

NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 215



CARCINOGENESIS BIOASSAY
OF
BISPHENOL A
(CAS NO. 80-05-7)
IN F344 RATS AND B6C3F₁ MICE
(FEED STUDY)

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

NATIONAL TOXICOLOGY PROGRAM

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

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NTP Technical Report
on the
CARCINOGENESIS BIOASSAY
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NATIONAL TOXICOLOGY PROGRAM
Research Triangle Park
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NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the the NTP carcinogenesis bioassay program are chosen primarily on the basis of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

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TABLE OF CONTENTS

	<u>Page</u>
Abstract	vii
Contributors	ix
Peer Review Panel and Comments	xi
I. Introduction	1
II. Materials and Methods	3
A. Chemical	3
B. Dietary Preparation	3
C. Animals	3
D. Animal Maintenance	4
E. Acute Oral Toxicity and 14-Day Repeated-Dose Studies . .	4
F. Subchronic Studies	9
G. Chronic Studies	12
H. Clinical Examinations and Pathology	12
I. Data Recording and Statistical Analyses	14
III. Results - Rats	17
A. Body Weights and Clinical Signs (Rats)	17
B. Survival (Rats)	17
C. Pathology (Rats)	17
D. Statistical Analyses of Results (Rats)	20
IV. Results - Mice	33
A. Body Weights and Clinical Signs (Mice)	33
B. Survival (Mice)	33
C. Pathology (Mice)	33
D. Statistical Analyses of Results (Mice)	36
V. Discussion	45
VI. Conclusion	47
VII. Bibliography	49

TABLES

Table 1	Specifications and Sources of Materials Used for Animal Maintenance	5
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	<u>Page</u>
Table 2 Doses and Survival of Rats and Mice Administered A Single Dose of Bisphenol A by Gavage	6
Table 3 Dosage, Survival, and Mean Body Weights of Rats Fed Diets Containing Bisphenol A for 14 Days	7
Table 4 Dosage, Survival, and Mean Body Weights of Mice Fed Diets Containing Bisphenol A for 14 Days	8
Table 5 Dosage, Survival, and Mean Body Weights of Rats Fed Diets Containing Bisphenol A for 13 Weeks	10
Table 6 Dosage, Survival, and Mean Body Weights of Mice Fed Diets Containing Bisphenol A for 13 Weeks	11
Table 7 Experimental Design of Chronic Feeding Studies with Bisphenol A in Rats and Mice	13
Table 8 Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Bisphenol A	23
Table 9 Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Bisphenol A	29
Table 10 Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing Bisphenol A	38
Table 11 Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Bisphenol A	42

FIGURES

Figure 1 Growth Curves for Rats Fed Diets Containing Bisphenol A	18
Figure 2 Survival Curves for Rats Fed Diets Containing Bisphenol A	19
Figure 3 Growth Curves for Mice Fed Diets Containing Bisphenol A	34
Figure 4 Survival Curves for Mice Fed Diets Containing Bisphenol A	35
Figure 5 Infrared Absorption Spectrum of Bisphenol A	101
Figure 6 Nuclear Magnetic Resonance Spectrum of Bisphenol A	103

APPENDIXES

Appendix A	Summary of the Incidence of Neoplasms in Rats Fed Diets Containing Bisphenol A	51
Table A1	Summary of the Incidence of Neoplasms in Male Rats Fed Diets Containing Bisphenol A	53
Table A2	Summary of the Incidence of Neoplasms in Female Rats Fed Diets Containing Bisphenol A	57
Appendix B	Summary of the Incidence of Neoplasms in Mice Fed Diets Containing Bisphenol A	61
Table B1	Summary of the Incidence of Neoplasms in Male Mice Fed Diets Containing Bisphenol A	63
Table B2	Summary of the Incidence of Neoplasms in Female Mice Fed Diets Containing Bisphenol A	67
Appendix C	Summary of the Incidence of Nonneoplastic Lesions in Rats Fed Diets Containing Bisphenol A	71
Table C1	Summary of the Incidence of Nonneoplastic Lesions in Male Rats Fed Diets Containing Bisphenol A	73
Table C2	Summary of the Incidence of Nonneoplastic Lesions in Female Rats Fed Diets Containing Bisphenol A	78
Appendix D	Summary of the Incidence of Nonneoplastic Lesions in Mice Fed Diets Containing Bisphenol A	83
Table D1	Summary of the Incidence of Nonneoplastic Lesions in Male Mice Fed Diets Containing Bisphenol A	85
Table D2	Summary of the Incidence of Nonneoplastic Lesions in Female Mice Fed Diets Containing Bisphenol A	91
Appendix E	Analysis of Bisphenol A -- Midwest Research Institute	97
Appendix F	Analysis of Formulated Diets for Stability of Bisphenol A -- Midwest Research Institute	105
Appendix G	Analysis of Formulated Diets for Concentrations of Bisphenol A -- Litton Bionetics, Inc..	109

APPENDIXES

Appendix H	Feed and Compound Consumption in Rats Fed Diets Containing Bisphenol A in the Chronic Study	113
Table H1	Feed and Compound Consumption in Male Rats Fed Diets Containing Bisphenol A in the Chronic Study	115
Table H2	Feed and Compound Consumption in Female Rats Fed Diets Containing Bisphenol A in the Chronic Study	116

ABSTRACT

A carcinogenesis bioassay of bisphenol A, an intermediate used in the manufacture of epoxy, polycarbonate, and polyester-styrene resins, was conducted by feeding diets containing 1,000 or 2,000 ppm of the test chemical to groups of 50 F344 rats of either sex, 1,000 or 5,000 ppm to groups of 50 male B6C3F1 mice, and 5,000 or 10,000 ppm to groups of 50 female B6C3F1 mice for 103 weeks. Groups of 50 rats and 50 mice of either sex served as controls.

Mean body weights of rats of either sex and of high- and low-dose female mice and high-dose male mice were lower than those of the controls throughout the study. Since food consumption of dosed female rats was only 70% to 80% that of the controls throughout most of this study, reduced body weight gain was probably due to reduced food consumption. Food consumption by dosed male rats was 90% that of controls. Food consumption among all groups of mice appear to be similar.

Leukemias occurred at increased incidences in dosed rats of both sexes. In male rats, the dose-related (13/50, 12/50, 23/50) trend was statistically significant ($P=0.021$) by a Cochran-Armitage test, but neither the trend nor the increase in the high-dose group was significant by life table analyses, which adjust for survival differences among groups. The increased incidences in dosed female rats were also not statistically significant (7/50, 13/50, 12/50).

Interstitial-cell tumors of the testes occurred at statistically significant incidences in low- and high-dose male rats; however, since this lesion normally occurs at a high incidence in aging F344 male rats, the increased incidence observed in this study was not considered compound related (35/49, 48/50, 46/49).

In male mice, there was an increased incidence of leukemias or lymphomas (2/49, 9/50, 5/50), but this increase was not statistically significant.

A compound-related increased incidence of multinucleated giant hepatocytes was observed in male mice (1/49, 41/49, 41/50), but there was no increase of liver tumors in male mice.

The marginally significant increase in leukemias in male rats, along with an increase (not statistically significant) in leukemias in female rats and a marginally significant increase in the combined incidence of lymphomas and leukemias in male mice, suggests that exposure to bisphenol A may be associated with increased cancers of the hematopoietic system. A statistically significant increase in interstitial-cell tumors of the testes in male rats was also suggestive of carcinogenesis, but was not considered to be convincing evidence of a compound-related effect because this lesion normally occurs at a high incidence in aging F344 rats.

Under the conditions of this bioassay, there was no convincing evidence that bisphenol A was carcinogenic for F344 rats or B6C3F1 mice of either sex.

CONTRIBUTORS

The bioassay of bisphenol A was conducted by Litton Bionetics, Inc., Kensington, Maryland, under a subcontract to Tracor Jitco, Inc., the prime contractor for the NCI Carcinogenesis Testing Program. Studies were begun in February 1977 and completed in February 1979.

The bioassay was conducted under the supervision of Dr. E. Gordon (1,2), principal investigator. Doses of the test chemical were selected by Drs. W. MacDonald (3), J. Robens (3,4), C. Cueto (5), R. Schueler (3), and E. Gordon (1). Mr. D. Kinsel (1) and Ms. J. Sheldon (1) were in charge of animal care, and Mr. G. North (1) supervised the preparation of the feed mixtures and collected samples of the diets for analysis. Drs. R. Montali and R. Cardy (1), pathologists, directed the necropsies and performed the histopathologic examinations. The pathology report and selected slides were evaluated by the NCI Pathology Working Group as described in Ward et al. (1978). The diagnoses represent a consensus of contracting pathologists and the NCI Pathology Working Group with final approval by the NCI Pathology Working Group.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute, Rockville, Maryland (8). The statistical analyses were performed by Dr. J. R. Joiner (3) and Ms. S. Vatsan (3,9) using methods selected for the bioassay program by Dr. J. J. Gart (10). Chemicals used in this bioassay were analyzed at Midwest Research Institute (10) and Litton Bionetics, Inc. (1).

This report was prepared at Tracor Jitco (3) and reviewed by NCI. Those responsible for the report at Tracor Jitco were Dr. C. Cueto, Director of the Bioassay Program; Dr. S. S. Olin, Associate Director; Dr. M. A. Stedham, pathologist; Dr. A. C. Jacobs, bioscience writer; and Dr. W. D. Theriault and Ms. M. W. Glasser, technical editors.

The following scientists at NCI/NTP (6) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. J. Fielding Douglas, Dr. Charles K. Grieshaber, Dr. Larry Hart, Dr. William V. Hartwell, Dr. Joseph Haseman, Dr. James Huff, Dr. C. W. Jameson, Dr. Mary R. Kornreich, Dr. Ernest E. McConnell, Dr. John A. Moore, Dr. Sherman F. Stinson, Dr. Raymond Tennant, and Dr. Jerrold M. Ward.

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PEER REVIEW PANEL AND COMMENTS

On October 15, 1980, this report was peer reviewed by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9 a.m. in Conference Room 6, Building 31C, National Institutes of Health, Bethesda, Maryland. Members of the Subcommittee are: Drs. Margaret Hitchcock (Chairperson), Curtis Harper, Thomas Shepard, and Alice Whittemore. Members of the Panel are: Drs. Norman Breslow, Joseph Highland, Charles Irving, Frank Mirer, Sheldon Murphy, Svend Nielsen, Bernard Schwetz, Roy Shore, James Swenberg, and Gary Williams. Drs. Highland, Irving, Whittemore, and Williams were unable to attend the review.

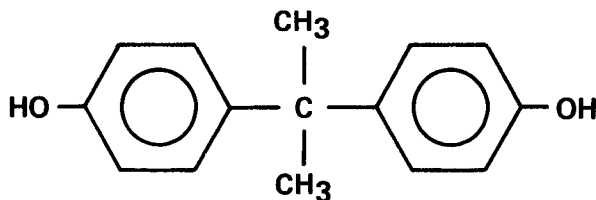
Dr. Murphy, the principal reviewer for the report on the bioassay of bisphenol A, agreed with the conclusion that under the conditions of this bioassay, bisphenol A was not carcinogenic for F344 rats or B6C3F1 mice. He noted a significant reduction in the incidence of endometrial stromal polyps in high-dose female rats. He considered the increased incidence of multinucleated giant hepatocytes in dosed male mice to be striking. He noted that the dose levels administered to male mice might have been too low, since the upper level of 5,000 ppm did not cause a decreased weight gain in the subchronic study and caused only a small reduction in weight gain in the chronic study. He stated that the 20% to 40% reduction of food consumption in rats on the chronic study needed further explanation.

The panel felt that the conclusion that "bisphenol A is not carcinogenic" should be qualified to reflect the facts that leukemia in male rats showed a significant positive trend, that leukemia incidence in high-dose male rats was considered not significant only on the basis of the Bonferroni criteria, that leukemia incidence was also elevated in female rats and male mice, and that the significance of interstitial-cell tumors of the testes in rats was dismissed on the basis of historical control data.

Drs. Shore and Breslow agreed that the leukemia incidence in female rats suggested a trend comparable with that occurring in male rats, and appropriate statistical tests across both sexes should be performed. Dr. Haseman (NTP) said that when a life table analysis, which adjusts for survival, was applied to the rat leukemia data, the increases in these lesions in both sexes were not as significant as indicated by an unadjusted analysis.

Dr. Murphy moved that the report on the bioassay of bisphenol A be accepted with the provisions that the statement regarding the lack of significance of the leukemias be modified to reflect the additional data analysis of this cancer in male and female rats, and that there be comment in the summary concerning the interstitial cell tumors and their lack of significance when compared with historical controls. The motion was seconded by Dr. Hitchcock, and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION



BISPHENOL A

Bisphenol A --4,4'-isopropylidenediphenol -- (CAS No. 80-05-7) is a monomer used in the manufacture of epoxy, polycarbonate, and corrosion resistant unsaturated polyester-styrene resins found in interior coatings for cans and drums, reinforced pipe, adhesives, flooring, water main filters, artificial teeth, nail polish, and food packaging materials (Knaak and Sullivan, 1966; Patents 1974, 1975, and 1978; Chemical & Engineering News, 1979; Kirk-Othmer, 1978 and 1979). Although insoluble in water, unreacted bisphenol A can migrate from the resins used in food packaging to food surfaces (Knaak and Sullivan, 1966). Since exposure to air containing bisphenol A causes skin, eye, and upper respiratory tract irritation, worker exposure is limited to a ceiling concentration of 0.5 ppm or 2.8 mg/m³ of air (CFR, 1974). Production of bisphenol A in 1978 was 470 million pounds (USITC, 1979).

The oral LD₅₀ for bisphenol A has been reported to be 4.24 g/kg for rats and 2.5 g/kg for mice (AIHA, 1967). When administered as a single dose by gavage to male CFE rats, 28% of the ¹⁴C-labeled bisphenol A was excreted in the urine (primarily as the glucosamide) and 56% in the feces (20% as free bisphenol A, 20% as a hydroxylated bisphenol A, and the rest as an unidentified conjugate). No carbon-labeled residues were detected in animals killed after 8 days (Knaak and Sullivan, 1966).

Bisphenol A was tested for potential carcinogenicity by the Bioassay Program because of widespread occupational and consumer exposure to the substance and because no other studies had been done.

II. MATERIALS AND METHODS

A. Chemical

Bisphenol A --4,4'-isopropylidenediphenol -- (CAS No. 80-05-7) was obtained as a single batch (Lot No. DC6-24-75) from the Dow Chemical Company (Midland, MI). The results of purity and identity analyses performed at Midwest Research Institute were consistent with the structure and the literature values for bisphenol A (Appendix E). Four impurities were detected by thin-layer chromatography. Five unidentified impurities, one being 1.8% of the major peak, were detected by vapor-phase chromatography.

The chemical was stored in the original container at 4°C.

B. Dietary Preparation

Samples of feed mixtures containing 100,000 ppm bisphenol A were analyzed at Midwest Research Institute by vapor-phase chromatography and were found to be stable for 2 weeks at temperatures up to 45°C (Appendix F). Test diets were formulated by mixing a small amount of Purina® Lab Chow and the required amount of bisphenol A with a mortar and pestle and then adding this premix to the required amount of animal meal and mixing in a Patterson-Kelly® twin shell blender equipped with an intensifier bar for 20 minutes. Test diets were stored in the dark at 4°C for no longer than 2 weeks. Control diets consisted of Purina® Lab Chow. The mean analytical concentrations of bisphenol A in selected samples from test diets administered during the chronic study were usually within +10% of the theoretical level (Appendix G).

C. Animals

Three-week old male and female F344 (Fischer) rats and B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center, Frederick, Maryland, observed for 2 weeks, and assigned to test groups according to a table of random numbers.

D. Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages covered with non-woven polyester filter sheets (Table 1). Racks and filters were changed once every 2 weeks. Cages, bedding, and glass water bottles equipped with stainless steel sipper tubes were changed twice per week. Stainless steel feed hoppers were changed once per week. Control and test diets and tap water acidified with hydrochloric acid to pH 2.5 were available ad libitum. The animal rooms were maintained at 22^o-26^oC and humidity was 30%-70%.

Incoming air was first filtered through AG-55 Ameriglass Roughing filters and then through HEPA-100 filters at a rate of 10 changes of room air per hour. Fluorescent lighting provided illumination 12 hours per day.

Rats fed bisphenol A were housed in a room in which feeding studies on caprolactam (CAS 105-60-2) were also being carried out. Mice fed bisphenol A were housed in a room in which feeding studies on caprolactam (CAS 105-60-2), 11-aminoundecanoic acid (CAS 2432-99-7), and 2,6-dichloro-p-phenylenediamine (CAS 609-20-1) were also being conducted.

E. Acute Oral Toxicity and 14-Day Repeated-Dose Studies

Acute toxicity and 14-day repeated-dose studies were conducted using F344 rats and B6C3F1 mice to determine the concentrations of bisphenol A to be used in the subchronic studies.

In the acute toxicity study, single doses of bisphenol A with 1.5% acacia as the vehicle were administered by gavage to groups of five males and five females of each species in the amounts shown in Table 2. All surviving animals were killed on day 15. The LD₅₀ values (calculated as in Horn, 1956) were 4.1 g/kg for male rats, 3.3 g/kg for female rats, 5.2 g/kg for male mice and 4.1 g/kg for female mice.

In the 14-day repeated-dose study, groups of five males and five females of each species were administered the test substance in feed for 2 weeks at the concentrations shown in Tables 3 and 4. Groups of five males and five females of each species served as controls.

Table 1. Specifications and Sources of Materials Used for Animal Maintenance

Item	Specifications	Manufacturer or Supplier
Bedding	Absorb-dri [®] hardwood chips	Lab Products, Inc. Garfield, NJ
Cages	Polycarbonate	Lab Products, Inc. Garfield, NJ
Feed	Purina [®] Laboratory Chow	Ralston Purina Co. Richmond, IN
Filters	AG-55 Ameriglass Roughing Filter	American Air Filter Louisville, KY
Filters	HEPA-100	American Air Filter Louisville, KY
Filter Sheets	Non-woven polyester	Snow Filtration Cincinnati, Ohio

Table 2. Doses and Survival of Rats and Mice Administered A Single Dose of Bisphenol A by Gavage

	Dose (mg/kg)	Survival (a)	
		Male	Female
<u>Rats</u>			
	2,150	5/5	4/5
	3,160	4/5	1/5
	4,640	2/5	3/5
	6,810	0/5	0/5
<u>Mice</u>			
	1,470	5/5	4/5
	2,150	(b)	5/5
	3,160	5/5	5/5
	4,640	4/5	1/5
	6,810	0/5	0/5
	10,000	0/5	(b)

(a) Number surviving/number per group

(b) Not tested at this dose

Table 3. Dosage, Survival, and Mean Body Weights of Rats Fed Diets Containing Bisphenol A for 14 Days

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Control (b) (Percent)
		Initial	Final	Gain	
MALE					
0	5/5	226	253	27	
500	5/5	224	251	27	0
1,000	5/5	215	244	29	+7
2,500	5/5	227	236	9	-67
5,000	5/5	220	222	2	-93
10,000	5/5	220	190	-30	-211
FEMALE					
0	5/5	137	144	7	
500	5/5	151	162	11	+57
1,000	5/5	146	160	14	+100
2,500	5/5	138	149	11	+57
5,000	5/5	146	150	4	-43
10,000	5/5	147	139	-8	-214

(a) Number surviving/number per group

(b) Weight Change Relative to Controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

Table 4. Dosage, Survival, and Mean Body Weights of Mice Fed Diets Containing Bisphenol A for 14 Days

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			
		Initial	Final	Gain	
<u>MALE</u>					
0	5/5	27	26	-1	
500	5/5	25	25	0	
1,000	5/5	24	25	+1	
2,500	5/5	26	23	-3	
5,000	5/5	23	23	0	
10,000	5/5	25	24	-1	
<u>FEMALE</u>					
0	5/5	19	19	0	
500	5/5	20	20	0	
1,000	5/5	20	18	-2	
2,500	5/5	20	20	0	
5,000	5/5	20	20	0	
10,000	5/5	19	19	0	

(a) Number surviving/number per group

No deaths occurred in the rats. Mean weight gain was depressed 60% or more in male rats at doses of 2,500 ppm or more and 40% in female rats at doses of 5,000 ppm or more. Male and female rats receiving 10,000 ppm lost weight. No deaths occurred in the mice, and mean weight gains of dosed mice were comparable with those of the controls.

F. Subchronic Studies

Subchronic studies were conducted to determine the two concentrations of bisphenol A to be used in the chronic studies (Tables 5 and 6). Animals were observed twice daily and weighed weekly. At the end of the 91-day period, survivors were killed, necropsies were performed on all animals, and tissues (those listed in section H) were taken for histopathologic examination.

Rats: Two of 10 male rats receiving 1,000 ppm bisphenol A in the diet died. No other deaths occurred in male or female rats. Weight gain was depressed 18% or more in males receiving 1,000 ppm or more and by more than 10% in females receiving 1,000 ppm or more. Feed consumption was not affected by bisphenol A, even at the highest doses.

Hyaline masses were found in the bladder lumen of 4/10 male rats receiving 4,000 ppm, 6/10 males receiving 2,000 ppm, 3/10 males receiving 1,000 ppm, 3/10 males receiving 500 ppm, and 5/10 males receiving 250 ppm, compared with none in control males. Cecal enlargement was noted in 60%-100% of the animals of each dosed group with the exception of the low-dose females (250 ppm) and was considered to be compound related. No inflammatory changes or other mucosal abnormalities were detected when the cecal walls were examined histologically.

Based on the data for weight gain depression, doses selected for the rats for the chronic study were 1,000 and 2,000 ppm bisphenol A in feed.

Mice: Two of 10 female mice that received 5,000 ppm (the lowest dose) died. No other deaths occurred. Weight gain was depressed by 14% or more in male mice receiving 15,000 to 25,000 ppm and by 17% or more in all dosed groups of female mice. The depression in weight gain was not dose related in females.

Table 5. Dosage, Survival, and Mean Body Weights of Rats Fed Diets Containing Bisphenol A for 13 Weeks

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Control (b) (Percent)
		Initial	Final	Gain	
MALE					
0	10/10	129	309	180	
250	10/10	130	297	167	-7
500	10/10	130	293	163	-9
1,000	8/10	130	269	139	-23
2,000	10/10	129	277	148	-18
4,000	10/10	130	259	129	-28
FEMALE					
0	10/10	100	174	74	
250	10/10	101	163	62	-16
500	10/10	101	176	75	+1
1,000	10/10	101	167	66	-11
2,000	10/10	101	166	65	-12
4,000	10/10	102	155	53	-28

(a) Number surviving/number per group

(b) Weight Change Relative to Controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

Table 6. Dosage, Survival, and Mean Body Weights of Mice Fed Diets Containing Bisphenol A for 13 Weeks

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Control (b) (Percent)
		Initial	Final	Gain	
<u>MALE</u>					
0	10/10	18	25	7	
5,000	10/10	18	26	8	+14
10,000	10/10	18	25	7	0
15,000	10/10	18	23	5	-29
20,000	10/10	18	24	6	-14
25,000	10/10	18	23	5	-29
<u>FEMALE</u>					
0	10/10	16	22	6	
5,000	8/10	16	21	5	-17
10,000	10/10	16	20	4	-33
15,000	10/10	16	19	3	-50
20,000	10/10	16	20	4	-33
25,000	10/10	16	21	5	-17

(a) Number surviving/number per group

(b) Weight Change Relative to Controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

Multinucleated giant hepatocytes were observed in all dosed groups of male mice with an incidence and severity that were dose related. Multinucleated giant hepatocytes were found in 9/10 male mice receiving the highest dose (25,000 ppm) compared with 0/10 female mice receiving the high dose.

Doses selected for the chronic study were 1,000 and 5,000 ppm bisphenol A in feed for male mice and 5,000 and 10,000 ppm for females.

G. Chronic Studies

The test groups, doses administered, and the durations of the chronic studies are shown in Table 7.

H. Clinical Examinations and Pathology

All animals were observed twice daily for signs of toxicity. Mean body weights of animals by cage were recorded every 2 weeks for the first 13 weeks and monthly thereafter. Clinical signs were recorded monthly. Moribund animals and animals that survived to the end of the bioassay were killed with carbon dioxide and necropsied.

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

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Preparations of the following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals,

Table 7. Experimental Design of Chronic Feeding Studies with Bisphenol A in Rats and Mice

Test Group	Initial No. of Animals	Bisphenol A in Diet (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
<u>MALE RATS</u>				
Control	50	0	0	108
Low-Dose	50	1,000	103	5
High-Dose	50	2,000	103	5
<u>FEMALE RATS</u>				
Control	50	0	0	108
Low-Dose	50	1,000	103	5
High-Dose	50	2,000	103	5
<u>MALE MICE</u>				
Control	50	0	0	107
Low-Dose	50	1,000	103	4
High-Dose	50	5,000	103	4
<u>FEMALE MICE</u>				
Control	50	0	0	107
Low-Dose	50	5,000	103	4
High-Dose	50	10,000	103	4

bladder, seminal vesicles/prostate/testes, ovaries/uterus, nasal cavity, brain, pituitary, eyes, and spinal cord. Special staining techniques were utilized as necessary.

I. Data Recording and Statistical Analyses

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is reported only when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed

animals at each dose level. When results from two dosed groups are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality criterion (Miller, 1966) requires that the P values for any comparison be less than or equal to 0.025. When this correction was used, it is discussed in the narrative section. It is not presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. When a linear trend is assumed, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive relationship. This method also provides a two-tailed test of departure from linear trend.

Life table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was killed was entered as the time point of tumor observation. The methods of Cox and of Tarone were used for the statistical tests of the groups. The statistical tests were one-tailed.

A time-adjusted analysis was applied. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

The approximate 95% confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that, in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the

interval calculated from the experiment. When the lower limit of the confidence intervals is greater than one, it can be inferred that a statistically significant result has occurred (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero). When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Throughout the bioassay, mean body weights of dosed rats of either sex were lower than those of the corresponding controls (Figure 1). No other compound-related clinical signs were observed. A dose-related decrease in feed consumption was observed at week 12, and thereafter feed consumption of dosed female groups was 70%-80% that of the controls and feed consumption of dosed males was 90% that of the controls (Appendix H).

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered bisphenol A in feed at the doses of this bioassay, and those of the controls, are shown by the Kaplan and Meier curves in Figure 2. The survival among all three groups was comparable in either sex.

In male rats, 23/50 (46%) of the untreated control group, 30/50 (60%) of the low-dose group, and 27/50 (54%) of the high-dose group lived to the end of the study at week 108. In females, 35/50 (70%) of the controls and the low-dose group and 37/50 (74%) of the high-dose group lived to the end of the study at week 108.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2.

A variety of tumors was observed in dosed and control rats. The incidence and types of tumors were generally similar in these groups. A few tumor types, including leukemias in males and females and testicular tumors in males, appeared to be more common in high-dose rats, but the incidence was not significantly elevated. A variety of nonneoplastic lesions were seen in

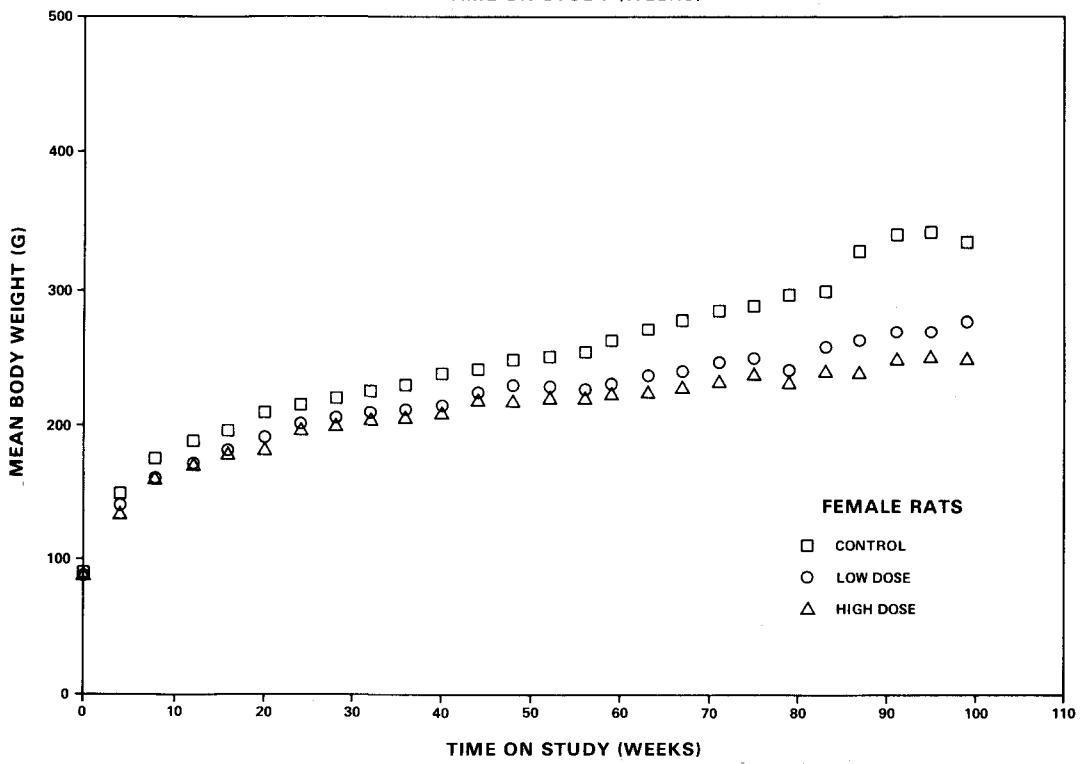
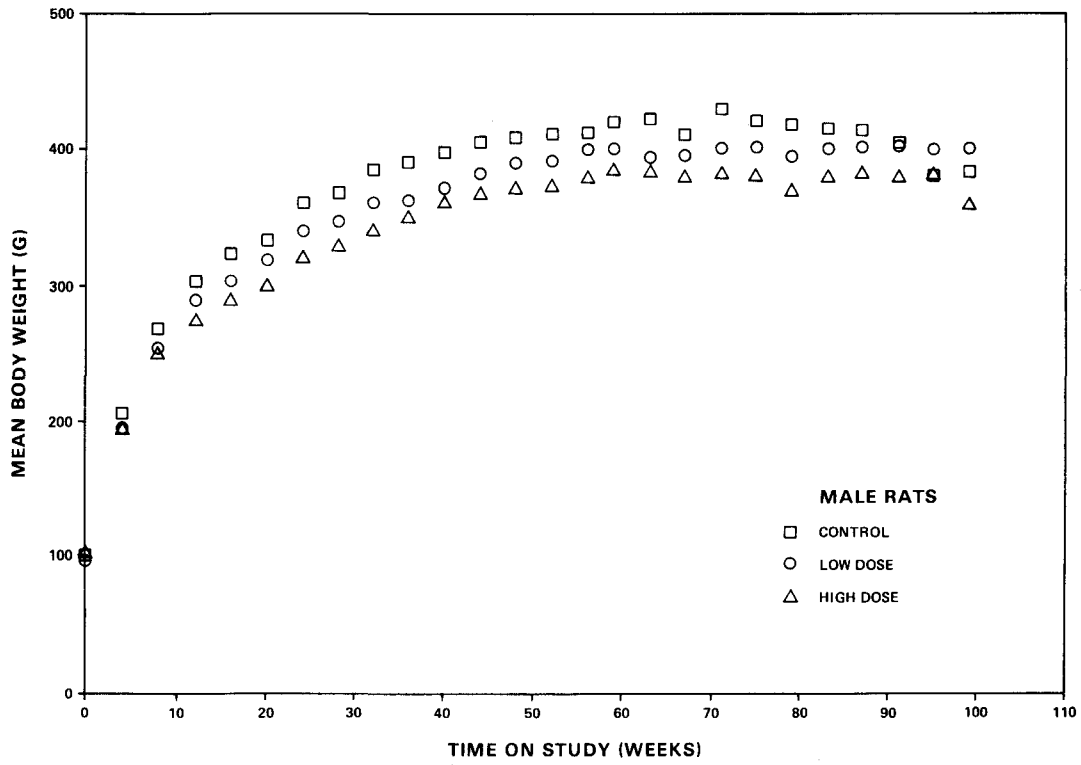


