.8	62	31.4	88	60	35.3	48	31.6	90	49
30	40.7	62	32.6	80	60	39.9	48	33.1	83	49
34	44.7	62	34.5	77	59	43.5	48	34.8	80	49
38	46.0	62	33.8	74	59	45.1	48	33.6	75	49
42	42.5	62	33.8	80	59	41.7	48	33.8	81	49
46	41.1	62	34.1	83	59	40.4	48	34.4	85	48
50	40.4	62	32.7	81	59	39.7	48	32.7	82	48
54	42.6	62	33.8	79	59	42.0	48	33.6	80	48
58	49.6	62	36.6	74	59	48.9	48	36.8	75	48
62	49.5	62	35.8	72	59	48.5	48	36.0	74	48
66[a]	48.9	53	34.9	71	49	47.5	47	34.7	73	48
70	47.8	52	34.6	72	49	46.4	47	34.5	74	48
74	46.9	51	34.5	74	48	45.5	47	34.2	75	48
78	45.0	51	33.6	75	48	43.9	47	33.6	77	48
82	43.9	51	32.2	73	48	42.9	45	32.1	75	48
86	41.8	51	31.0	74	48	40.4	44	31.2	77	48
90	44.1	49	34.7	79	47	42.5	44	34.7	82	47
94	45.8	47	34.8	76	44	44.3	44	34.4	78	46
98	47.6	45	34.8	73	44	45.2	44	34.6	77	46
102	49.4	45	35.8	73	44	46.5	44	35.2	76	46
106						46.7	42	35.0	75	44
110						46.5	39	35.6	77	44
114						46.0	39	35.2	77	44
118						45.3	35	33.6	74	44
122						43.8	35	33.4	76	43
126						43.0	30	34.0	79	43
130						41.3	29	33.2	80	42
134						41.4	27	33.6	81	40
138						39.3	24	32.5	83	40
142						39.3	23	32.8	84	40
146						38.5	22	32.8	85	40
150						36.2	22	30.5	84	38
154						35.7	21	31.8	89	36
Mean for weeks										
1-13	26.2		24.8	95		26.1		25.0	96	
14-52	39.2		32.0	82		38.4		32.2	84	
53-102	46.4		34.4	74		45.0		34.3	76	
103-154						41.8		33.4	80	

[a] Interim evaluation occurred during week 66 of the 2-year protocol.

TABLE J5a
Mean Body Weights and Survival of Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols

Weeks on Study	*Ad Libitum*-Fed Control		Weight-Matched Control		25 mg/kg			
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of *ad libitum*-fed controls)	Wt. (% of weight-matched controls)	No. of Survivors
Male								
1	24.3	70	24.1	60	24.1	99	100	70
2	26.1	70	23.4	59	25.4	97	109	70
3	26.6	70	22.7	56	25.7	97	113	70
4	28.0	70	25.8	54	27.0	96	105	70
5	29.2	70	26.6	54	27.8	95	105	70
6	30.2	70	27.5	54	27.8	92	101	70
7	30.9	70	27.6	54	28.2	91	102	70
8	31.4	70	28.9	54	28.5	91	99	70
9	31.9	70	26.7	54	28.7	90	108	70
10	32.5	70	26.4	54	29.2	90	111	70
11	33.4	70	27.6	54	30.1	90	109	70
12	33.7	70	27.4	54	30.5	91	111	70
13	34.5	70	27.0	54	30.5	88	113	70
17	38.0	70	28.5	54	31.9	84	112	70
21	40.9	70	29.4	54	33.4	82	114	70
25	42.1	70	34.8	54	34.0	81	98	70
29	43.8	70	37.8	54	34.9	80	92	70
33	45.5	70	34.8	54	35.6	78	102	70
37	47.9	70	36.3	54	37.6	79	104	70
41	47.8	70	39.3	54	38.3	80	98	70
45	49.7	69	40.4	54	38.9	78	96	69
49	49.7	69	42.1	54	39.7	80	94	69
53	49.7	69	42.4	54	39.8	80	94	69
57	49.8	69	43.5	54	39.1	79	90	69
61	50.5	69	40.9	54	39.8	79	97	67
65	50.9	67	39.5	54	40.8	80	103	66
69[a]	51.7	48	44.4	44	41.6	81	94	46
73	52.0	48	42.9	44	40.8	79	95	46
77	52.4	48	45.7	43	41.4	79	91	46
81	51.9	47	45.7	43	41.1	79	90	46
85	51.4	47	43.1	43	41.3	80	96	45
89	51.8	47	40.8	42	41.3	80	101	44
93	51.2	46	39.5	42	41.5	81	105	42
97	49.8	46	39.3	42	41.0	82	104	42
101	49.7	42	36.4	42	40.1	81	110	40
Mean for weeks								
1-13	30.2		26.3		28.0	93	106	
14-52	45.0		35.9		36.0	80	100	
53-101	51.0		41.9		40.7	80	97	

TABLE J5a
Mean Body Weights and Survival of Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

Weeks on Study	*Ad Libitum*-Fed Control		Weight-Matched Control		25 mg/kg			
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of *ad libitum*-fed controls)	Wt. (% of weight-matched controls)	No. of Survivors
Female								
1	19.8	70	19.6	60	19.7	100	101	70
2	21.4	69	19.6	59	20.9	98	107	70
3	22.6	69	20.5	59	22.4	99	109	70
4	23.9	69	21.6	59	23.2	97	107	70
5	25.0	69	22.8	59	24.1	96	106	70
6	25.6	69	22.8	59	24.4	95	107	70
7	26.6	69	23.0	59	25.3	95	110	70
8	28.2	69	24.6	59	26.2	93	107	70
9	28.7	69	23.1	59	26.3	92	114	70
10	29.6	69	23.8	59	26.5	90	111	70
11	30.1	69	25.3	59	27.1	90	107	70
12	30.7	69	24.6	59	27.6	90	112	70
13	31.2	69	24.0	59	27.6	89	115	70
17	34.8	69	25.3	59	29.3	84	116	70
21	37.7	69	26.6	59	31.8	84	120	70
25	38.7	69	30.1	59	32.1	83	107	70
29	41.0	69	33.5	59	33.6	82	100	70
33	43.5	69	31.0	59	35.1	81	113	70
37	45.8	69	32.0	59	36.2	79	113	70
41	47.0	69	34.7	59	37.9	81	109	70
45	49.5	69	38.3	59	38.5	78	101	70
49	51.0	69	39.2	59	39.1	77	100	70
53	51.4	69	40.1	59	39.7	77	99	69
57	52.0	68	41.1	59	39.5	76	96	69
61	53.0	68	40.8	59	40.0	76	98	68
65	54.0	68	40.5	59	41.1	76	102	67
69[a]	54.7	49	42.3	48	42.3	77	100	47
73	56.0	48	42.4	48	42.0	75	99	47
77	55.3	47	43.4	48	42.0	76	97	47
81	53.9	47	42.2	48	41.4	77	98	45
85	52.9	46	41.8	47	41.6	79	100	45
89	53.3	40	40.8	44	42.3	79	104	44
93	52.4	40	39.3	43	42.4	81	108	43
97	50.2	39	39.7	43	41.1	82	104	41
101	47.9	38	37.6	42	40.3	84	107	38
Mean for weeks								
1-13	26.4		22.7		24.7	94	109	
14-52	43.2		32.3		34.8	81	108	
53-101	52.8		40.9		41.2	78	101	

[a] Interim evaluation occurred during week 66.