Figure 1. Growth Curves for Rats Fed Diets Containing Bisphenol A

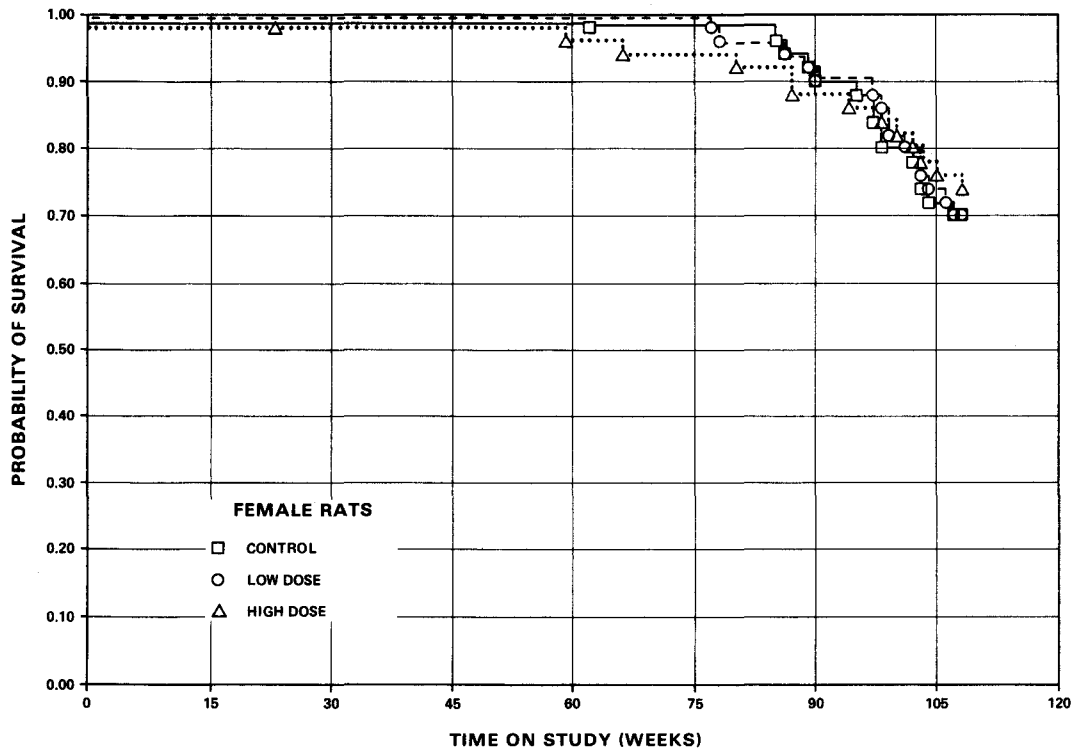
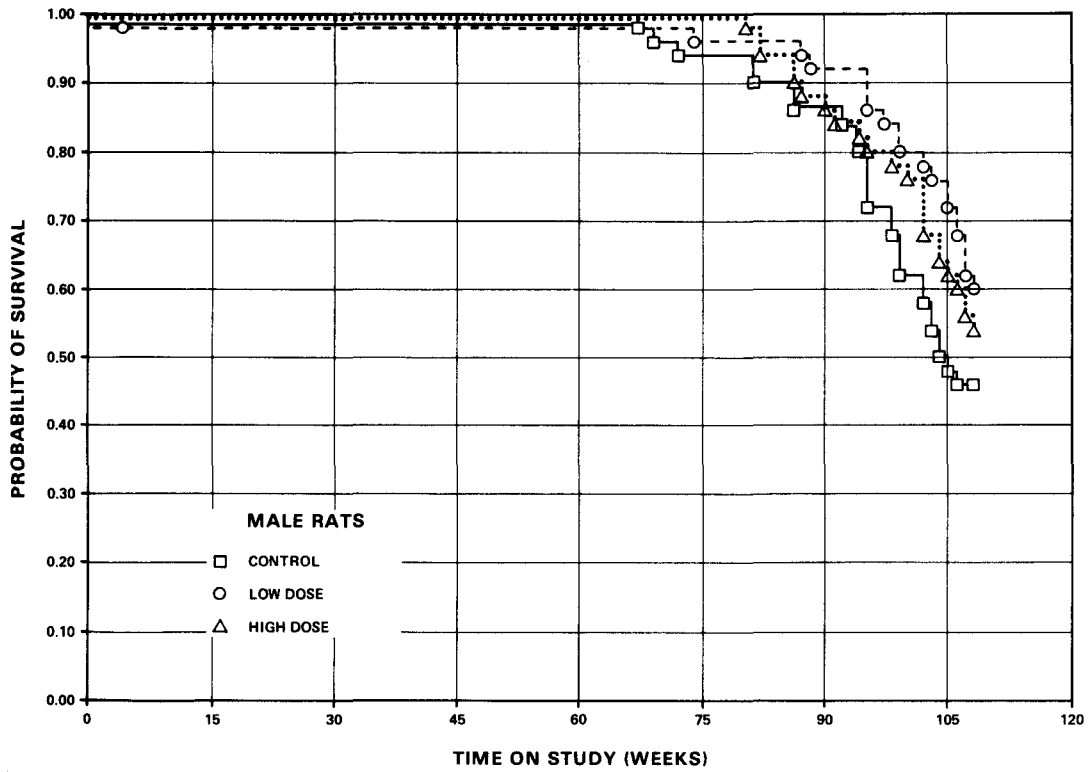


Figure 2. Survival Curves for Rats Fed Diets Containing Bisphenol A

both dosed and control rats, and none appeared to be related to chemical administration.

D. Statistical Analyses of Results (Rats)

Tables 8 and 9 contain the statistical analyses of those primary tumors that occurred in at least two animals of one group and with an incidence of at least 5% in one or more groups. Survival in all groups was comparable in either sex.

Leukemias of the hematopoietic system in male rats were observed in increased proportion in the high-dose group compared with the control group (13/50, 26% in the controls; 12/50, 24% in the low-dose; and 23/50, 46% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ($P=0.021$). The Fisher exact test between the high-dose group and the control group indicated a value of $P=0.030$, which is above the value of $P=0.025$ required by the Bonferroni inequality criterion for an overall significance of $P=0.05$ when two dosed groups are compared with a common control group. In female rats, this tumor was not observed in statistically significant proportions. Life table analyses which adjusted for intercurrent mortality were also carried out for the leukemia data. It was found that for male rats, neither the high-dose effect nor the dose-response trend were statistically significant ($P=0.141$ and $P=0.074$, respectively). The female rats likewise showed no significant effects.

Fibroadenomas of the mammary gland in male rats were observed in increased proportions in the high-dose group (0/50, 0% in the controls; 0/50, 0% in the low-dose; and 4/50, 8% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ($P=0.015$). The Fisher exact tests were not significant. In female rats, this tumor was not observed in statistically significant proportions.

Interstitial-cell tumors of the testis in male rats were observed in a statistically significant positive relation in the dosed groups compared with the control group (35/49, 71% in the controls; 48/50, 96% in the low-dose; and 46/49, 94% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ($P=0.001$), but there

was an apparent departure from linear trend ($P=0.021$). The Fisher exact test between the control group and either of the dosed groups was significant ($P=0.003$ in the high-dose and $P=0.001$ in the low-dose); however, aging F344 male rats have a high incidence (more than 90%) of this lesion. The incidence rate of this tumor, estimated from historical records for untreated controls and in bioassays of at least 104 weeks duration at this laboratory, is 88%. At this rate of incidence, there is more than a 5% chance of observing 48/50 with the tumor and more than a 14% chance of finding 46/49 with the tumor. Thus the statistical significance of this tumor incidence, compared with the incidence in the concurrent control, may be due to the lowered control incidence rate.

Pheochromocytomas of the adrenal in male rats occurred in decreased incidence in the dosed groups compared with the control group. The Cochran-Armitage test for linear trend was statistically significant in the negative direction ($P=0.031$). The P values of the Fisher exact tests were both below $P=0.050$ ($P=0.049$ in the high-dose and $P=0.035$ in the low-dose), but were both above the significance value of $P=0.025$ required by the Bonferroni inequality criterion for an overall significance of $P=0.05$ when two dosed groups are compared with a common control group. In female rats, this tumor was not observed in statistically significant proportions.

Cortical adenomas of the adrenal in female rats were observed in decreased proportion in the dosed groups compared with the control group (12/50, 24% in the controls; 5/50, 10% in the low-dose; and 4/50, 8% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the negative direction ($P=0.016$). The Fisher exact test between the high-dose group and the control group indicated a value of $P=0.027$, which is above the value of $P=0.025$ required by the Bonferroni inequality criterion for an overall significance of $P=0.05$ when two dosed groups are compared with a common control group. In male rats, this tumor was not observed in statistically significant proportions.

Endometrial stromal polyps of the uterus in female rats were observed in a statistically significant negative relation. The Cochran-Armitage test for linear trend was statistically significant in the negative direction ($P=0.015$). The Fisher exact test between the high-dose group and the control

group was significant ($P=0.018$). This tumor occurred in decreased incidence in the low-dose group compared with the control group.

Only one low-dose male and one high-dose female died prior to week 52. The elimination of these animals in the time-adjusted tests resulted in no positive significant results other than those previously discussed. Although the first observation of leukemia was at 4 weeks in the group of low-dose male rats, the next observation in this group was at week 88, which is comparable to that in the other two groups.

No increase in tumor incidence was clearly associated with the administration of the chemical. In each of the 95% confidence intervals for relative risk, except for the incidence of interstitial cell tumors in testes, the value of one or less than one is included: this indicates the absence of significant positive results. It should also be noted that each of the intervals, except for the incidence of endometrial stromal polyps in the uterus of high-dose females, has an upper limit greater than one indicating the theoretical possibility of tumor induction by bisphenol A, which could not be detected under the conditions of this test.

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Bisphenol A (a)

Topography: Morphology	Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma (b)	2/50(4)	3/50(6)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.500	0.500
Lower Limit		0.180	0.009
Upper Limit		17.329	9.290
Weeks to First Observed Tumor	104	108	108
Subcutaneous Tissue: Fibroma or Fibrosarcoma (b)	3/50(6)	3/50(6)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	0.333
Lower Limit		0.140	0.006
Upper Limit		7.133	3.983
Weeks to First Observed Tumor	102	108	108
Hematopoietic System: Leukemia, NOS (b)	13/50(26)	12/50(24)	23/50(46)
P Values (c),(d)	P=0.021	N.S.	P=0.030
Relative Risk (Control) (e)		0.923	1.769
Lower Limit		0.428	0.979
Upper Limit		1.971	3.313
Weeks to First Observed Tumor	86	4	80

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Neoplastic Nodule (b)	4/50(8)	6/49(12)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.531	0.250
Lower Limit		0.387	0.005
Upper Limit		6.952	2.411
Weeks to First Observed Tumor	95	108	108
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	4/50(8)	7/49(14)	2/50(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.786	0.500
Lower Limit		0.486	0.047
Upper Limit		7.830	3.318
Weeks to First Observed Tumor	95	108	82
Pituitary: Adenoma, NOS (b)	13/47(28)	12/48(25)	15/49(31)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.904	1.107
Lower Limit		0.422	0.554
Upper Limit		1.919	2.244
Weeks to First Observed Tumor	86	95	95

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Adenoma, NOS, or Carcinoma, NOS (b)	13/47(28)	12/48(25)	15/49(31)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.904	1.107
Lower Limit		0.422	0.554
Upper Limit		1.919	2.244
Weeks to First Observed Tumor	86	95	95
Adrenal: Cortical Adenoma (b)	1/48(2)	3/50(6)	4/47(9)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.880	4.085
Lower Limit		0.241	0.425
Upper Limit		148.076	196.668
Weeks to First Observed Tumor	108	95	100
Adrenal: Cortical Adenoma or Carcinoma (b)	1/48(2)	3/50(6)	5/47(11)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.880	5.106
Lower Limit		0.241	0.602
Upper Limit		148.076	235.906
Weeks to First Observed Tumor	108	95	100

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Adrenal: Pheochromocytoma (b)	15/48(31)	7/50(14)	7/47(15)
P Values (c),(d)	P=0.031(N)	P=0.035(N)	P=0.049(N)
Relative Risk (Control) (e)		0.448	0.477
Lower Limit		0.170	0.181
Upper Limit		1.057	1.120
Weeks to First Observed Tumor	95	105	82
Thyroid: C-Cell Adenoma (b)	5/48(10)	7/47(15)	4/47(9)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.430	0.817
Lower Limit		0.421	0.172
Upper Limit		5.324	3.560
Weeks to First Observed Tumor	81	74	108
Thyroid: C-Cell Adenoma or Carcinoma (b)	6/48(13)	9/47(19)	6/47(13)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.532	1.021
Lower Limit		0.530	0.294
Upper Limit		4.826	3.548
Weeks to First Observed Tumor	81	74	90

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma (b)	0/50(0)	0/50(0)	4/50(8)
P Values (c),(d)	P=0.015	N.S.	N.S.
Relative Risk (Control) (e)		--	Infinite
Lower Limit		--	0.927
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	102
Preputial Gland: Carcinoma, NOS or Adenoma, NOS (b)	2/50(4)	2/50(4)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	1.500
Lower Limit		0.075	0.180
Upper Limit		13.326	17.329
Weeks to First Observed Tumor	72	87	108
Testis: Interstitial-Cell Tumor (b)	35/49(71)	48/50(96)	46/49(94)
P Values (c),(d)	P=0.001	P=0.001	P=0.003
Departure from Linear Trend (f)	P=0.021		
Relative Risk (Control) (e)		1.344	1.314
Lower Limit		1.113	1.074
Upper Limit		1.466	1.478
Weeks to First Observed Tumor	81	87	82

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Bisphenol A (a)

(Continued)

- (a) Dosed groups received doses of 1,000 or 2,000 ppm in feed.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
- (f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Bisphenol A (a)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Leukemia, NOS (b)	7/50(14)	13/50(26)	12/50(24)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.857	1.714
Lower Limit		0.756	0.682
Upper Limit		5.032	4.714
Weeks to First Observed Tumor	85	78	66
Liver: Neoplastic Nodule (b)	4/50(8)	6/49(12)	0/50(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.531	0.000
Lower Limit		0.387	0.000
Upper Limit		6.952	1.079
Weeks to First Observed Tumor	108	86	--
Pituitary: Adenoma, NOS (b)	25/48(52)	20/49(41)	25/50(50)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.784	0.960
Lower Limit		0.488	0.630
Upper Limit		1.255	1.469
Weeks to First Observed Tumor	85	101	87

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Adrenal: Cortical Adenoma (b)	12/50(24)	5/50(10)	4/50(8)
P Values (c),(d)	P=0.016(N)	N.S.	P=0.027(N)
Relative Risk (Control) (e)		0.417	0.333
Lower Limit		0.124	0.084
Upper Limit		1.167	1.014
Weeks to First Observed Tumor	85	97	98
Adrenal: Pheochromocytoma (b)	2/50(4)	4/50(8)	2/50(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.000	1.000
Lower Limit		0.301	0.075
Upper Limit		21.316	13.326
Weeks to First Observed Tumor	108	99	105
Thyroid: C-Cell Adenoma (b)	2/45(4)	5/46(11)	4/47(9)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.446	1.915
Lower Limit		0.425	0.290
Upper Limit		24.643	20.351
Weeks to First Observed Tumor	108	108	103

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: C-Cell Adenoma or Carcinoma (b)	4/45(9)	6/46(13)	5/47(11)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.467	1.197
Lower Limit		0.374	0.275
Upper Limit		6.632	5.674
Weeks to First Observed Tumor	108	108	103
Mammary Gland: Fibroadenoma (b)	8/50(16)	8/50(16)	5/50(10)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	0.625
Lower Limit		0.355	0.172
Upper Limit		2.815	2.011
Weeks to First Observed Tumor	90	99	103
Uterus: Endometrial Stromal Polyp (b)	15/48(31)	10/50(20)	6/50(12)
P Values (c),(d)	P=0.015(N)	N.S.	P=0.018(N)
Relative Risk (Control) (e)		0.640	0.384
Lower Limit		0.287	0.134
Upper Limit		1.367	0.951
Weeks to First Observed Tumor	62	98	66

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Bisphenol A (a)

(Continued)

- (a) Dosed groups received doses of 1,000 or 2,000 ppm in feed.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Throughout the bioassay, mean body weights of high-dose male mice and of low- and high-dose female mice were lower than those of the controls (Figure 3). No other compound-related clinical signs were observed. Food consumption among all groups of mice appeared to be similar; data were incomplete due to excessive spilling of feed and could not be precisely evaluated.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered bisphenol A in feed at the doses of this bioassay, and those of the controls, are shown by the Kaplan and Meier curves in Figure 4. The survival among all groups was comparable in either sex. Two control male mice and two high-dose female mice were accidentally killed and were censored from the statistical analysis of survival.

In male mice, 42/49 (86%) of the untreated control group, 37/50 (74%) of the low-dose group, and 38/50 (76%) of the high-dose group were alive at the end of the study at week 107. In females, 39/50 (78%) of the controls, 37/48 (77%) of the low-dose group, and 41/48 (85%) of the high-dose group were alive at the end of the study at week 107.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2.

Neoplasms appeared with approximately equal frequency in dosed and control mice, except for lymphomas or leukemias in males (control 2/49; low dose, 9/50; and high dose, 5/50). The hematopoietic neoplasms were mainly mixed, histiocytic, and lymphocytic lymphomas. Several mice had lymphocytic

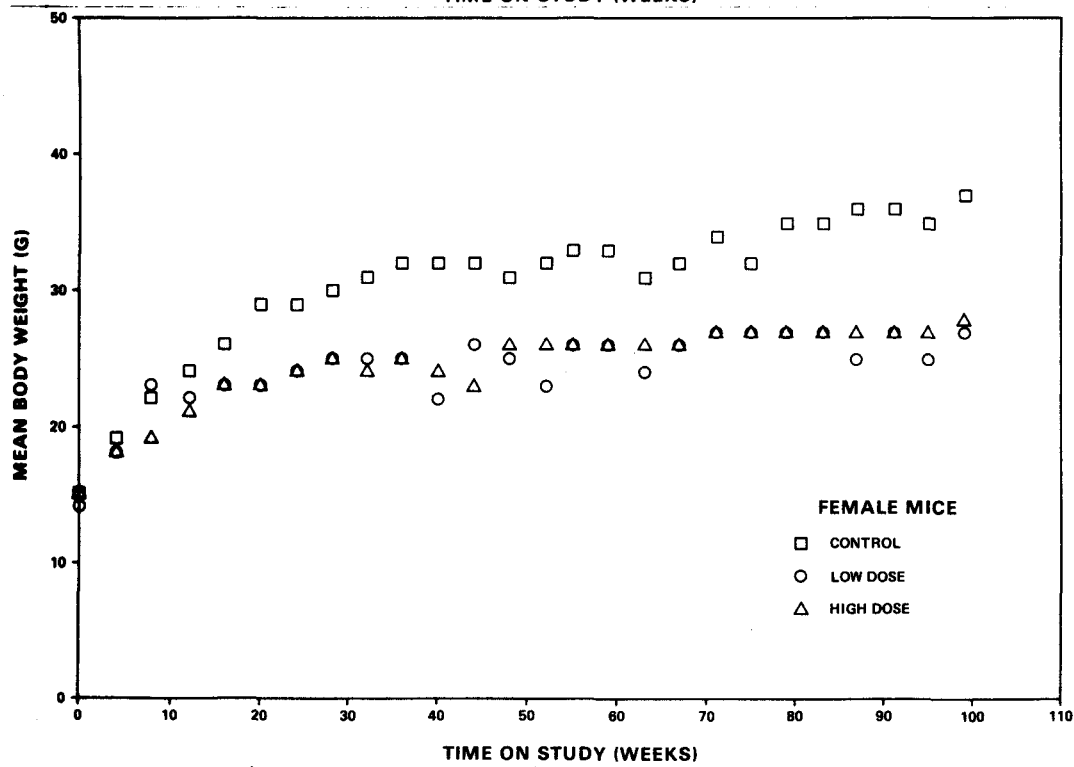
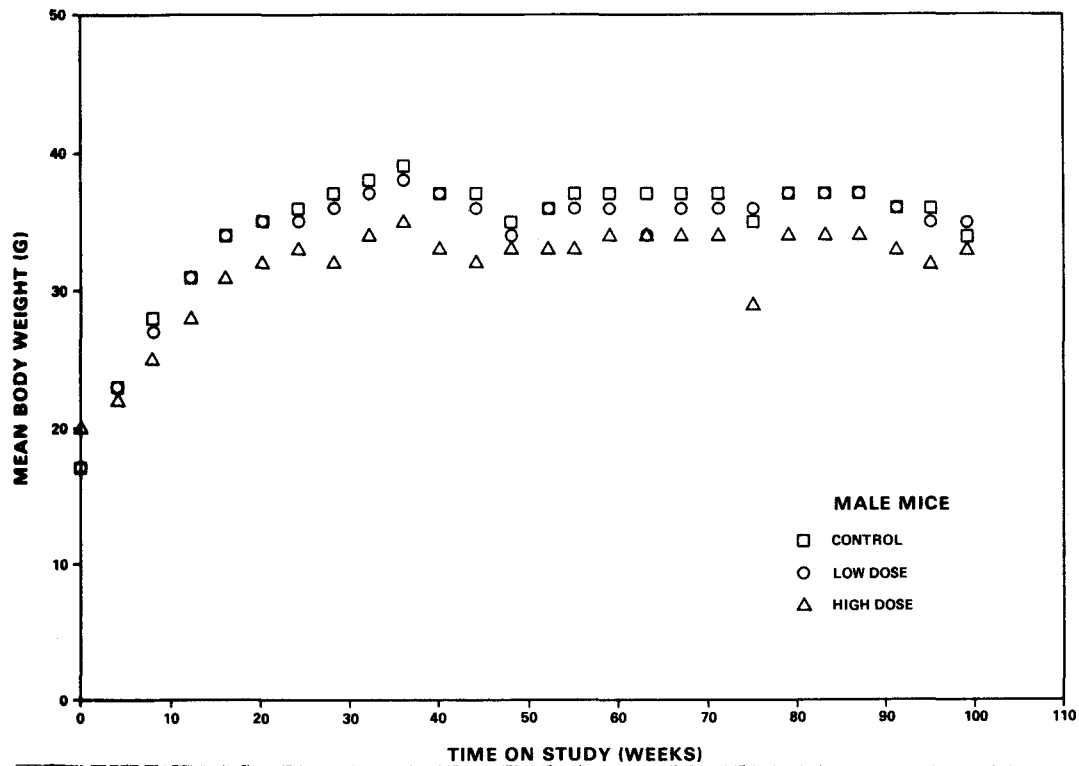


Figure 3. Growth Curves for Mice Fed Diets Containing Bisphenol A

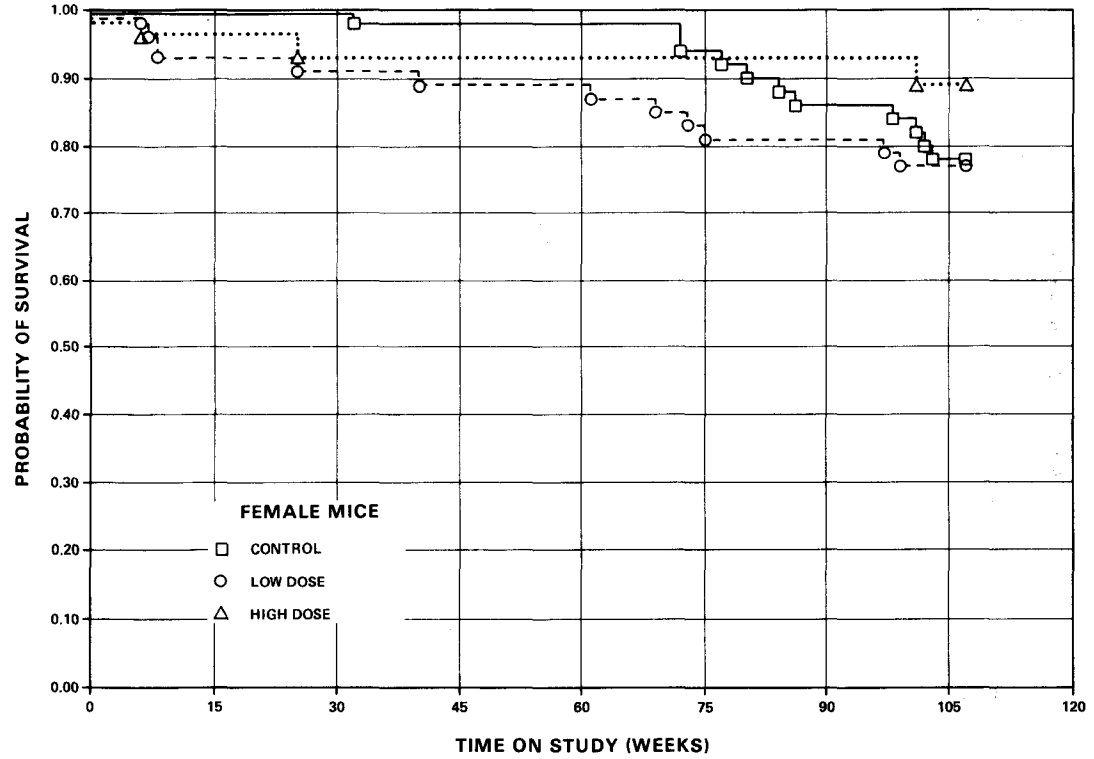
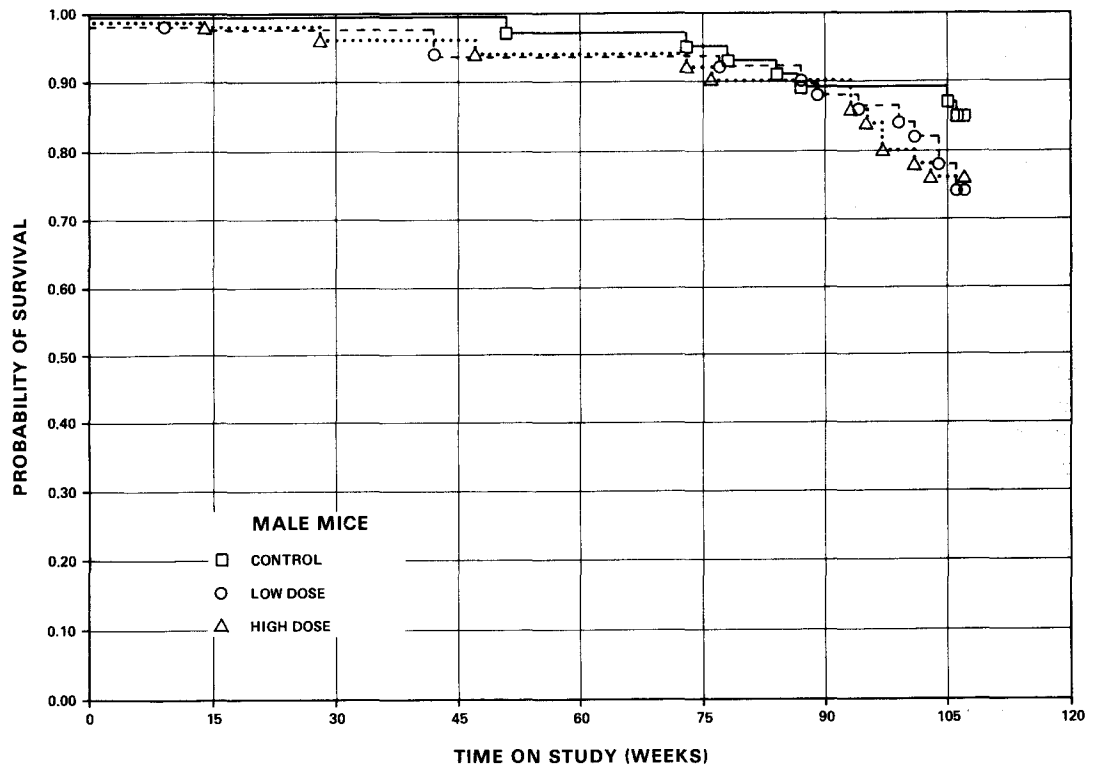


Figure 4. Survival Curves for Mice Fed Diets Containing Bisphenol A

or myelogenous leukemia. Overall, the hematopoietic tumors were typical of those arising spontaneously in aging mice. The increased incidence of tumors in the low- and high-dose males compared with controls was attributed to the variation of incidence that sometimes occurs with spontaneous tumors. In females, the incidence of tumors was not dose related, and fewer tumors were found in low- and high-dose females than in controls (13/50, 10/48, 8/48).

The degenerative, proliferative, and inflammatory changes encountered in control and dosed groups are commonly seen in aging mice; however, there was a high incidence of multinucleated hepatocellular giant cells present in the dosed male mice (control, 1/49, 2%; low dose, 41/49, 84%; high dose, 41/50, 82%). Although binucleate hepatocytes and hepatocytes with pleomorphic nuclei are also found frequently in aging mice, the hepatocytes in the dosed mice appeared to contain 6 to 20 small nuclei and thus appeared as giant cells and were considered as abnormal forms. The giant cells were found at an incidence that was dose related and were found most frequently in males.

D. Statistical Analyses of Results (Mice)

Tables 10 and 11 contain the statistical analyses of those primary tumors that occurred in at least two animals of one group and with an incidence of at least 5% in one or more groups. The survival in all groups was comparable in either sex.

Lymphomas or leukemias of the hematopoietic system in male mice were observed in increased proportion in the low-dose group compared with the other two groups (2/49, 9/50, 5/50). The Cochran-Armitage test for linear trend was not significant, but there was a departure from linear trend ($P=0.025$) due to the sharp increase of incidence in the low-dose group compared with the other two groups. The Fisher exact test between the low-dose group and the control group was significant ($P=0.028$), but this value of $P=0.028$ is above the value of $P=0.025$ required by the Bonferroni inequality criterion for an overall significance of $P=0.05$ when two dosed groups are compared with a common control group. No significant incidence was observed in the high-dose group. In female mice, this tumor was not observed in statistically significant proportions.

Chromophobe carcinomas of the pituitary in male mice were observed in increased proportions in the high-dose group (0/37, 0% in the controls; 0/36, 0% in the low-dose; and 3/42, 7% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ($P=0.016$). The Fisher exact tests were not significant. In female mice, this tumor was not observed in statistically significant proportions.