TABLE J5b
Mean Body Weights and Survival of Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols

Weeks on Study	2-Year Protocol					3-Year Protocol				
	Vehicle Control		25 mg/kg			Vehicle Control		25 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
Male										
1	24.7	60	24.7	100	60	24.4	50	24.1	99	50
2	24.6	60	24.3	99	60	24.1	50	23.8	99	50
3	23.9	60	23.7	99	60	24.5	50	23.9	98	50
4	24.9	60	24.5	98	60	25.0	50	23.4	94	50
5	26.9	60	25.8	96	60	26.6	50	25.4	96	50
6	25.6	60	25.1	98	60	26.0	50	25.1	97	50
7	23.8	60	23.1	97	60	23.3	50	23.2	100	50
8	22.9	60	22.6	99	60	23.7	50	21.9	92	50
9	22.7	60	23.2	102	60	24.8	50	22.7	92	50
10	25.0	60	24.6	98	59	27.3	50	25.2	92	50
11	24.2	60	23.3	96	59	25.2	50	23.6	94	50
12	27.3	60	25.9	95	59	27.8	50	26.2	94	50
13	28.4	60	27.2	96	59	27.9	50	26.2	94	50
17	29.6	60	28.2	95	59	29.9	49	27.7	93	50
21	30.0	60	28.2	94	59	30.3	49	27.8	92	50
25	32.8	60	29.5	90	59	33.1	49	29.9	90	50
29	30.4	60	27.6	91	59	30.3	49	27.2	90	50
33	31.0	60	28.3	91	59	30.3	49	28.7	95	49
37	30.8	60	29.1	95	59	31.3	49	28.8	92	49
41	32.2	60	30.6	95	59	33.9	49	31.3	92	49
45	32.4	60	30.3	94	59	33.6	49	30.2	90	49
49	32.9	60	30.5	93	59	34.5	49	31.3	91	49
53	34.2	60	31.9	93	59	37.2	49	31.7	85	49
57	34.7	60	32.0	92	59	37.0	49	32.2	87	49
61	32.2	60	29.8	93	59	34.7	49	29.9	86	49
65	37.1	60	34.2	92	59	38.2	49	33.8	89	49
69[a]	36.8	50	32.6	89	49	38.6	49	31.9	83	49
73	38.7	50	34.1	88	48	39.5	49	33.3	84	49
77	38.9	49	32.7	84	48	39.1	49	32.4	83	49
81	36.8	49	31.1	85	48	36.7	49	30.8	84	49
85	35.4	49	31.2	88	48	35.0	49	30.0	86	49
89	35.2	49	31.3	89	48	34.7	48	30.4	88	49
93	34.3	49	31.3	91	48	35.6	48	31.4	88	49
97	33.9	49	30.4	90	48	32.8	48	29.8	91	49
101	34.2	49	31.5	92	48	34.2	48	31.2	91	49
105						34.2	48	31.2	91	49
109						34.5	48	31.3	91	49
113						34.5	46	31.3	91	48
117						35.4	45	31.6	89	48
121						35.9	45	31.9	89	47
125						36.8	43	31.8	86	47
129						36.7	42	31.6	86	44
133						35.9	42	31.0	86	43
137						34.4	40	31.1	90	39
141						33.1	38	30.6	92	38
145						34.2	36	32.1	94	38
149						33.3	32	31.0	93	37
153						33.6	28	31.3	93	37
Mean for weeks										
1-13	25.0		24.5	98		25.4		24.2	95	
14-52	31.3		29.1	93		31.9		29.2	92	
53-101	35.6		31.9	90		36.4		31.4	86	
102-153						34.8		31.4	90	

TABLE J5b
Mean Body Weights and Survival of Mice in the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate: 2-Year and 3-Year Restricted Feed Protocols (continued)

Weeks on Study	2-Year Protocol					3-Year Protocol				
	Vehicle Control		25 mg/kg			Vehicle Control		25 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
Female										
1	20.1	60	20.0	100	60	19.8	50	19.7	100	50
2	20.6	60	20.2	98	60	20.2	50	19.6	97	50
3	20.6	60	20.1	98	60	21.1	50	20.7	98	49
4	22.3	60	21.1	95	60	21.4	50	20.5	96	49
5	23.5	60	22.7	97	60	23.1	50	22.4	97	49
6	23.0	60	22.2	97	60	22.9	50	22.4	98	49
7	22.6	60	22.1	98	60	22.5	50	21.6	96	49
8	22.9	60	22.1	97	60	22.2	50	21.5	97	49
9	23.0	60	21.9	95	60	22.3	50	22.3	100	49
10	24.2	60	23.5	97	60	24.3	50	23.6	97	49
11	22.9	60	22.4	98	60	22.9	50	21.9	96	49
12	24.9	60	24.3	98	60	25.0	50	24.0	96	49
13	26.0	60	24.7	95	60	25.0	50	24.3	97	49
17	26.8	60	25.6	96	60	26.5	50	25.1	95	49
21	28.1	60	26.5	94	60	27.7	50	25.6	92	49
25	29.6	60	28.3	96	60	30.2	50	27.5	91	49
29	28.3	60	26.8	95	60	28.2	50	25.7	91	49
33	29.2	60	28.3	97	60	29.9	50	27.8	93	49
37	29.4	60	27.6	94	60	29.5	50	27.1	92	49
41	30.2	60	28.8	95	60	32.2	50	28.4	88	49
45	30.4	60	28.9	95	60	32.2	50	28.0	87	49
49	31.0	60	29.5	95	60	32.6	50	29.5	91	49
53	32.5	60	30.2	93	60	33.2	50	30.1	91	49
57	31.8	60	30.5	96	59	32.5	50	30.4	94	49
61	30.3	60	28.7	95	58	31.4	50	28.6	91	49
65	34.0	60	32.8	97	58	34.7	50	31.6	91	49
69[a]	33.0	50	30.8	93	48	33.8	50	31.0	92	49
73	34.8	49	32.7	94	48	35.4	50	31.5	89	49
77	34.5	49	32.1	93	48	35.0	50	31.0	89	49
81	32.5	48	30.2	93	47	33.1	47	29.6	89	48
85	31.4	48	29.8	95	47	31.9	47	28.5	89	48
89	30.9	48	29.8	96	46	31.0	46	28.9	93	48
93	30.5	47	29.4	96	45	31.8	46	29.4	93	48
97	29.9	47	29.0	97	44	29.7	45	27.5	93	48
101	30.8	47	29.9	97	44	31.4	45	29.1	93	45
105						30.6	45	28.9	94	45
109						31.0	44	28.8	93	43
113						30.4	43	28.9	95	43
117						31.0	42	28.8	93	39
121						31.2	42	29.0	93	38
125						30.4	37	29.0	95	34
129						30.1	35	29.0	96	34
133						29.6	29	28.8	97	33
137						28.9	27	28.3	98	32
141						28.0	25	27.7	99	28
145						29.7	24	29.7	100	25
149						28.7	23	28.8	100	24
153						29.0	21	28.9	100	19
Mean for weeks										
1-13	22.8		22.1	97		22.5		21.9	97	
14-52	29.2		27.8	95		29.9		27.2	91	
53-101	32.1		30.5	95		32.7		29.8	91	
102-153						29.9		28.8	96	

[a] Interim evaluation occurred during week 66 of the 2-year protocol.