Two males in the control group, three males in the low-dose group, and three males in the high-dose group died before week 52 on study. The time adjusted analyses of the tumor incidences, eliminating these animals, resulted in no material change in the P values shown in the tables. Of the female mice, one control animal and five animals in each dosed group died prior to week 52. Eliminating these animals from the analysis of the incidences resulted in a value of $P=0.05$ in the trend of the new incidences (0/49, controls; 1/43, 2%, low dose; and 3/43, 7%, high dose) of female mice with hepatocellular adenomas or carcinomas of the liver. The Fisher exact tests remained nonsignificant. Life table analyses of the time to observation of tumors did not indicate any significant results.

The statistical conclusion was that there was no site at which an increase in tumor incidence could be associated unequivocally with the administration of the chemical. In each of the 95% confidence intervals for relative risk, the value of one or less than one is included: this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one indicating the theoretical possibility of tumor induction by bisphenol A, which could not be detected under the conditions of this test.

Table 10: Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing Bisphenol A (a)

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	5/48(10)	2/49(4)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.392	0.768
Lower Limit		0.039	0.162
Upper Limit		2.262	3.356
Weeks to First Observed Tumor	78	107	103
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	7/48(15)	2/49(4)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.280	0.549
Lower Limit		0.030	0.125
Upper Limit		1.380	2.013
Weeks to First Observed Tumor	78	107	103
Hematopoietic System: Malignant Lymphoma, Mixed Type (b)	2/49(4)	5/50(10)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.450	1.470
Lower Limit		0.424	0.176
Upper Limit		24.778	16.980
Weeks to First Observed Tumor	106	106	103

Table 10: Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
<hr/>			
Hematopoietic System:			
All Lymphomas (b)	2/49(4)	8/50(16)	3/50(6)
P Values (c),(d)	N.S.	P=0.049	N.S.
Departure from Linear Trend (f)	P=0.026		
Relative Risk (Control) (e)		3.920	1.470
Lower Limit		0.834	0.176
Upper Limit		36.399	16.980
Weeks to First Observed Tumor	106	77	103
<hr/>			
Hematopoietic System: Lymphomas or Leukemias (b)	2/49(4)	9/50(18)	5/50(10)
P Values (c),(d)	N.S.	P=0.028	N.S.
Departure from Linear Trend (f)	P=0.025		
Relative Risk (Control) (e)		4.410	2.450
Lower Limit		0.976	0.424
Upper Limit		40.254	24.778
Weeks to First Observed Tumor	106	77	95
<hr/>			
Liver: Hepatocellular Adenoma (b)	5/49(10)	5/49(10)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	0.588
Lower Limit		0.245	0.096
Upper Limit		4.076	2.851
Weeks to First Observed Tumor	107	107	107
<hr/>			

Table 10: Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	11/49(22)	9/49(18)	7/50(14)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.818	0.624
Lower Limit		0.330	0.223
Upper Limit		1.972	1.611
Weeks to First Observed Tumor	78	89	73
Liver: Hepatocellular Adenoma or Carcinoma (b)	16/49(33)	14/49(29)	10/50(20)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.875	0.613
Lower Limit		0.447	0.277
Upper Limit		1.694	1.287
Weeks to First Observed Tumor	78	89	73
Pituitary: Chromophobe Carcinoma (b)	0/37(0)	0/36(0)	3/42(7)
P Values (c),(d)	P=0.016	N.S.	N.S.
Relative Risk (Control) (e)		--	Infinite
Lower Limit		--	0.535
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	97

Table 10: Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing Bisphenol A (a)

(Continued)

- (a) Dosed groups received doses of 1,000 or 5,000 ppm in feed.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
- (f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 11. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Bisphenol A (a)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma, Mixed Type (b)	8/50(16)	3/48(6)	7/48(15)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.391	0.911
Lower Limit		0.070	0.305
Upper Limit		1.517	2.649
Weeks to First Observed Tumor	107	107	107
Hematopoietic System: Malignant Lymphoma, Histiocytic Type (b)	0/50(0)	3/48(6)	1/48(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		0.627	0.056
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	69	107
Hematopoietic System: All Lymphomas (b)	11/50(22)	8/48(17)	8/48(17)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.758	0.758
Lower Limit		0.289	0.289
Upper Limit		1.882	1.882
Weeks to First Observed Tumor	72	69	107

Table 11. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Lymphomas or Leukemias (b)	13/50(26)	10/48(21)	8/48(17)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.801	0.641
Lower Limit		0.348	0.253
Upper Limit		1.781	1.511
Weeks to First Observed Tumor	72	61	107
Liver: Hepatocellular Adenoma or Carcinoma (b)	0/50(0)	1/48(2)	3/48(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		0.056	0.627
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	107	107
Pituitary: Chromophobe Carcinoma (b)	2/44(5)	0/40(0)	0/40(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		3.695	3.695
Weeks to First Observed Tumor	98	--	--

Table 11. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Bisphenol A (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Chromophobe Carcinoma or Adenoma (b)	2/44(5)	0/40(0)	1/40(3)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.000	0.550
Lower Limit		0.000	0.010
Upper Limit		3.695	10.139
Weeks to First Observed Tumor	98	--	107

- (a) Dosed groups received doses of 5,000 or 10,000 ppm in feed.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

V. DISCUSSION

Mean body weights of rats of either sex and of high- and low-dose female mice and high-dose male mice were lower than those of the controls. Since feed consumption by dosed female rats was only 70%-80% that of the controls throughout most of the study, reduced mean body weight gain in these groups may have been due to reduced feed consumption. The compound-related weight gain depression in rats and mice indicates that the high doses used in this study approximated maximum tolerated dose levels.

Leukemias in male rats occurred at an incidence that showed a statistically significant positive association with the dose of bisphenol A. Although the incidence in high-dose male rats appeared to be statistically significant ($P=0.030$), it did not meet the Bonferroni inequality criterion of $P=0.025$ for comparing the dosed groups with a common control. The incidence of leukemias was also increased in female rats, but the observed increases were not statistically significant. Life table analyses, adjusted for intercurrent mortality, were also carried out for the leukemia data. It was found that, for male rats, neither the high-dose effect nor the dose-response trend was statistically significant ($P=0.141$ and $P=0.074$). The female rats likewise showed no significant effects. The increased incidence of leukemia in rats was therefore not considered to be convincing evidence of carcinogenicity in rats.

Interstitial-cell tumors in the testes in the low- and high-dose rats occurred at incidences significantly higher ($P=0.001$ and $P=0.003$), than those in the controls; however, since this type of lesion normally occurs at a high incidence in aging F344 rats (Goodman et al., 1979), the increased incidence is not clearly compound related.

In male mice, the combined incidence of leukemias and lymphomas appeared to be statistically significant ($P=0.028$) in the low-dose group, but did not meet the Bonferroni inequality criterion of $P=0.025$. In the high-dose group, the combined incidence of leukemias and lymphomas was increased (relative to controls) but was not statistically significant. Since the combined incidence of leukemias and lymphomas was not significant in the high-dose group

and did not meet the Bonferroni inequality criterion in the low-dose group, it was not considered convincing evidence of carcinogenicity in male mice.

Multinucleated giant hepatocytes observed in dosed male mice in sub-chronic studies were increased in dosed male mice in the chronic studies (control, 1/49; low-dose, 41/49; and high-dose 41/50); the incidence of hepatocellular carcinomas or adenomas was not any higher in dosed male mice than in the controls.

When the marginally significant increase of leukemias in male rats and the combined incidence of lymphomas and leukemias in male mice are considered along with the increase in leukemia incidence (not significant) in female rats, the evidence is suggestive of a carcinogenic effect on the hemato-poietic system.

VI. CONCLUSION

The marginally significant increase in leukemias in male rats, along with an increase (not statistically significant) in leukemias in female rats and a marginally significant increase in the combined incidence of lymphomas and leukemias in male mice, suggests that exposure to bisphenol A may be associated with increased cancers of the hematopoietic system. A statistically significant increase in interstitial-cell tumors of the testes in male rats was also suggestive of carcinogenesis, but was not considered to be convincing evidence of a compound-related effect because this lesion normally occurs at a high incidence in aging F344 rats.

Under the conditions of this bioassay, there was no convincing evidence that bisphenol A was carcinogenic for F344 rats or B6C3F1 mice of either sex.

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APPENDIX A

**Summary of the Incidence of
Neoplasms in Rats Fed Diets
Containing Bisphenol A**

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS
FED DIETS CONTAINING BISPHENOL A

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
PAPILLOMA, NOS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
PAPILLOMA, NOS	1 (2%)		
SQUAMOUS CELL CARCINOMA		1 (2%)	1 (2%)
BASAL-CELL TUMOR	1 (2%)		
BASAL-CELL CARCINOMA			1 (2%)
KERATOACANTHOMA	1 (2%)		
FIBROMA	2 (4%)	3 (6%)	1 (2%)
FIBROSARCOMA	1 (2%)		
LIPOMA	1 (2%)		
OSTEOSARCOMA		1 (2%)	1 (2%)
CHONDROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
NEOPLASM, NOS, MALIGNANT		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
C-CELL CARCINOMA, METASTATIC	1 (2%)		
FIBROSARCOMA, METASTATIC	1 (2%)		
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, NOS	13 (26%)	12 (24%)	23 (46%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
ANGIOSARCOMA	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN HEMANGIOSARCOMA	(50)	(50) 2 (4%)	(50)
DIGESTIVE SYSTEM			
#SALIVARY GLAND ADENOMA, NOS	(48)	(48) 1 (2%)	(49) 1 (2%)
#LIVER NEOPLASTIC NODULE HEPATOCELLULAR CARCINOMA C-CELL CARCINOMA, METASTATIC SARCOMA, NOS	(50) 4 (8%) 1 (2%)	(49) 6 (12%) 1 (2%)	(50) 1 (2%) 1 (2%) 1 (2%)
#PANCREAS SARCOMA, NOS	(49)	(50)	(50) 1 (2%)
#COLON ADENOCARCINOMA, NOS	(50) 1 (2%)	(50)	(48)
*RECTUM ADENOMA, NOS	(50) 1 (2%)	(50)	(50)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY CARCINOMA, NOS ADENOMA, NOS	(47) 13 (28%)	(48) 1 (2%) 12 (25%)	(49) 15 (31%)
#ADRENAL CORTICAL ADENOMA CORTICAL CARCINOMA PHEOCHROMOCYTOMA	(48) 1 (2%) 15 (31%)	(50) 3 (6%) 7 (14%)	(47) 4 (9%) 1 (2%) 7 (15%)
#THYROID C-CELL ADENOMA C-CELL CARCINOMA	(48) 5 (10%) 1 (2%)	(47) 7 (15%) 2 (4%)	(47) 4 (9%) 2 (4%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ISLETS ISLET-CELL ADENOMA	(49) 2 (4%)	(50) 2 (4%)	(50)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND FIBROADENOMA	(50)	(50)	(50) 4 (8%)
*PREPUTIAL GLAND CARCINOMA, NOS ADENOMA, NOS	(50) 1 (2%) 1 (2%)	(50) 2 (4%)	(50) 1 (2%) 2 (4%)
#TESTIS INTERSTITIAL-CELL TUMOR	(49) 35 (71%)	(50) 48 (96%)	(49) 46 (94%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*TUNICA VAGINALIS MESOTHELIOMA, NOS	(50) 1 (2%)	(50) 1 (2%)	(50) 1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS MESOTHELIOMA, NOS	(50)	(50)	(50) 1 (2%)
ADIPOSE TISSUE NEOPLASM, NOS, MALIGNANT		1	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	8	13	6
MORIBUND SACRIFICE	19	7	17
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	23	30	27
ANIMAL MISSING			
^a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	48	50	50
TOTAL PRIMARY TUMORS	104	116	120
TOTAL ANIMALS WITH BENIGN TUMORS	44	49	48
TOTAL BENIGN TUMORS	80	84	84
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	22	28
TOTAL MALIGNANT TUMORS	19	25	33
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	
TOTAL SECONDARY TUMORS	3	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	5	7	3
TOTAL UNCERTAIN TUMORS	5	7	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS
FED DIETS CONTAINING BISPHENOL A

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
PAPILLOMA, NOS	1 (2%)		
KERATOACANTHOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
NEOPLASM, NOS, MALIGNANT			1 (2%)
PAPILLOMA, NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)		
KERATOACANTHOMA	1 (2%)	1 (2%)	
FIBROMA		1 (2%)	
FIBROSARCOMA		1 (2%)	
FIBROADENOMA	1 (2%)		
OSTEOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
C-CELL CARCINOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, NOS	7 (14%)	13 (26%)	12 (24%)
#SPLEEN	(50)	(49)	(50)
FIBROMA			1 (2%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
ANGIOSARCOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND ADENOMA, NOS	(47) 1 (2%)	(50)	(49)
#LIVER NEOPLASTIC NODULE	(50) 4 (8%)	(49) 6 (12%)	(50)
#PANCREAS NEOPLASM, NOS, MALIGNANT	(50)	(48)	(49) 1 (2%)
URINARY SYSTEM			
#KIDNEY FIBROSARCOMA	(50)	(50)	(50) 1 (2%)
#URINARY BLADDER PAPILLOMA, NOS	(47)	(50) 1 (2%)	(49)
ENDOCRINE SYSTEM			
#PITUITARY ADENOMA, NOS	(48) 25 (52%)	(49) 20 (41%)	(50) 25 (50%)
#ADRENAL NEOPLASM, NOS, METASTATIC	(50)	(50)	(50) 1 (2%)
CORTICAL ADENOMA	12 (24%)	5 (10%)	4 (8%)
PHEOCHROMOCYTOMA	2 (4%)	4 (8%)	2 (4%)
GANGLIONEUROMA	1 (2%)		1 (2%)
#THYROID	(45)	(46)	(47)
C-CELL ADENOMA	2 (4%)	5 (11%)	4 (9%)
C-CELL CARCINOMA	2 (4%)	1 (2%)	1 (2%)
#PANCREATIC ISLETS ISLET-CELL ADENOMA	(50) 1 (2%)	(48)	(49) 1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND ADENOMA, NOS	(50)	(50) 1 (2%)	(50)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROADENOMA	8 (16%)	8 (16%)	5 (10%)
*CLITORAL GLAND CARCINOMA, NOS	(50)	(50)	(50) 1 (2%)
#UTERUS	(48)	(50)	(50)
SARCOMA, NOS	1 (2%)		
ENDOMETRIAL STROMAL POLYP	15 (31%)	10 (20%)	6 (12%)
FIBROADENOMA	1 (2%)	1 (2%)	
#OVARY/OVIDUCT	(48)	(50)	(50)
FIBROSARCOMA	1 (2%)		
#OVARY	(48)	(49)	(50)
GRANULOSA-CELL TUMOR	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYELID	(50)	(50)	(50)
PAPILLOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	5	3	5
MORIBUND SACRIFICE	10	12	8
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	35	35	37
ANIMAL MISSING			
^a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	45	38
TOTAL PRIMARY TUMORS	91	82	67
TOTAL ANIMALS WITH BENIGN TUMORS	39	39	33
TOTAL BENIGN TUMORS	72	59	49
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	15	17
TOTAL MALIGNANT TUMORS	14	16	18
TOTAL ANIMALS WITH SECONDARY TUMORS#			2
TOTAL SECONDARY TUMORS			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	5	7	
TOTAL UNCERTAIN TUMORS	5	7	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

APPENDIX B

**Summary of the Incidence of
Neoplasms in Mice Fed Diets
Containing Bisphenol A**

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE
FED DIETS CONTAINING BISPHENOL A

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
FIBROSARCOMA	1 (2%)		
RHABDOMYOSARCOMA	1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(50)
RHABDOMYOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(48)	(49)	(50)
CARCINOMA, NOS, UNC PRIM OR META		1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST	3 (6%)	3 (6%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	2 (4%)	4 (8%)
SEBACEOUS ADENOCARCINOMA, METAST			1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	2 (4%)	2 (4%)
LEUKEMIA, NOS			2 (4%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	
#MESENTERIC L. NODE	(31)	(34)	(28)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (3%)	2 (6%)	
#PEYER'S PATCH	(47)	(50)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*EXTERNAL EAR HEMANGIOMA	(49) 1 (2%)	(50)	(50)
#SPLEEN HEMANGIOMA HEMANGIOSARCOMA	(48)	(48)	(48) 1 (2%) 1 (2%)
#LIVER HEMANGIOSARCOMA	(49)	(49)	(50) 1 (2%)
DIGESTIVE SYSTEM			
#LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	(49) 5 (10%) 11 (22%)	(49) 5 (10%) 9 (18%)	(50) 3 (6%) 7 (14%)
#DUODENUM ADENOMATOUS POLYP, NOS	(47)	(50) 1 (2%)	(49)
#JEJUNUM ADENOCARCINOMA, NOS	(47)	(50) 1 (2%)	(49)
URINARY SYSTEM			
#KIDNEY TUBULAR-CELL ADENOMA	(49) 1 (2%)	(49)	(50)
ENDOCRINE SYSTEM			
#PITUITARY CHROMOPHOBE CARCINOMA	(37)	(36)	(42) 3 (7%)
#ADRENAL CORTICAL ADENOMA SARCOMA, NOS	(46) 1 (2%)	(49) 1 (2%)	(48) 2 (4%) 1 (2%)
REPRODUCTIVE SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND PAPILLARY ADENOMA	(49) 1 (2%)	(50) 2 (4%)	(50) 1 (2%)
*ZYMBA'S GLAND SEBACEOUS ADENOCARCINOMA	(49)	(50)	(50) 1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS HEPATOCELLULAR CARCINOMA, METAST	(49)	(50)	(50) 1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH [ⓐ]	2	5	10
MORIBUND SACRIFICE	5	8	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	2		
TERMINAL SACRIFICE	40	37	38
ANIMAL MISSING	1		
[ⓐ] INCLUDES AUTOLYZED ANIMALS			
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	23	28	24
TOTAL PRIMARY TUMORS	32	31	30
TOTAL ANIMALS WITH BENIGN TUMORS	10	9	7
TOTAL BENIGN TUMORS	11	9	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	20	19
TOTAL MALIGNANT TUMORS	21	21	23
TOTAL ANIMALS WITH SECONDARY TUMORS#	4	3	2
TOTAL SECONDARY TUMORS	4	3	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC		1	
TOTAL UNCERTAIN TUMORS		1	
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE
FED DIETS CONTAINING BISPHENOL A

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		2	2
ANIMALS NECROPSIED	50	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(48)	(48)
BASAL-CELL TUMOR		1 (2%)	
*SUBCUT TISSUE	(50)	(48)	(48)
FIBROSARCOMA	2 (4%)		1 (2%)
RHABDOMYOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(46)	(48)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	2 (4%)
ADENOCARCINOMA/SQUAMOUS METAPLASIA, MET			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(48)	(48)
MALIGNANT LYMPHOMA, NOS	2 (4%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		3 (6%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	7 (14%)	2 (4%)	5 (10%)
LYMPHOCYTIC LEUKEMIA	1 (2%)	1 (2%)	
GRANULOCYTIC LEUKEMIA	1 (2%)	1 (2%)	
#ABDOMINAL LYMPH NODE	(38)	(37)	(38)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (3%)		
#PANCREATIC L.NODE	(38)	(37)	(38)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
#LUMBAR LYMPH NODE	(38)	(37)	(38)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (3%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE ADENOCARCINOMA/SQUAMOUS METAPLASIA, MET	(38)	(37)	(38) 1 (3%)
#PEYER'S PATCH MALIGNANT LYMPHOMA, MIXED TYPE	(49)	(47)	(48) 1 (2%)
#JEJUNUM MALIGNANT LYMPHOMA, MIXED TYPE	(49)	(47) 1 (2%)	(48) 1 (2%)
CIRCULATORY SYSTEM			
*SITE UNKNOWN HEMANGIOMA	(50) 1 (2%)	(48)	(48)
#SPLEEN HEMANGIOMA HEMANGIOSARCOMA	(50) 1 (2%)	(46) 1 (2%)	(46)
#UTERUS HEMANGIOSARCOMA	(50)	(47)	(47) 1 (2%)
#OVARY HEMANGIOMA	(43)	(44)	(46) 1 (2%)
DIGESTIVE SYSTEM			
#LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	(50)	(48) 1 (2%)	(48) 1 (2%) 2 (4%)
#STOMACH ADENOMATOUS POLYP, NOS	(50)	(47) 2 (4%)	(48)
#FORESTOMACH SQUAMOUS CELL PAPILLOMA	(50)	(47) 1 (2%)	(48)
URINARY SYSTEM			
#URINARY BLADDER ADENOCARCINOMA/SQUAMOUS METAPLASIA, MET	(49)	(45)	(45) 1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(40)	(40)
CHROMOPHOBE ADENOMA			1 (3%)
CHROMOPHOBE CARCINOMA	2 (5%)		
#THYROID	(39)	(29)	(36)
FOLLICULAR-CELL ADENOMA	1 (3%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(48)	(48)
ADENOCARCINOMA, NOS		1 (2%)	
ADENOC/SQUAMOUS METAPLASIA			1 (2%)
#UTERUS	(50)	(47)	(47)
LEIOMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP		1 (2%)	1 (2%)
#OVARY	(43)	(44)	(46)
PAPILLARY ADENOMA			1 (2%)
GRANULOSA-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(48)	(48)
PAPILLARY ADENOMA	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(48)	(48)
LIPOMA	1 (2%)		
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	5	10	3
MORIBUND SACRIFICE	6	1	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			2
TERMINAL SACRIFICE	39	37	41
ANIMAL MISSING		2	2
^a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	21	17	19
TOTAL PRIMARY TUMORS	24	19	23
TOTAL ANIMALS WITH BENIGN TUMORS	4	7	6
TOTAL BENIGN TUMORS	4	7	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	11	15
TOTAL MALIGNANT TUMORS	20	12	16
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			3
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

APPENDIX C

**Summary of the Incidence of
Nonneoplastic Lesions in Rats
Fed Diets Containing
Bisphenol A**

TABLE C1.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
FED DIETS CONTAINING BISPENOL A**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC			2 (4%)
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)		1 (2%)
METAPLASIA, OSSEOUS			1 (2%)
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
#LUNG	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)	3 (6%)	1 (2%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
PNEUMONIA, CHRONIC MURINE	3 (6%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC DIFFUSE	14 (28%)	12 (24%)	12 (24%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(49)	(48)
ATROPHY, DIFFUSE	1 (2%)		2 (4%)
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS	2 (4%)	4 (8%)	4 (8%)
CONGESTION, ACUTE	1 (2%)		
INFARCT, NOS		1 (2%)	
HEMOSIDEROSIS	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	2 (4%)
HEMATOPOIESIS	6 (12%)	2 (4%)	1 (2%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE	(49)	(50)	(50)
CYST, NOS	1 (2%)	1 (2%)	5 (10%)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)		
HYPERPLASIA, LYMPHOID			1 (2%)
CIRCULATORY SYSTEM			
#LUNG	(50)	(50)	(50)
THROMBUS, MURAL	1 (2%)		
#HEART	(50)	(49)	(50)
THROMBUS, MURAL	3 (6%)	1 (2%)	2 (4%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
FIBROSIS, FOCAL	43 (86%)	40 (82%)	36 (72%)
#AURICULAR APPENDAGE	(50)	(49)	(50)
THROMBUS, MURAL			1 (2%)
*BLOOD VESSEL	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#ADRENAL	(48)	(50)	(47)
THROMBOSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
CONGESTION, NOS	1 (2%)	3 (6%)	5 (10%)
CONGESTION, ACUTE	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	6 (12%)	2 (4%)	1 (2%)
INFLAMMATION, FOCAL GRANULOMATOUS	1 (2%)		
FIBROSIS			1 (2%)
METAMORPHOSIS FATTY	5 (10%)	2 (4%)	4 (8%)
BASOPHILIC CYTO CHANGE	10 (20%)	6 (12%)	3 (6%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	
EOSINOPHILIC CYTO CHANGE	7 (14%)	2 (4%)	2 (4%)
CLEAR-CELL CHANGE	1 (2%)	2 (4%)	1 (2%)
#BILE DUCT	(50)	(49)	(50)
INFLAMMATION, CHRONIC	7 (14%)	1 (2%)	5 (10%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	18 (36%)	11 (22%)	5 (10%)
#PANCREAS	(49)	(50)	(50)
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)		
FIBROSIS, FOCAL		1 (2%)	1 (2%)
FIBROSIS, DIFFUSE	4 (8%)	5 (10%)	7 (14%)
LIPOIDOSIS	1 (2%)		
#PANCREATIC DUCT	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#STOMACH	(50)	(49)	(49)
MINERALIZATION	1 (2%)		
ULCER, ACUTE	1 (2%)		
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
#LARGE INTESTINE	(50)	(50)	(48)
PARASITISM		1 (2%)	
#COLON	(50)	(50)	(48)
PARASITISM	4 (8%)	1 (2%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
NEPHROPATHY	43 (86%)	34 (68%)	37 (74%)
GLOMERULOSCLEROSIS, NOS	5 (10%)		4 (8%)
INFARCT, HEALED		1 (2%)	
#KIDNEY/GLOMERULUS	(50)	(50)	(50)
BACTERIAL SEPTICEMIA	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
MINERALIZATION	1 (2%)	3 (6%)	
HEMOSIDEROSIS	33 (66%)	36 (72%)	42 (84%)
#URINARY BLADDER	(47)	(48)	(46)
CALCULUS, NOS	1 (2%)		2 (4%)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(48)	(49)
HEMORRHAGE, CHRONIC		2 (4%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	6 (13%)	2 (4%)	
#ADRENAL	(48)	(50)	(47)
CYST, NOS		1 (2%)	
HEMORRHAGE, CHRONIC			1 (2%)
INFARCT, NOS			1 (2%)
ANGIECTASIS	13 (27%)	18 (36%)	14 (30%)
#ADRENAL CORTEX	(48)	(50)	(47)
HYPERPLASIA, NODULAR	6 (13%)	4 (8%)	3 (6%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	
#THYROID	(48)	(47)	(47)
EPIDERMAL INCLUSION CYST		1 (2%)	
HYPERPLASIA, C-CELL	5 (10%)	3 (6%)	7 (15%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)	3 (6%)	3 (6%)
#PROSTATE	(44)	(45)	(42)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION ACUTE AND CHRONIC	6 (14%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
CALCULUS, NOS	1 (2%)		
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
ATROPHY, DIFFUSE			1 (2%)
#TESTIS	(49)	(50)	(49)
MINERALIZATION	13 (27%)	9 (18%)	6 (12%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
GRANULOMA, NOS	1 (2%)		
ATROPHY, NOS			1 (2%)
ATROPHY, DIFFUSE	25 (51%)	5 (10%)	11 (22%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(48)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFARCT, FOCAL	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE	2 (4%)	2 (4%)	5 (10%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
TAIL			
INFLAMMATION, ACUTE	1		
INFLAMMATION, CHRONIC DIFFUSE			1
HYPERKERATOSIS	1		
ADIPOSE TISSUE			
INFLAMMATION, ACUTE DIFFUSE	1		
INFLAMMATION, CHRONIC DIFFUSE		1	1
SPECIAL MORPHOLOGY SUMMARY			
NONE			
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
FED DIETS CONTAINING BISPENOL A

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(50)	(50)	(50)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)
#LUNG	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	2 (4%)
CONGESTION, ACUTE	2 (4%)		
PNEUMONIA, CHRONIC MURINE			1 (2%)
INFLAMMATION, CHRONIC DIFFUSE	13 (26%)	5 (10%)	8 (16%)
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(49)	(50)
CONGESTION, NOS	1 (2%)		2 (4%)
HEMOSIDEROSIS	14 (28%)	5 (10%)	2 (4%)
HYPERPLASIA, RETICULUM CELL	1 (2%)	1 (2%)	
HEMATOPOIESIS	1 (2%)	1 (2%)	1 (2%)
#LYMPH NODE	(50)	(50)	(49)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HEMOSIDEROSIS	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
#SALIVARY GLAND	(47)	(50)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(50)
THROMBUS, MURAL	1 (2%)	1 (2%)	
FIBROSIS, FOCAL	25 (51%)	35 (70%)	29 (58%)
#AURICULAR APPENDAGE	(49)	(50)	(50)
THROMBUS, MURAL			1 (2%)
*PULMONARY ARTERY	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
#UTERUS	(48)	(50)	(50)
THROMBUS, FIBRIN			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
CONGESTION, NOS		2 (4%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL	28 (56%)	19 (39%)	17 (34%)
INFLAMMATION, FOCAL GRANULOMATOUS	1 (2%)	1 (2%)	
NECROSIS, FOCAL	1 (2%)		
METAMORPHOSIS FATTY	5 (10%)	2 (4%)	2 (4%)
BASOPHILIC CYTO CHANGE	16 (32%)	12 (24%)	9 (18%)
FOCAL CELLULAR CHANGE			2 (4%)
EOSINOPHILIC CYTO CHANGE	1 (2%)	2 (4%)	1 (2%)
CLEAR-CELL CHANGE	2 (4%)		
HYPERTROPHY, DIFFUSE		1 (2%)	
#BILE DUCT	(50)	(49)	(50)
INFLAMMATION, CHRONIC	1 (2%)	5 (10%)	6 (12%)
HYPERPLASIA, NOS	2 (4%)	5 (10%)	9 (18%)
#PANCREAS	(50)	(48)	(49)
FIBROSIS, DIFFUSE	4 (8%)	2 (4%)	2 (4%)
#STOMACH	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
#LARGE INTESTINE	(49)	(49)	(47)
PARASITISM			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#COLON	(49)	(49)	(47)
ULCER, ACUTE		1 (2%)	
PARASITISM	1 (2%)	1 (2%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION			1 (2%)
CYST, NOS			1 (2%)
CONGESTION, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
NEPHROPATHY	28 (56%)	11 (22%)	5 (10%)
GLOMERULOSCLEROSIS, NOS	2 (4%)		1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
MINERALIZATION	1 (2%)	1 (2%)	
NECROSIS, CORTICAL			1 (2%)
HEMOSIDEROSIS	47 (94%)	40 (80%)	42 (84%)
#KIDNEY/PELVIS	(50)	(50)	(50)
MINERALIZATION	2 (4%)	1 (2%)	1 (2%)
#URINARY BLADDER	(47)	(50)	(49)
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(49)	(50)
CYST, NOS	9 (19%)	3 (6%)	3 (6%)
HYPERPLASIA, NOS	2 (4%)	2 (4%)	3 (6%)
#ADRENAL	(50)	(50)	(50)
CYST, NOS			1 (2%)
NECROSIS, FOCAL		1 (2%)	
ANGIECTASIS	21 (42%)	33 (66%)	27 (54%)
#ADRENAL CORTEX	(50)	(50)	(50)
NECROSIS, DIFFUSE		1 (2%)	
HYPERPLASIA, NODULAR	11 (22%)	13 (26%)	7 (14%)
ANGIECTASIS		1 (2%)	
#THYROID	(45)	(46)	(47)
HYPERPLASIA, C-CELL	10 (22%)	8 (17%)	7 (15%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	7 (14%)	9 (18%)	7 (14%)
HYPERPLASIA, NOS		1 (2%)	
#UTERUS	(48)	(50)	(50)
HEMORRHAGE	1 (2%)		
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
FIBROSIS	1 (2%)		1 (2%)
FIBROSIS, FOCAL	1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(50)	(50)
HYPERPLASIA, CYSTIC	8 (17%)	6 (12%)	9 (18%)
#OVARY	(48)	(49)	(50)
CYST, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(49)
HYDROCEPHALUS, NOS	1 (2%)		
INFARCT, FOCAL	1 (2%)	1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE		2 (4%)	4 (8%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
MINERALIZATION			1 (2%)
*EYE/CONJUNCTIVA	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MESENTERY INFLAMMATION ACUTE AND CHRONIC	(50) 1 (2%)	(50)	(50)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE INFLAMMATION, ACUTE DIFFUSE			1
INFLAMMATION, ACUTE/CHRONIC		1	
INFLAMMATION, CHRONIC DIFFUSE	2		1
SPECIAL MORPHOLOGY SUMMARY			
NONE			
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