APPENDIX K
FEED AND COMPOUND CONSUMPTION IN THE DIETARY RESTRICTION STUDIES

TABLE K1a
Feed and Compound Consumption by Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

Week	*Ad Libitum*-Fed Control		Weight-Matched Control		12,000 ppm				
	Feed (g/day)[b]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/Control Feed[c] *Ad Libitum*-Fed Control	Feed/Control Feed[c] Weight-Matched Control	Dose/ Day[d] (mg/kg)
Male									
1			14.6	110					
2	14.6	149	15.5	146	14.1	141	0.97	0.91	1,198
3	15.9	183	16.7	181					
4	15.6	205	16.8	210					
5	17.8	233	16.7	234	19.7	226	1.11	1.18	1,043
6	17.5	253	16.9	252	18.4	243	1.05	1.09	905
7	16.5	266							
8	17.4	286	16.3	282					
9	16.5	298	17.0	297	15.6	284	0.95	0.92	660
10	16.2	310	16.4	306	16.6	291	1.02	1.01	686
11	15.3	319	16.4	319					
12	16.4	326	16.1	325					
13	16.4	339	16.4	335	16.8	315	1.02	1.02	642
17	17.3	370	14.3	365	12.3	338	0.71	0.86	438
21	15.9	391	13.6	352	17.5	351	1.10	1.29	599
25	20.5	391	14.1	364	15.5	362	0.76	1.10	512
29	14.7	416	14.2	381	14.4	377	0.98	1.01	458
33	14.7	423	13.0	399	15.6	382	1.06	1.20	490
37	15.0	429	10.4	395	15.2	389	1.01	1.46	469
41	17.1	437	12.3	378	16.5	394	0.96	1.34	502
45	17.5	443	12.4	391	17.0	405	0.97	1.37	503
49	16.1	449	13.2	365	15.9	413	0.99	1.20	463
53	16.3	451	14.3	400	16.7	414	1.02	1.17	484
57	15.3	450	14.4	391	16.2	412	1.06	1.13	470
61	15.7	451	13.8	413	16.1	413	1.03	1.17	468
65	15.4	451	14.0	412	15.1	420	0.98	1.08	431
69	14.2	446	13.9	422	15.1	419	1.06	1.09	434
73	15.1	448	13.7	427	15.4	427	1.02	1.12	433
77	14.1	446	13.7	427	14.4	428	1.02	1.05	404
81	13.5	440	12.9	432	13.3	422	0.99	1.03	378
85	13.6	440	13.8	433	14.3	418	1.05	1.04	409
89	13.9	439	12.1	438	13.6	413	0.98	1.12	396
93			13.1	438	13.0	422		0.99	370
97	14.5	433	12.5	434	12.7	411	0.88	1.02	372
101	12.4	426	13.3	433	11.6	402	0.94	0.87	347
Mean for weeks									
1-13	16.3	264	16.3	250	16.9	250	1.02	1.02	856
14-52	16.5	417	13.1	377	15.5	379	0.95	1.20	493
53-101	14.5	443	13.5	423	14.4	417	1.00	1.07	415

TABLE K1a
Feed and Compound Consumption by Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

Week	*Ad Libitum*-Fed Control		Weight-Matched Control		24,000 ppm				
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/Control Feed *Ad Libitum*-Fed Control	Feed/Control Feed Weight-Matched Control	Dose/ Day (mg/kg)
Female									
1			11.0	97					
2	10.3	121	11.2	120	7.5	114	0.73	0.67	1,582
3	11.0	135	11.2	134					
4	11.3	142	11.0	142					
5	11.1	153	11.1	151					
6	10.6	159	11.4	159	11.3	151	1.07	0.99	1,791
7	10.9	167	11.8	166					
8	10.9	171	10.6	170					
9	11.3	175	10.3	174					
10	10.9	178	10.7	180	10.5	171	0.96	0.98	1,478
11	10.8	180	10.5	183					
12	11.0	186	9.9	186					
13	10.3	185	10.3	184	9.8	176	0.95	0.95	1,338
17	10.2	198	9.6	193	9.7	183	0.95	1.01	1,274
21	10.3	204	10.4	203	9.9	187	0.96	0.95	1,269
25			9.7	209	10.1	193		1.04	1,254
29	9.3	218	8.5	221	9.0	197	0.97	1.06	1,090
33	9.7	223	7.3	211	9.3	199	0.96	1.27	1,127
37	10.7	231	5.8	204	9.6	203	0.90	1.66	1,133
41	10.7	238	6.6	198					
45	11.4	240	6.8	196	9.7	207	0.85	1.43	1,119
49	12.5	258	7.4	194	10.4	212	0.83	1.41	1,177
53	11.6	269	7.7	199	10.1	214	0.87	1.31	1,130
57	11.1	276	7.8	200	10.6	214	0.95	1.36	1,184
61	11.4	281	7.6	202	9.7	216	0.85	1.28	1,073
65	11.7	286	7.4	203	10.1	220	0.86	1.36	1,104
69	11.1	296	7.5	216	9.9	222	0.89	1.32	1,068
73	11.1	298	7.5	208	9.8	226	0.88	1.31	1,046
77	11.3	300	8.2	228	9.8	230	0.87	1.20	1,028
81	11.7	300	7.2	228	10.0	222	0.85	1.39	1,084
85	11.8	312	8.2	239	10.8	231	0.92	1.32	1,126
89	12.1	321	8.1	245	10.6	237	0.88	1.31	1,074
93	10.6	320	8.4	238	10.5	236	0.99	1.25	1,069
97	11.4	319	9.1	247	10.4	233	0.91	1.14	1,070
101	10.2	318	8.0	254	10.1	232	0.99	1.26	1,049
Mean for weeks									
1-13	10.9	163	10.8	157	9.8	153	0.93	0.90	1,547
14-52	10.6	226	8.0	203	9.7	198	0.92	1.23	1,180
53-101	11.3	300	7.9	224	10.2	226	0.90	1.29	1,085

[a] Feed consumption by controls was measured weekly for 13 weeks and monthly thereafter.
[b] Grams of feed consumed per animal per day
[c] Grams of feed consumed per exposed animal per day divided by grams of feed consumed per control animal per day
[d] Milligrams of butyl benzyl phthalate consumed per kilogram body weight per day

TABLE K1b
Feed and Compound Consumption by Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and Long-Term Restricted Feed Protocols