APPENDIX D

**Summary of the Incidence of
Nonneoplastic Lesions in Mice
Fed Diets Containing
Bisphenol A**

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
FED DIETS CONTAINING BISPENOL A

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
CYST, NOS			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
ATROPHY, NOS		1 (2%)	
ALOPECIA		1 (2%)	
HYPERKERATOSIS		1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(48)	(49)	(50)
CONGESTION, NOS			1 (2%)
HEMORRHAGE	1 (2%)		
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
LEUKEMOID REACTION			1 (2%)
#BONE MARROW	(47)	(49)	(49)
HYPERPLASIA, HEMATOPOIETIC	2 (4%)		1 (2%)
#SPLEEN	(48)	(48)	(48)
HEMATOPOIESIS	2 (4%)	1 (2%)	2 (4%)
#SPLENIC FOLLICLES	(48)	(48)	(48)
HYPERPLASIA, NOS	1 (2%)	2 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC L.NODE INFLAMMATION, GRANULOMATOUS	(31)	(34) 1 (3%)	(28)
#MESENTERIC L. NODE HEMORRHAGE	(31) 5 (16%)	(34) 10 (29%)	(28) 4 (14%)
INFLAMMATION, GRANULOMATOUS		1 (3%)	
HYPERPLASIA, NOS	1 (3%)	1 (3%)	
HYPERPLASIA, LYMPHOID	1 (3%)		
#LIVER HEMATOPOIESIS	(49)	(49)	(50) 2 (4%)
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE LYMPHANGIECTASIS	(31) 1 (3%)	(34)	(28) 1 (4%)
#LUNG PERIVASCULITIS	(48) 1 (2%)	(49)	(50)
#MYOCARDIUM FIBROSIS, FOCAL	(48) 1 (2%)	(49)	(50)
#SALIVARY GLAND PERIVASCULITIS	(48) 1 (2%)	(48)	(46)
#PERIPANCREATIC TISSU LYMPHANGIECTASIS	(48)	(49)	(48) 1 (2%)
#KIDNEY PERIVASCULITIS	(49) 1 (2%)	(49)	(50)
DIGESTIVE SYSTEM			
#SALIVARY GLAND INFLAMMATION, ACUTE/CHRONIC	(48)	(48)	(46) 1 (2%)
#LIVER CYST, NOS	(49) 1 (2%)	(49)	(50) 1 (2%)
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
NECROSIS, FOCAL		1 (2%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFARCT, NOS			1 (2%)
HEMOSIDEROSIS	1 (2%)		
BASOPHILIC CYTO CHANGE			4 (8%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	1 (2%)
CLEAR-CELL CHANGE			1 (2%)
MULTINUCLEATE GIANT-CELL	1 (2%)	41 (84%)	41 (82%)
CYTOLOGIC DEGENERATION			1 (2%)
HYPERTROPHY, FOCAL			1 (2%)
ANGIECTASIS	1 (2%)		
#LIVER/CENTRIOLOBULAR DEGENERATION, NOS	(49) 1 (2%)	(49)	(50)
#LIVER/PERIportal INFLAMMATION, CHRONIC	(49) 1 (2%)	(49)	(50)
#PANCREAS	(48)	(49)	(48)
CYSTIC DUCTS	1 (2%)		
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOUS	1 (2%)		
CYTOLOGIC DEGENERATION	1 (2%)		
#PANCREATIC ACINUS	(48)	(49)	(48)
ATROPHY, FOCAL	3 (6%)	1 (2%)	
#STOMACH	(49)	(49)	(49)
MINERALIZATION		1 (2%)	
#PEYER'S PATCH	(47)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)		2 (4%)
HYPERPLASIA, FOCAL	1 (2%)		
#COLON	(46)	(48)	(50)
PARASITISM		2 (4%)	
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(50)
MINERALIZATION	1 (2%)	1 (2%)	2 (4%)
HYDRONEPHROSIS		1 (2%)	1 (2%)
PYELONEPHRITIS, NOS		1 (2%)	
INFLAMMATION, FOCAL	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, INTERSTITIAL	5 (10%)		2 (4%)
ABSCISS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
NEPHROPATHY	3 (6%)	2 (4%)	2 (4%)
NEPHROSIS, NOS		1 (2%)	
METAPLASIA, OSSEOUS			1 (2%)
#KIDNEY/CORTEX	(49)	(49)	(50)
CYST, NOS	2 (4%)		
ABSCISS, NOS			2 (4%)
#KIDNEY/GLOMERULUS	(49)	(49)	(50)
AMYLOIDOSIS			1 (2%)
#KIDNEY/TUBULE	(49)	(49)	(50)
BASOPHILIC CYTO CHANGE	1 (2%)		
ATROPHY, FOCAL	1 (2%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(37)	(36)	(42)
CYST, NOS	1 (3%)		
#ADRENAL	(46)	(49)	(48)
ACCESSORY STRUCTURE	1 (2%)		
#ADRENAL CORTEX	(46)	(49)	(48)
HYPERTROPHY, FOCAL	4 (9%)		
#THYROID	(32)	(43)	(35)
HYPERPLASIA, FOLLICULAR-CELL	1 (3%)		
REPRODUCTIVE SYSTEM			
*PENIS	(49)	(50)	(50)
HYPERKERATOSIS		1 (2%)	
*PREPUCE	(49)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#PROSTATE	(44)	(45)	(48)
INFLAMMATION, ACUTE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#TESTIS	(48)	(48)	(49)
MINERALIZATION		3 (6%)	
CYTOMEGALY			1 (2%)
ATROPHY, NOS		1 (2%)	
*EPIDIDYMIS	(49)	(50)	(50)
GRANULOMA, SPERMATIC			2 (4%)
NERVOUS SYSTEM			
#BRAIN	(49)	(49)	(50)
MINERALIZATION	18 (37%)	16 (33%)	28 (56%)
HEMORRHAGE			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*STERNUM	(49)	(50)	(50)
FIBROUS DYSPLASIA			1 (2%)
BODY CAVITIES			
*MESENTERY	(49)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING			2 (4%)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	7	1	
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL MISSING/NO NECROPSY AUTO/NECROPSY/HISTO PERF	1	1	1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
FED DIETS CONTAINING BISPHENOL A

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		2	2
ANIMALS NECROPSIED	50	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(48)	(48)
EDEMA, NOS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
ALOPECIA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(46)	(48)
HEMORRHAGE	1 (2%)		
FIBROSIS, FOCAL	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(46)	(47)
FIBROUS DYSPLASIA		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
#SPLEEN	(50)	(46)	(46)
INFLAMMATION, FOCAL GRANULOMATOUS			1 (2%)
HEMATOPOIESIS	2 (4%)	3 (7%)	2 (4%)
#SPLENIC FOLLICLES	(50)	(46)	(46)
HYPERPLASIA, NOS	4 (8%)		2 (4%)
#MANDIBULAR L. NODE	(38)	(37)	(38)
HYPERPLASIA, LYMPHOID	1 (3%)		
#MESENTERIC L. NODE	(38)	(37)	(38)
HEMORRHAGE	1 (3%)		
INFLAMMATION, GRANULOMATOUS			1 (3%)
INFLAMMATION, PYOGRANULOMATOUS		1 (3%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS HYPERPLASIA, LYMPHOID	1 (3%)		1 (3%)
#LUNG HEMATOPOIESIS	(50)	(46) 1 (2%)	(48)
#LIVER HEMATOPOIESIS	(50) 2 (4%)	(48)	(48)
#THYROID LYMPHOCYTOSIS	(39) 1 (3%)	(29)	(36)
CIRCULATORY SYSTEM			
#LUNG PERIVASCULITIS	(50) 1 (2%)	(46)	(48) 1 (2%)
#HEART PERIVASCULITIS	(50)	(48)	(48) 1 (2%)
*BLOOD VESSEL EMBOLUS, SEPTIC	(50) 1 (2%)	(48)	(48)
#UTERUS PERIVASCULITIS	(50)	(47)	(47) 1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND INFLAMMATION, CHRONIC DIFFUSE	(49) 1 (2%)	(44)	(45)
#LIVER CONGESTION, NOS INFLAMMATION, CHRONIC FOCAL NECROSIS, FOCAL INFARCT, NOS HEMOSIDEROSIS MITOTIC ALTERATION BASOPHILIC CYTO CHANGE CLEAR-CELL CHANGE MULTINUCLEATE GIANT-CELL CYTOLOGIC DEGENERATION HYPERPLASIA, FOCAL	(50) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	(48) 1 (2%) 1 (2%) 1 (2%)	(48) 1 (2%) 1 (2%) 2 (4%) 1 (2%) 2 (4%) 1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER/PERIORTAL INFLAMMATION, CHRONIC	(50) 5 (10%)	(48) 1 (2%)	(48) 1 (2%)
#PANCREAS CYSTIC DUCTS	(50)	(46) 1 (2%)	(47)
#PANCREATIC ACINUS ATROPHY, FOCAL	(50) 2 (4%)	(46) 1 (2%)	(47)
#STOMACH INFLAMMATION, CHRONIC FOCAL	(50)	(47)	(48) 1 (2%)
#PEYER'S PATCH HYPERPLASIA, NOS HYPERPLASIA, FOCAL	(49)	(47) 1 (2%)	(48) 1 (2%)
URINARY SYSTEM			
#KIDNEY MINERALIZATION HYDRONEPHROSIS INFLAMMATION, INTERSTITIAL NEPHROPATHY AMYLOIDOSIS	(50) 1 (2%) 1 (2%) 4 (8%) 1 (2%) 1 (2%)	(48) 1 (2%)	(48) 1 (2%) 1 (2%) 1 (2%)
#KIDNEY/TUBULE NECROSIS, FOCAL	(50)	(48) 1 (2%)	(48)
#KIDNEY/PELVIS INFLAMMATION, SUPPURATIVE	(50) 1 (2%)	(48)	(48)
#URINARY BLADDER HYPERPLASIA, EPITHELIAL	(49)	(45)	(45) 1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY CYST, NOS HYPERPLASIA, CHROMOPHOBE-CELL ANGIECTASIS	(44) 1 (2%) 2 (5%) 1 (2%)	(40) 1 (3%)	(40) 1 (3%)
#PITUITARY/BASOPHIL HYPERPLASIA, FOCAL	(44)	(40) 1 (3%)	(40)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL ACCESSORY STRUCTURE	(48)	(46) 1 (2%)	(48)
#ADRENAL CORTEX HYPERTROPHY, FOCAL	(48) 1 (2%)	(46)	(48)
#THYROID INFLAMMATION, CHRONIC FOCAL HYPERPLASIA, FOLLICULAR-CELL	(39) 1 (3%) 1 (3%)	(29)	(36) 1 (3%)
#PARATHYROID CYST, NOS	(13)	(11) 1 (9%)	(14)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND DILATATION/DUCTS CYST, NOS CYSTIC DUCTS	(50) 1 (2%) 1 (2%) 1 (2%)	(48)	(48)
#UTERUS MINERALIZATION HYDROMETRA INFLAMMATION, ACUTE SUPPURATIVE FIBROSIS, FOCAL	(50) 2 (4%) 1 (2%)	(47) 1 (2%)	(47) 1 (2%)
#CERVIX UTERI INFLAMMATION, SUPPURATIVE	(50) 1 (2%)	(47)	(47)
#UTERUS/ENDOMETRIUM HYPERPLASIA, CYSTIC	(50) 35 (70%)	(47) 23 (49%)	(47) 21 (45%)
#UTERUS/MYOMETRIUM HEMATOMA, NOS	(50)	(47) 1 (2%)	(47)
#OVARY CYST, NOS HEMORRHAGE HEMORRHAGIC CYST	(43) 10 (23%) 1 (2%)	(44) 3 (7%) 1 (2%)	(46) 5 (11%)
#MESOVARIVM INFLAMMATION, ACUTE	(43) 1 (2%)	(44)	(46)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(49)	(46)	(47)
MINERALIZATION	7 (14%)	11 (24%)	5 (11%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(48)	(48)
OSTEOSCLEROSIS			1 (2%)
FIBROUS DYSPLASIA	33 (66%)	33 (69%)	38 (79%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(48)	(48)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
*MESENTERY	(50)	(48)	(48)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	3	3
ANIMAL MISSING/NO NECROPSY		2	2
AUTO/NECROPSY/HISTO PERF		1	
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

APPENDIX E

**Analysis of Bisphenol A
Midwest Research Institute**

Appendix E

Analysis of Bisphenol A
Midwest Research Institute

A. ELEMENTAL ANALYSIS

Element	C	H
Theory	78.92	7.07
Determined	78.74 78.76	7.24 7.30

B. MELTING POINT

<u>Determined</u>	<u>Literature Values</u>
m.p. 155.4°-157.6°C (Du Pont 900 DTA) 154°-157°C (visual, capillary)	155.2°C (Negoro and Saeki, 1956)

C. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel 60F254
Amount Spotted: 100 and 300 µg

Ref. Standard: Phenol
Visualization: Ultraviolet, 254 nm,
and potassium ferricyanide-ferric
chloride

System 1: Ethyl acetate, 100%

R_f: 0.78
R_{st}: 1.00

System 2: Chloroform:methanol (95:5)

R_f: 0.78 (slight trace, not
visualized with ultraviolet), 0.63
(slight trace, not visualized with
ultraviolet), 0.48 (trace), 0.34
(major), 0.11 (slight trace, not
visualized with ultraviolet)
R_{st}: 1.66, 1.34, 0.72, 0.72, 0.23

D. VAPOR-PHASE CHROMATOGRAPHY

System 1

Instrument: Tracor MT-220
Column: 3% Dexsil 400 on 100/120 Supelcoport, 1.8 m x 2mm I.D., glass
Detector: Flame ionization
Oven Temperature Program: 100^o-230^oC, 10^o/min
Results: Major peak and four impurities

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Retention Time Relative to Bisphenol A</u>	<u>Area (Relative to Bisphenol A)</u>
Minor	4.4	0.37	0.09
Minor	8.7	0.72 }	
Minor	9.0	0.75 }	0.10
Minor	10.7	0.89	1.80
Major	12.0	1.00	100

System 2

Instrument: Tracor MT-220
Column: 3% OV-1, 1.8 m x 2mm I.D.
Oven Temperature Program: 100^o-235^oC, 10^o/min
Results: Major peak and five impurities

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Retention Time Relative to Bisphenol A</u>	<u>Area (Relative to Bisphenol A)</u>
Minor	7.4	0.73	< 0.1
Minor	7.6	0.75	< 0.1
Minor	8.0	0.79	< 0.1
Minor	8.6	0.85	< 0.1
Minor	9.0	0.89	1.4
Major	10.1	1.00	100

E. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12
Cell: 1.0% KBr pellet
Results: See Figure 5

Consistent with literature
spectrum (Sadtler Standard Spectra)