	2-Year Protocol						30-Month Protocol					
	0 ppm		12,000 ppm				0 ppm		12,000 ppm			
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed[b]	Dose/ Day[c] (mg/kg)	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed	Dose/ Day (mg/kg)
Male												
1	14.3	103	13.8	101	0.97	1,643	14.6	103	13.9	101	0.95	1,649
2	12.2	140	11.6	138	0.95	1,013	12.1	139	11.7	138	0.97	1,024
3	11.9	146	12.2	143	1.03	1,023	11.9	146	12.2	143	1.03	1,023
4	12.6	156	12.7	155	1.01	983	12.5	155	12.6	154	1.01	979
5	14.1	176	14.0	168	0.99	998	14.1	182	13.9	167	0.99	1,002
6	13.8	200	14.1	180	1.02	943	14.0	204	14.1	179	1.01	944
7	14.2	208	13.8	199	0.97	834	14.2	210	13.9	204	0.98	821
8	14.9	227	15.3	216	1.03	850	14.8	233	15.3	217	1.03	843
9	13.3	246	13.5	234	1.02	690	13.0	246	14.4	244	1.11	707
10	13.3	260	13.5	248	1.02	652	13.2	262	13.8	254	1.05	655
11	13.7	258	13.7	249	1.00	661	13.7	261	13.7	258	1.00	639
12	15.5	261	15.9	251	1.03	760	15.7	263	16.2	256	1.03	759
13	13.6	285	14.0	274	1.03	615	13.6	287	14.2	280	1.04	611
17	14.6	301	14.8	294	1.01	604	14.7	307	14.9	303	1.01	589
21	14.5	339	14.5	324	1.00	537	14.7	349	14.4	323	0.98	533
25	13.3	358	13.8	339	1.04	488	13.3	363	13.7	342	1.03	480
29	13.1	349	13.1	340	1.00	461	13.0	356	13.2	344	1.02	459
33	12.8	362	12.9	347	1.01	447	12.8	376	13.0	351	1.02	444
37	13.1	366	13.0	344	0.99	454	13.1	378	13.2	346	1.01	457
41	13.0	383	12.9	349	0.99	443	12.9	390	12.9	351	1.00	442
45	12.0	372	12.2	345	1.02	426	11.9	376	12.3	357	1.03	413
49	12.5	366	12.3	343	0.98	432	12.4	371	12.4	344	1.00	434
53	13.8	368	13.7	351	0.99	468	13.8	376	13.6	357	0.99	457
57	13.4	378	13.5	370	1.01	439	13.4	398	13.4	373	1.00	430
61	13.5	399	13.5	375	1.00	432	13.3	404	13.5	378	1.02	427
65	13.3	388	13.4	374	1.01	430	13.2	405	13.4	379	1.02	425
69	12.1	406	12.2	377	1.01	388	12.1	408	12.1	381	1.00	380
73	10.9	403	10.7	378	0.98	339	10.8	410	10.8	374	1.00	346
77	9.4	377	9.6	354	1.02	325	9.4	376	11.9	347	1.27	413
81	11.2	395	11.1	372	0.99	356	11.2	389	11.0	364	0.98	364
85	9.8	398	9.8	362	1.00	325	9.9	399	9.9	364	1.00	327
89	10.3	371	10.8	342	1.05	380	9.9	371	10.9	345	1.10	379
93	10.1	365	10.0	362	0.99	332	10.1	378	10.2	367	1.01	334
97	10.2	371	10.3	341	1.01	361	10.2	386	10.3	348	1.01	354
101	10.2	354	10.0	340	0.98	353	10.3	370	10.3	342	1.00	360
105							10.1	360	10.3	334	1.02	369
109							10.2	359	10.1	327	0.99	371
113							9.8	359	10.2	332	1.04	368
117							10.0	332	10.2	314	1.02	389
121							9.9	324	10.1	304	1.02	400
125							10.0	329	10.2	307	1.02	397
Mean for weeks												
1-13	13.6	205	13.7	197	1.00	898	13.6	207	13.8	200	1.01	897
14-52	13.2	355	13.3	336	1.00	477	13.2	363	13.3	340	1.01	472
53-101	11.4	383	11.4	361	1.00	379	11.4	390	11.6	363	1.03	384
102-125							10.0	344	10.2	320	1.02	382

TABLE K1b
Feed and Compound Consumption by Rats in the Dietary Restriction Study of Butyl Benzyl Phthalate: 2-Year and Long-Term Restricted Feed Protocols (continued)

	2-Year Protocol						32-Month Protocol					
	0 ppm		24,000 ppm				0 ppm		24,000 ppm			
Week	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed	Dose/ Day (mg/kg)
Female												
1	11.1	94	7.7	88	0.69	2,105	11.4	95	8.4	87	0.74	2,302
2	11.6	116	12.0	107	1.03	2,684	11.7	118	12.0	105	1.03	2,749
3	12.0	128	11.9	118	0.99	2,411	12.1	128	11.8	116	0.98	2,437
4	9.1	131	8.9	124	0.98	1,715	9.2	131	8.8	122	0.96	1,730
5	8.1	133	8.0	127	0.99	1,515	8.1	134	8.1	127	1.00	1,519
6	8.0	146	8.0	134	1.00	1,435	8.0	146	8.0	133	1.00	1,447
7	8.1	141	8.1	130	1.00	1,494	8.2	142	8.1	130	0.99	1,493
8	8.3	141	8.3	141	1.00	1,421	8.3	141	8.4	139	1.01	1,450
9	9.1	159	9.0	148	0.99	1,465	9.1	158	9.0	147	0.99	1,473
10	8.3	155	8.2	145	0.99	1,358	8.4	155	8.3	145	0.99	1,387
11	8.0	157	8.1	146	1.01	1,323	8.0	157	8.1	146	1.01	1,328
12	8.0	160	8.1	152	1.01	1,272	8.0	161	8.1	151	1.01	1,280
13	8.1	162	8.0	155	0.99	1,247	8.1	163	8.2	151	1.01	1,311
17	8.1	170	8.2	164	1.01	1,197	8.1	170	8.2	164	1.01	1,195
21	8.0	176	8.1	164	1.01	1,182	8.0	180	8.0	164	1.00	1,180
25	8.0	189	8.0	178	1.00	1,081	8.0	188	8.0	176	1.00	1,086
29	7.7	193	7.9	180	1.03	1,047	7.7	194	8.4	180	1.09	1,115
33	7.0	194	6.9	175	0.99	954	7.0	195	6.9	173	0.99	957
37	7.2	182	7.3	176	1.01	989	7.3	183	7.3	180	1.00	969
41	7.9	191	7.8	175	0.99	1,073	7.9	199	7.8	173	0.99	1,085
45	8.6	190	9.1	180	1.06	1,214	8.6	192	9.1	178	1.06	1,225
49	8.6	198	8.6	184	1.00	1,114	8.5	200	8.5	184	1.00	1,104
53	10.0	206	9.3	191	0.93	1,168	10.0	209	9.2	191	0.92	1,154
57	10.4	217	9.6	194	0.92	1,183	10.4	221	9.2	191	0.88	1,159
61	10.2	222	9.5	198	0.93	1,157	10.4	227	9.6	196	0.92	1,175
65	10.0	228	9.3	197	0.93	1,126	10.2	232	9.1	197	0.89	1,109
69	10.4	233	9.9	202	0.95	1,175	9.8	238	9.8	199	1.00	1,184
73	10.0	244	9.0	208	0.90	1,038	10.4	247	9.0	203	0.87	1,065
77	10.9	254	9.2	208	0.84	1,058	10.5	257	9.0	207	0.86	1,041
81	11.1	263	9.5	210	0.86	1,086	11.0	269	9.3	205	0.85	1,084
85	10.6	273	10.0	211	0.94	1,136	10.7	280	9.8	206	0.92	1,145
89	11.0	276	9.6	212	0.87	1,094	10.9	284	9.4	207	0.86	1,083
93	11.0	282	10.0	212	0.91	1,130	10.7	289	10.1	210	0.94	1,161
97	9.9	284	9.7	211	0.98	1,109	10.1	294	9.4	210	0.93	1,078
101	10.2	276	10.0	213	0.98	1,127	10.2	293	10.0	209	0.98	1,147
105							10.1	288	9.7	210	0.96	1,116
109							10.1	290	10.0	211	0.99	1,138
113							9.6	283	9.9	211	1.03	1,134
117							9.9	283	9.8	210	0.99	1,123
121							10.1	282	10.0	208	0.99	1,155
125							9.9	291	9.6	206	0.97	1,124
129							10.0	288	9.6	203	0.96	1,139
133							10.2	294	9.1	198	0.89	1,101
137							10.3	286	9.6	189	0.93	1,227
Mean for weeks												
1-13	9.1	140	8.8	132	0.98	1,650	9.1	141	8.9	131	0.98	1,685
14-52	7.9	187	8.0	175	1.01	1,094	7.9	189	8.0	175	1.01	1,102
53-101	10.4	251	9.6	205	0.92	1,122	10.4	257	9.5	202	0.91	1,122
102-137							10.0	287	9.7	205	0.97	1,140

[a] Grams of feed consumed per animal per day
[b] Grams of feed consumed per exposed animal per day divided by grams of feed consumed per control animal per day
[c] Milligrams of butyl benzyl phthalate consumed per kilogram body weight per day

TABLE K2a
Feed and Compound Consumption by Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

Week	*Ad Libitum*-Fed Control		Weight-Matched Control		5,000 ppm				
	Feed (g/day)[b]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/Control Feed[c] *Ad Libitum*-Fed Control	Feed/Control Feed[c] Weight-Matched Control	Dose/ Day[d] (mg/kg)
Male									
1	13.9	99	14.3	97					
2	15.2	141	14.3	139	15.7	127	1.03	1.10	619
3	16.5	175	13.0	161					
4	18.2	209	13.4	188					
5	17.4	233	14.0	189					
6	20.8	267	16.3	215	18.3	244	0.88	1.12	375
7	17.2	283	14.6	247					
8	17.0	299	14.0	250					
9	16.9	313	15.1	260					
10	13.1	316	15.7	273	17.5	299	1.34	1.11	293
11	19.2	324	14.9	296					
12	17.4	344	15.0	314					
13	16.8	356	16.1	323	17.6	320	1.05	1.09	275
17	16.5	379	14.9	364	17.2	346	1.04	1.15	248
21	16.4	400	13.0	336	17.2	358	1.05	1.32	241
25	15.6	413	13.4	348	15.9	376	1.02	1.19	211
29	16.5	419	14.1	384	16.4	386	0.99	1.16	213
33	16.4	428	13.8	380	16.7	392	1.02	1.21	213
37	17.4	437	13.3	389	16.4	402	0.94	1.23	204
41	14.7	450	13.4	393	15.2	416	1.03	1.13	182
45	16.5	452	14.0	406	16.9	415	1.02	1.21	203
49	16.9	444	13.7	398	16.0	415	0.95	1.17	193
53	19.9	468	13.8	417	20.8	431	1.05	1.51	242
57	14.8	468	14.7	415	16.8	435	1.14	1.14	193
61	16.1	467	14.7	419	17.7	440	1.10	1.20	202
65	16.3	470	14.0	429	17.6	440	1.08	1.26	200
69	15.8	468	14.1	428	16.7	437	1.06	1.18	191
73	15.3	472	13.2	423	16.0	433	1.05	1.21	185
77	17.0	463	13.6	435	16.3	438	0.96	1.20	186
81	16.6	464	14.3	432	17.3	436	1.04	1.21	199
85	15.4	462	13.8	428	15.1	429	0.98	1.09	176
89	15.1	455	13.6	431	14.0	425	0.93	1.03	164
93	14.3	458	13.3	429	15.1	419	1.06	1.14	180
97	15.4	455	13.7	434	16.0	421	1.04	1.17	190
101	15.2	447	12.8	430	15.7	421	1.03	1.23	186
105	14.5	440	13.4	426	16.4	409	1.13	1.22	201
109	15.7	420	13.6	416	14.2	412	0.90	1.04	173
113	14.8	429	12.9	419	15.7	395	1.06	1.22	198
117	14.0	428	9.9	399	15.0	397	1.07	1.52	189
121	14.4	417	10.7	406	15.5	386	1.08	1.45	200
Mean for weeks									
1-13	16.9	258	14.7	227	17.3	247	1.07	1.11	390
14-52	16.3	425	13.7	378	16.4	390	1.01	1.20	212
53-121	15.6	453	13.3	423	16.2	422	1.04	1.22	192

TABLE K2a
Feed and Compound Consumption by Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: *Ad Libitum* Feeding and Weight-Matched Controls Protocols (continued)

Week	*Ad Libitum*-Fed Control		Weight-Matched Control		5,000 ppm				
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/Control Feed *Ad Libitum*-Fed Control	Feed/Control Feed Weight-Matched Control	Dose/ Day (mg/kg)
Female									
1	10.8	92	11.1	92					
2	11.3	121	10.9	121	11.9	110	1.05	1.09	541
3	11.3	135	7.3	126					
4	11.6	147	7.5	130					
5	11.1	159	7.4	123					
6	13.7	171	8.2	129	11.3	154	0.82	1.38	367
7	11.6	177	12.0	155					
8	10.8	181	7.3	161					
9	10.7	186	7.2	149					
10	9.4	176	7.9	150	11.1	176	1.18	1.41	316
11	11.9	193	11.7	168					
12	10.5	196	9.6	175					
13	10.2	198	9.8	180	11.2	184	1.10	1.14	304
17	10.7	203	10.6	192	9.8	188	0.92	0.92	262
21	10.7	224	8.8	192	10.8	200	1.01	1.23	270
25	9.4	222	8.7	207	9.5	203	1.01	1.09	235
29	9.2	229	8.8	213	10.1	210	1.10	1.15	240
33	10.1	231	8.7	210	10.0	210	0.99	1.15	239
37	10.9	232	8.5	219	10.4	213	0.95	1.22	244
41	10.1	240	8.6	227	9.1	219	0.90	1.06	207
45	10.8	248	8.6	225	11.0	227	1.02	1.28	242
49	11.6	257	8.7	231	10.7	232	0.92	1.23	232
53	15.3	264	8.7	227	14.1	236	0.92	1.62	299
57	9.6	279	9.4	236	10.8	246	1.13	1.15	219
61	11.3	285	9.4	240	11.2	257	0.99	1.19	217
65	12.2	292	9.2	243	11.5	263	0.94	1.25	219
69	11.6	301	9.6	245	10.7	265	0.92	1.11	202
73	12.2	309	9.2	250	11.0	270	0.90	1.20	204
77	12.4	315	8.9	259	11.5	274	0.93	1.29	209
81	12.3	323	10.4	257	11.8	278	0.96	1.13	213
85	11.5	327	9.8	266	11.3	282	0.98	1.15	200
89	11.7	333	10.3	272	10.9	287	0.93	1.06	190
93	12.3	342	10.0	274	11.1	290	0.90	1.11	191
97	12.6	348	10.3	270	12.5	299	0.99	1.21	209
101	12.0	347	10.8	282	11.9	301	0.99	1.10	197
105	13.0	345	10.9	285	12.3	303	0.95	1.13	203
109	12.5	341	10.5	287	12.0	300	0.96	1.14	200
113	11.1	337	12.1	295	12.4	301	1.12	1.02	205
117	11.7	348	10.5	295	11.4	309	0.97	1.09	184
121	12.3	341	10.6	294	12.0	315	0.98	1.13	190
125	11.9	336	10.5	289	12.0	307	1.01	1.14	196
Mean for weeks									
1-13	11.2	164	9.1	143	11.4	156	1.04	1.25	382
14-52	10.4	232	8.9	213	10.2	211	0.98	1.15	241
53-125	12.1	322	10.0	267	11.7	283	0.97	1.17	208