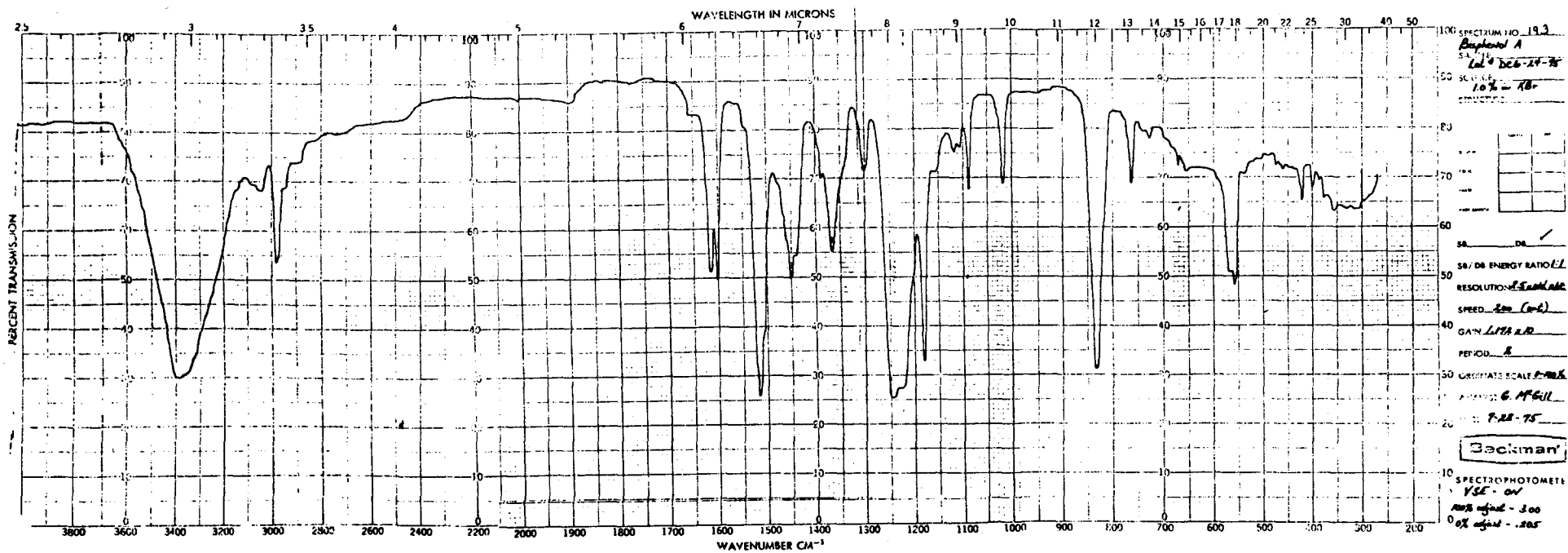


Figure 5. Infrared Absorption Spectrum of Bisphenol A

2. Ultraviolet/Visible

Literature Values

Instrument: Cary 118

<u>λ max (nm)</u>	<u>$\epsilon \times 10^{-3}$</u>	<u>λ max (nm)</u>	<u>$\epsilon \times 10^{-3}$</u>
227	15.4+0.2 (δ)	226.5	15.0
278.5	3.72+0.02 (δ)	279	3.63
285 shoulder	3.24+0.02 (δ)		

Solvent: 95% Ethanol

Solvent: Methanol (Sadtler
Standard Spectra)

No absorbance between 350 and 800 nm (visible range) at mg/ml.

3. Nuclear Magnetic Resonance

Instrument: Varian HA-100
Solvent: Deuterated methanol
with internal tetramethyl-
silane
Assignments (See Figure 6)

Literature (Smith, 1964)
(c) 6.88 ppm, (d) 7.18 ppm
Solvent: Acetone
(c) 6.79 ppm, (d) 7.07 ppm
Solvent: Dimethylformamide
 $J_{cd} = 8.9$ Hz

- (a) s, δ 1.51 ppm
- (b) s, δ 4.91 ppm
- (c) d, δ 6.59 ppm ($J_{cd} = 9$ Hz)
- (d) d, δ 6.96 ppm
- (e) 2.06 ppm (impurity)

Integration Ratios:

- (a) 5.94
- (b) 2.49
- (c) 3.96
- (d) 4.10
- (e) 0.07

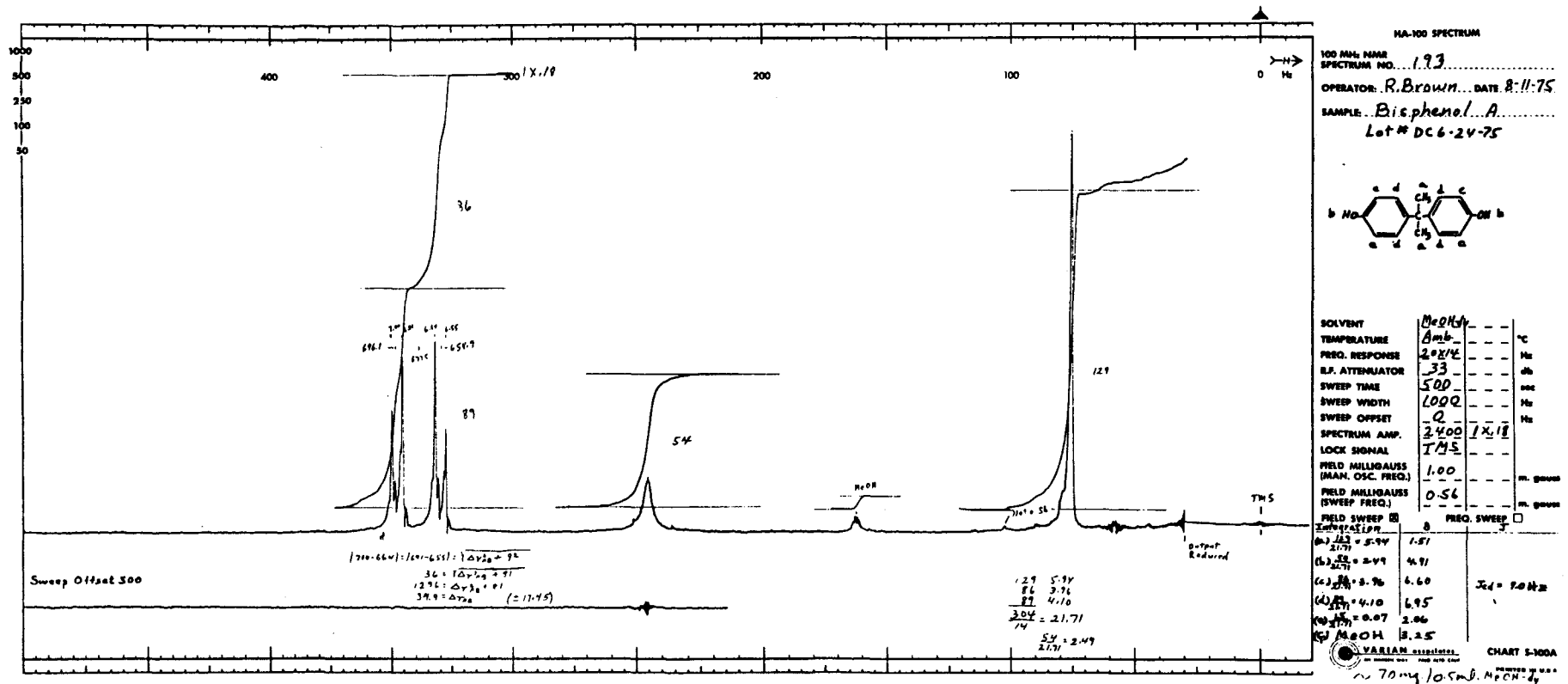


Figure 6. Nuclear Magnetic Resonance Spectrum of Bisphenol A

APPENDIX F

**Analysis of Formulated Diets for
Stability of Bisphenol A
Midwest Research Institute**

Appendix F

Midwest Research Institute

Analysis of Formulated Diets for Stability of Bisphenol A

A. METHOD

Bisphenol A (20 g) and Wayne Lab-Blox[®] Rodent Feed (180 g) were mixed for 30 minutes. Samples of the mix were then removed and stored for 2 weeks at -20°, 5°, 25°, and 45°C, respectively. Samples of the chemical/feed mixtures were triturated with methanol using a Polytron mixer, and the subsequent mixture was centrifuged. The supernatant solutions were analyzed by vapor-phase chromatography under the following conditions:

Instrument: Tracor MT-220

Column: 3% OV-225 on Chromosorb W (HP), 80/100, 4 mm x 1.8 m glass,
silanized

Detection: Flame ionization

Oven Temperature: 230°C, isothermal

B. RESULTS

<u>Sample No.</u>	<u>Temperature (°C)</u>	<u>Percent Compound in feed</u>	<u>Average Percent</u>
1	45	9.9	9.7+1.0
2	45	9.4	
3	25	9.7	9.4+1.0
4	25	9.1	
5	5	9.5	9.7+1.0
6	5	10.0	
7	-20	10.1	10.1+1.0
8	-20	10.2	

No significant difference was found between the samples stored at the various temperatures as determined by vapor-phase chromatography.

C. CONCLUSION

Bisphenol A mixed with feed is stable for 2 weeks at temperatures up to 45°C.

APPENDIX G

**Analysis of Formulated Diets for
Concentrations of Bisphenol A
Litton Bionetics, Inc.**

Appendix G

Analysis of Formulated Diets for Concentrations of Bisphenol A Litton Bionetics, Inc.

Five grams of formulated diet were weighed into a Falcon tube. The samples were extracted with 50 ml methanol by mixing for 10 minutes in a mechanical shaker followed by centrifugation at 1,350 rpm for 10 minutes. The extracts were diluted with methanol so that the final concentration was approximately 100 ppm.

Analysis of the extract was performed by Waters Model 204 High-Pressure Liquid Chromatograph with a UV detector at 280nm. The column was stainless steel 25 cm x 4.6 mm I.D., packed with μ Bondapack/C18. The solvent system was methanol at a flow rate of 1.5 ml/min.

Theoretical Concentration (ppm)	Number of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
1,000	4	978	11.7	872 - 1,057
2,000	13	2,061	9.4	1,780 - 2,575
5,000	10	4,954	11.2	4,436 - 5,484
10,000	3	9,950	7.2	9,466 - 10,770

APPENDIX H

**Feed and Compound Consumption in Rats
Fed Diets Containing Bisphenol A
in the Chronic Study**

Table H1. Feed and Compound Consumption in Male Rats Fed Diets Containing Bisphenol A in the Chronic Study

Week	Control		Low				High			
	Grams Feed/Day(a)	Body Weight (grams)	Grams Feed/Day(a)	Body Weight (grams)	Low/Control (b)	Dose/Day (c)	Grams Feed/Day(a)	Body Weight (grams)	High/Control (b)	Dose/Day (c)
4	23.3	207	21.6	195	0.9	111	23.8	194	1.0	246
8	29.0	268	28.0	255	1.0	110	24.9	250	0.9	199
12	28.8	304	29.4	289	1.0	102	26.9	276	0.9	195
16	28.0	324	22.3	304	0.8	73	21.6	290	0.8	149
20	24.1	334	22.5	318	0.9	71	22.0	301	0.9	146
24	24.1	360	26.5	340	1.1	78	25.3	323	1.1	157
28	23.5	367	21.8	347	0.9	63	20.7	329	0.9	126
32	31.9	385	25.7	360	0.8	71	24.7	342	0.8	144
36	31.4	390	26.2	362	0.8	72	23.9	351	0.8	136
40	29.0	397	25.3	373	0.9	68	25.1	360	0.9	140
44	27.5	406	26.1	382	0.9	68	21.7	367	0.8	118
48	28.1	408	28.4	388	1.0	73	24.1	371	0.9	130
52	28.2	413	28.6	391	1.0	73	26.3	373	0.9	141
56	29.6	414	26.8	398	0.9	67	27.0	377	0.9	143
59	26.0	420	26.4	396	1.0	67	25.4	385	1.0	132
63	30.3	423	27.8	394	0.9	70	26.4	384	0.9	138
67	27.0	413	21.8	395	0.8	55	20.9	378	0.8	110
71	29.1	429	24.5	401	0.8	61	26.1	383	0.9	136
75	25.8	423	27.4	402	1.1	68	26.7	381	1.0	140
79	32.6	418	28.4	395	0.9	72	27.4	368	0.8	149
83	31.6	416	28.2	399	0.9	71	26.0	379	0.8	137
87	31.0	415	25.8	401	0.8	64	27.7	383	0.9	145
91	30.5	406	25.9	403	0.8	64	27.4	379	0.9	145
95	26.2	381	30.2	399	1.2	76	29.7	382	1.1	155
99	32.7	384	34.1	400	1.0	85	24.3	359	0.7	135
Mean	28.4	380	26.4	363	0.9	74	25.0	347	0.9	148
SD(d)	2.8		2.9		0.1	14	2.3		0.1	28
CV(e)	9.9		11.0		11.1	18.9	9.2		11.1	18.9

(a) Grams of feed per animal per day.

(b) Grams of feed per day for the dosed group divided by the same value for the controls.

(c) Mg of compound consumed per day per kg of body weight.

(d) Standard Deviation.

(e) Coefficient of Variation (Standard deviation/mean x 100).

Table H2. Feed and Compound Consumption in Female Rats Fed Diets Containing Bisphenol A in the Chronic Study

Week	Control		Low				High			
	Grams Feed/Day(a)	Body Weight (grams)	Grams Feed/Day(a)	Body Weight (grams)	Low/Control (b)	Dose/Day (c)	Grams Feed/Day(a)	Body Weight (grams)	High/Control (b)	Dose/Day (c)
FEMALES										
4	16.9	148	15.2	139	0.9	109	15.6	134	0.9	232
8	19.6	175	17.1	161	0.9	106	16.9	160	0.9	211
12	18.9	187	15.4	173	0.8	89	13.9	169	0.7	164
16	16.7	196	13.3	182	0.8	73	11.7	177	0.7	132
20	19.0	209	15.1	190	0.8	79	13.1	183	0.7	143
24	15.3	216	13.5	202	0.9	67	13.0	196	0.8	132
28	13.7	220	11.7	206	0.9	57	10.9	200	0.8	109
32	17.2	226	14.3	210	0.8	68	12.5	205	0.7	122
36	19.7	231	14.9	212	0.8	70	12.9	204	0.7	127
40	17.7	238	13.2	215	0.7	61	12.6	209	0.7	121
44	19.1	243	15.4	225	0.8	68	13.4	218	0.7	123
48	21.9	249	17.5	230	0.8	76	13.7	217	0.6	126
52	20.0	253	17.7	229	0.9	77	14.0	219	0.7	128
56	18.7	255	17.2	227	0.9	76	13.5	219	0.7	124
59	16.9	264	15.4	233	0.9	66	13.3	224	0.8	118
63	23.1	273	17.1	237	0.7	72	14.0	225	0.6	124
67	21.3	278	14.1	241	0.7	58	11.1	228	0.5	97
71	18.6	286	16.0	247	0.9	65	14.3	233	0.8	122
75	20.4	289	16.4	251	0.8	65	14.2	237	0.7	119
79	21.4	297	17.1	243	0.8	70	15.8	232	0.7	136
83	21.7	300	18.0	258	0.8	70	15.2	240	0.7	126
87	24.9	229	19.6	264	0.8	74	16.8	239	0.7	141
91	22.4	242	19.9	270	0.9	74	17.2	248	0.8	139
95	23.7	244	20.7	270	0.9	77	17.8	249	0.8	143
99	21.4	236	22.3	278	1.0	80	14.7	248	0.7	118
Mean	19.6	239	16.3	224	0.8	74	14.1	213	0.7	135
SD(d)	2.7		2.5		0.1	12	1.8		0.1	29
CV(e)	13.8		15.3		12.5	16.2	12.8		14.3	21.5

(a) Grams of feed per animal per day.

(b) Grams of feed per day for the dosed group divided by the same value for the controls.

(c) Mg of compound consumed per day per kg of body weight.

(d) Standard Deviation.

(e) Coefficient of Variation (Standard deviation/mean x 100).

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