[a] Feed consumption by controls was measured weekly for 13 weeks and monthly thereafter.
[b] Grams of feed consumed per animal per day
[c] Grams of feed consumed per exposed animal per day divided by grams of feed consumed per control animal per day
[d] Milligrams of *t*-butylhydroquinone consumed per kilogram body weight per day

TABLE K2b
Feed and Compound Consumption by Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: 30-Month Restricted Feed Protocol

Week	0 ppm		5,000 ppm			
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed[b]	Dose/Day[c] (mg/kg)
Male						
1	14.3	107	13.8	94	0.97	732
2	16.2	151	13.2	139	0.81	476
3	14.1	185	12.0	167	0.85	360
4	12.7	185	12.6	163	0.99	387
5	12.2	195	12.0	179	0.98	334
6	13.1	208	12.8	195	0.98	329
7	14.1	231	14.4	216	1.02	333
8	14.2	246	14.2	229	1.00	310
9	14.0	255	14.2	240	1.01	295
10	14.2	266	14.5	250	1.02	290
11	14.7	274	14.8	260	1.01	286
12	14.1	289	14.0	276	0.99	254
13	14.8	291	15.1	281	1.02	270
17	14.7	314	14.3	309	0.97	232
21	15.8	351	15.6	341	0.99	229
25	14.6	343	14.4	342	0.99	211
29	14.4	348	14.6	344	1.01	212
33	14.4	358	14.5	362	1.01	200
37	14.5	371	14.6	370	1.01	196
41	14.0	390	14.0	387	1.00	182
45	14.7	404	14.7	397	1.00	185
49	13.1	403	13.3	393	1.02	170
53	12.6	386	12.7	391	1.01	162
57	12.1	392	12.2	394	1.01	155
61	12.4	395	12.3	391	0.99	158
65	12.0	398	12.4	396	1.03	156
69	12.9	399	13.0	395	1.01	165
73	12.4	395	12.0	389	0.97	154
77	12.3	382	12.4	378	1.01	165
81	13.1	393	13.3	393	1.02	169
85	12.7	395	12.8	390	1.01	164
89	12.8	401	12.6	397	0.98	158
93	12.3	400	12.1	391	0.98	155
97	11.9	403	11.7	389	0.98	151
101	12.0	401	12.2	387	1.02	158
105	13.1	369	12.6	364	0.96	173
109	11.9	383	11.9	372	1.00	161
113	11.4	370	10.9	367	0.96	149
117	11.6	364	11.1	348	0.96	159
121	12.1	360	11.4	348	0.94	164
125	11.6	350	11.5	343	0.99	168
129	11.3	324	11.1	315	0.98	177
Mean for weeks						
1-13	14.0	222	13.7	207	0.97	358
14-52	14.5	365	14.5	361	1.00	202
53-129	12.2	383	12.1	377	0.99	161

TABLE K2b
Feed and Compound Consumption by Rats in the Dietary Restriction Study of *t*-Butylhydroquinone: 30-Month Restricted Feed Protocol (continued)

Week	0 ppm Feed (g/day)	0 ppm Body Weight (g)	5,000 ppm Feed (g/day)	5,000 ppm Body Weight (g)	5,000 ppm Feed/ Control Feed	5,000 ppm Dose/Day (mg/kg)
Female						
1	11.4	92	11.0	82	0.96	669
2	11.7	128	11.2	120	0.96	465
3	8.8	129	8.2	120	0.93	341
4	7.5	128	7.8	120	1.04	323
5	7.6	132	7.3	124	0.96	294
6	7.1	134	7.3	129	1.03	283
7	7.7	141	7.6	135	0.99	281
8	7.9	146	7.8	141	0.99	279
9	8.4	150	7.2	145	0.86	251
10	8.3	153	7.6	144	0.92	264
11	8.5	157	8.0	148	0.94	273
12	8.7	162	8.0	155	0.92	257
13	9.1	181	8.9	175	0.98	255
17	8.3	172	8.1	171	0.98	236
21	8.7	189	8.8	188	1.01	233
25	8.8	181	8.8	183	1.00	241
29	8.5	184	8.4	183	0.99	230
33	8.9	194	9.0	195	1.01	230
37	8.9	212	9.0	213	1.01	210
41	8.1	213	7.7	214	0.95	180
45	7.7	208	7.6	210	0.99	181
49	7.4	209	7.5	211	1.01	178
53	7.9	204	7.9	204	1.00	192
57	8.6	221	8.7	224	1.01	195
61	9.0	224	8.8	226	0.98	196
65	9.3	231	9.2	235	0.99	196
69	10.1	236	10.3	237	1.02	217
73	10.4	240	10.5	243	1.01	216
77	10.4	244	10.5	244	1.01	216
81	12.2	254	12.2	258	1.00	237
85	11.5	264	11.2	262	0.97	214
89	12.2	279	11.6	274	0.95	212
93	12.2	294	11.9	283	0.98	211
97	12.1	302	11.5	290	0.95	198
101	11.9	308	11.5	296	0.97	195
105	12.4	317	11.8	289	0.95	204
109	11.2	315	11.2	295	1.00	189
113	10.6	317	10.4	296	0.98	176
117	9.7	308	9.0	285	0.93	158
121	10.0	300	9.4	278	0.94	169
125	9.5	285	9.1	273	0.96	166
129	8.9	270	9.1	264	1.02	172
Mean for weeks						
1-13	8.7	141	8.3	134	0.96	326
14-52	8.4	196	8.3	196	0.99	213
53-129	10.5	271	10.3	263	0.98	196

[a] Grams of feed consumed per animal per day
[b] Grams of feed consumed per exposed animal per day divided by grams of feed consumed per control animal per day
[c] Milligrams of *t*-butylhydroquinone consumed per kilogram body weight per day

TABLE K3a
Feed Consumption by Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

Week	*Ad Libitum*-Fed Control		Weight-Matched Control		337.5 mg/kg			
	Feed (g/day)[b]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/Control Feed[c] *Ad Libitum*-Fed Control	Feed/Control Feed[c] Weight-Matched Control
1	12.9	102	13.9	103	12.8	102	0.99	0.92
2	15.1	139	14.4	136	14.9	135	0.99	1.03
3	13.6	171	15.8	174				
4	15.9	196	15.7	200				
5	15.6	216	15.1	220	14.4	215	0.92	0.95
6	14.8	238	15.7	243	8.4	240	0.57	0.54
7	15.6	258	15.7	259				
8			14.9	273				
9	15.2	287	14.3	286	14.0	280	0.92	0.98
10	14.6	299	15.0	298	18.5	296	1.27	1.23
11	14.1	307	14.6	305				
12	14.2	317	14.0	316				
13	15.4	324	14.5	324	13.2	316	0.86	0.91
14	13.3	333	14.5	337	15.0	331	1.13	1.03
18	14.2	360	13.0	364	18.5	358	1.30	1.42
21	15.1	374	13.5	371	13.2	363	0.87	0.98
25	15.5	393	16.0	394	13.9	386	0.90	0.87
29	13.5	416	14.3	410	13.2	400	0.98	0.92
33	13.3	424	12.6	425	11.7	413	0.88	0.93
37	13.1	439	13.7	431	11.6	423	0.89	0.85
41	13.7	447	14.1	437	12.2	428	0.89	0.87
45	12.7	457	13.7	451	11.2	439	0.88	0.82
49	12.3	461	11.9	459	11.4	444	0.93	0.96
53	15.8	469	11.9	463	13.2	451	0.84	1.11
57	8.2	471	11.7	467	8.3	460	1.01	0.71
61	11.0	477	12.5	468	10.2	453	0.93	0.82
65	12.3	477	11.1	474	11.1	459	0.90	1.00
69	15.4	474	12.9	471	10.5	461	0.68	0.81
73	11.9	477	12.5	470	12.9	463	1.08	1.03
77			12.5	469	13.7	451		1.10
81	10.9	468	11.7	468	11.5	449	1.06	0.98
85	9.7	467	11.8	458	9.0	450	0.93	0.76
89	9.9	461	10.7	460	11.5	444	1.16	1.07
93	8.8	453	10.5	449	12.4	439	1.41	1.18
97	9.0	442	9.8	437	12.0	437	1.33	1.22
101	8.0	422	9.4	426	15.3	417	1.91	1.63
Mean for weeks								
1-13	14.7	238	14.9	241	13.8	226	0.93	0.94
14-52	13.7	410	13.7	408	13.2	398	0.96	0.96
53-101	10.9	463	11.5	460	11.7	449	1.10	1.03

[a] Feed consumption by controls was measured weekly for 13 weeks and monthly thereafter.
[b] Grams of feed consumed per animal per day
[c] Grams of feed consumed per dosed animal per day divided by grams of feed consumed per control animal per day.

TABLE K3b
Feed Consumption by Male Rats in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 30-Month Restricted Feed Protocols

	2-Year Protocol					30-Month Protocol				
	Vehicle Control		337.5 mg/kg			Vehicle Control		337.5 mg/kg		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed[b]	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed
1	13.4	107	13.4	108	1.00	13.9	109	13.3	109	0.96
2	11.6	140	11.5	140	0.99	11.6	143	11.4	141	0.98
3	11.9	167	11.9	167	1.00	11.9	171	11.9	168	1.00
4	12.6	183	12.5	181	0.99	12.6	183	12.6	181	1.00
5	12.8	205	12.8	205	1.00	12.7	204	12.8	204	1.01
6	12.1	216	12.0	215	0.99	12.1	217	12.1	217	1.00
7	12.2	230	12.3	230	1.01	12.3	232	12.3	231	1.00
8	12.1	241	12.1	240	1.00	12.2	243	12.1	238	0.99
9	12.2	250	12.2	248	1.00	12.3	253	12.3	245	1.00
10	12.3	261	12.1	255	0.98	12.1	261	12.2	254	1.01
11	12.0	270	11.9	267	0.99	12.3	273	11.8	264	0.96
12	11.9	283	11.6	281	0.97	11.9	289	11.7	277	0.98
14	12.1	298	11.9	296	0.98	12.2	302	12.0	290	0.98
17	11.1	306	11.0	298	0.99	11.2	315	11.0	295	0.98
20	11.1	318	10.9	308	0.98	10.8	320	10.7	306	0.99
24	11.3	336	11.1	324	0.98	11.4	339	11.5	319	1.01
28	11.4	345	11.4	325	1.00	11.4	344	11.4	324	1.00
32	10.9	359	11.3	341	1.04	10.9	357	11.1	339	1.02
37	11.2	363	11.3	343	1.01	11.3	363	11.2	347	0.99
40	11.3	370	11.3	354	1.00	11.1	375	11.3	351	1.02
44	11.2	383	11.1	356	0.99	11.1	381	11.2	357	1.01
48	11.0	384	11.1	359	1.01	11.2	387	11.1	362	0.99
53	11.8	383	11.9	360	1.01	11.8	384	11.9	361	1.01
56	11.6	408	10.8	382	0.93	11.6	408	10.9	385	0.94
60	12.1	420	11.6	387	0.96	12.0	422	11.8	388	0.98
64	11.2	425	11.4	382	1.02	11.5	424	11.3	381	0.98
68	11.1	427	10.8	386	0.97	11.1	433	10.8	386	0.97
72	10.3	423	10.3	378	1.00	10.3	425	10.3	378	1.00
76	9.8	409	9.6	361	0.98	9.6	408	9.7	361	1.01
80	9.8	403	9.7	349	0.99	9.7	407	9.8	348	1.01
84	9.8	405	9.8	345	1.00	9.7	401	9.8	348	1.01
89	9.9	402	9.8	342	0.99	9.8	400	9.9	346	1.01
92	9.7	396	9.9	340	1.02	9.7	394	9.9	341	1.02
96	10.0	400	10.0	339	1.00	10.0	398	9.9	340	0.99
100	9.7	400	9.7	329	1.00	9.4	386	9.3	329	0.99
104	8.5	384	8.5	317	1.00	8.6	388	8.5	327	0.99
108						8.1	375	8.4	311	1.04
112						8.5	380	8.3	304	0.98
116						8.1	365	8.1	295	1.00
120						8.1	351	8.0	282	0.99
124						8.1	335	8.0	273	0.99
128						8.2	304	8.1	255	0.99
Mean for weeks										
1-13	12.3	213	12.2	211	0.99	12.3	215	12.2	211	0.99
14-52	11.2	346	11.2	330	1.00	11.3	348	11.2	329	1.00
53-104	10.4	406	10.3	357	0.99	10.3	405	10.3	358	0.99
105-128						8.2	352	8.2	286	1.00

[a] Grams of feed consumed per animal per day
[b] Grams of feed consumed per dosed animal per day divided by grams of feed consumed per control animal per day

TABLE K4a
Feed Consumption by Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: *Ad Libitum* Feeding and Weight-Matched Controls Protocols[a]

Week	*Ad Libitum*-Fed Control		Weight-Matched Control		2,700 mg/kg			
	Feed (g/day)[b]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/Control Feed[c] *Ad Libitum*-Fed Control	Feed/Control Feed[c] Weight-Matched Control
1			5.3	23.4				
2	5.7	25.3	5.1	24.7	6.6	25.0	1.16	1.29
3	5.3	25.9	5.5	26.0				
4	5.6	27.7	5.4	27.3				
5	5.7	28.4	5.5	28.0				
6	6.0	29.1	5.5	28.5	6.5	28.3	1.08	1.18
7	5.2	30.0	5.7	29.0				
8	7.3	31.4	5.8	30.2				
9	4.6	31.6	5.2	31.0				
10	5.9	32.0	5.4	31.0	7.3	30.8	1.24	1.35
11	5.7	32.9	5.2	31.9				
12	5.0	33.5	5.2	32.3				
13	5.8	34.6	4.7	33.7				
14	5.2	35.2	4.7	33.5	6.3	32.5	1.21	1.34
18	5.6	38.2	5.2	36.5	6.1	34.2	1.09	1.17
22	5.8	40.7	5.3	40.1	7.0	37.0	1.21	1.32
26	5.6	44.7	5.9	42.4	6.6	37.9	1.18	1.12
30	5.7	45.2	3.5	37.5	6.3	39.2	1.11	1.80
34	5.3	47.7	4.0	35.3	6.3	39.4	1.19	1.58
38	5.1	48.7	4.6	39.6	6.6	40.0	1.29	1.43
42	4.8	49.2	4.7	41.7	5.6	40.1	1.17	1.19
46	4.9	49.7	4.3	45.1	6.4	41.0	1.31	1.49
50	4.9	50.2	3.9	42.2	6.0	41.8	1.22	1.54
54	4.8	51.7	4.0	43.6	5.5	43.1	1.15	1.38
58	5.0	52.6	3.8	45.3	5.9	44.7	1.18	1.55
62	4.4	52.8	3.8	47.7	5.7	45.9	1.30	1.50
66	5.7	53.3			6.7	46.2	1.18	
68			3.9	47.1				
70	5.5	54.0	3.9	46.8	7.2	45.2	1.31	1.85
74	5.8	53.6	4.0	45.1	8.3	48.2	1.43	2.08
78	5.2	54.4	3.8	45.3	6.8	45.8	1.31	1.79
82	5.2	54.3	3.9	43.8	7.1	47.2	1.37	1.82
86	5.0	52.7	4.2	45.4	6.4	46.2	1.28	1.52
90	4.5	52.9	4.0	49.0	6.1	46.8	1.36	1.53
94	4.4	53.4	3.9	49.5	5.7	47.2	1.30	1.46
98	4.3	52.3	4.0	49.9	5.5	44.8	1.28	1.38
102	4.8	52.0	3.6	50.5	6.7	45.7	1.40	1.86
Mean for weeks								
1-13	5.7	30.2	5.3	29.0	6.8	28.0	1.16	1.28
14-52	5.3	45.0	4.6	39.4	6.3	38.3	1.20	1.40
53-102	5.0	53.1	3.9	46.9	6.4	45.9	1.29	1.64

[a] Feed consumption by controls was measured weekly for 13 weeks and monthly thereafter.
[b] Grams of feed consumed per animal per day
[c] Grams of feed consumed per dosed animal per day divided by grams of feed consumed per control animal per day

TABLE K4b
Feed Consumption by Male Mice in the Dietary Restriction Study of Salicylazosulfapyridine: 2-Year and 3-Year Restricted Feed Protocols

Week	2-Year Protocol					3-Year Protocol				
	Vehicle Control		2,700 mg/kg			Vehicle Control		2,700 mg/kg		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed[b]	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Feed/ Control Feed
1	3.7	23.4	4.8	23.2	1.30	3.7	23.7	4.8	23.5	1.30
2	3.7	25.1	3.8	24.7	1.03	3.7	25.3	3.9	25.3	1.05
3	3.0	24.9	3.0	24.3	1.00	3.0	24.9	3.0	24.7	1.00
4	3.1	23.4	3.1	22.8	1.00	3.1	23.3	3.1	23.1	1.00
5	3.3	24.9	3.3	23.5	1.00	3.3	24.7	3.3	23.9	1.00
6	3.5	24.9	3.6	23.2	1.03	3.5	24.7	3.6	23.4	1.03
7	3.5	25.9	3.5	23.7	1.00	3.5	25.6	3.5	23.9	1.00
8	3.5	27.0	3.5	25.2	1.00	3.5	27.0	3.5	24.9	1.00
9	3.7	27.1	3.7	25.5	1.00	3.7	26.8	3.7	25.8	1.00
10	3.6	27.9	3.6	26.1	1.00	3.7	27.9	3.6	26.5	0.97
11	3.6	27.8	3.6	26.5	1.00	3.6	27.7	3.6	26.7	1.00
12	3.6	29.0	3.6	26.2	1.00	3.6	29.0	3.6	26.4	1.00
13	3.6	29.4	3.6	27.2	1.00	3.6	29.3	3.6	27.4	1.00
17	3.6	32.4	3.6	28.3	1.00	3.6	32.0	3.6	28.5	1.00
18	3.6	32.9	3.7	28.6	1.03	3.6	32.4	3.7	28.7	1.03
22	3.6	35.0	3.6	30.1	1.00	3.6	34.4	3.6	30.3	1.00
26	3.9	35.8	3.9	31.4	1.00	3.9	35.3	3.9	31.6	1.00
30	4.3	40.7	4.4	32.6	1.02	4.3	39.9	4.5	33.1	1.05
34	4.3	44.7	4.4	34.5	1.02	4.4	43.5	4.4	34.8	1.00
38	3.3	46.0	3.6	33.8	1.09	3.3	45.1	3.5	33.6	1.06
42	3.2	42.5	4.0	33.8	1.25	3.2	41.7	4.0	33.8	1.25
46	3.5	41.1	4.0	34.1	1.14	3.5	40.4	4.0	34.4	1.14
50	3.6	40.4	4.0	32.7	1.11	3.6	39.7	4.0	32.7	1.11
54	4.5	42.6	4.6	33.8	1.02	4.6	42.0	4.6	33.6	1.00*
58	4.3	49.6	4.3	36.6	1.00	4.3	48.9	4.4	36.8	1.02
62	3.7	49.5	3.6	35.8	0.97	3.7	48.5	3.6	36.0	0.97
66	3.6	48.9	3.6	34.9	1.00	3.5	47.5	3.6	34.7	1.03
70	3.5	47.8	3.6	34.6	1.03	3.6	46.4	3.6	34.5	1.00
74	3.4	46.9	3.3	34.5	0.97	3.4	45.5	3.3	34.2	0.97
78	3.3	45.0	3.3	33.6	1.00	3.3	43.9	3.3	33.6	1.00
82	3.5	43.9	3.5	32.2	1.00	3.6	42.9	3.5	32.1	0.97
86	3.6	41.8	3.6	31.0	1.00	3.6	40.4	3.6	31.2	1.00
90	4.0	44.1	3.9	34.7	0.98	4.0	42.5	3.9	34.7	0.98
94	3.9	45.8	4.0	34.8	1.03	3.9	44.3	3.9	34.4	1.00
98	4.5	47.6	4.6	34.8	1.02	4.5	45.2	4.6	34.6	1.02
102	3.8	49.4	3.9	35.8	1.03	3.8	46.5	3.9	35.2	1.03
106						3.5	46.7	3.5	35.0	1.00
110						3.6	46.5	3.5	35.6	0.97
114						3.6	46.0	3.7	35.2	1.03
118						3.6	45.3	3.7	33.6	1.03
122						3.6	43.8	3.6	33.4	1.00
126						3.7	43.0	3.7	34.0	1.00
130						3.7	41.3	3.7	33.2	1.00
134						3.6	41.4	3.6	33.6	1.00
138						3.3	39.3	3.3	32.5	1.00
142						3.5	39.3	3.5	32.8	1.00
146						3.5	38.5	3.6	32.8	1.03
150						3.6	36.2	3.6	30.5	1.00
154						3.4	35.7	3.4	31.8	1.00
Mean for weeks										
1-13	3.5	26.2	3.6	24.8	1.03	3.5	26.1	3.6	25.0	1.03
14-52	3.7	39.2	3.9	32.0	1.07	3.7	38.4	3.9	32.2	1.06
53-102	3.8	46.4	3.8	34.4	1.00	3.8	45.0	3.8	34.3	1.00
103-154						3.6	41.8	3.6	33.4	1.00

[a] Grams of feed consumed per animal per day
[b] Grams of feed consumed per dosed animal per day divided by grams of feed consumed per control animal per day

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