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BIOASSAY OF

PHENOL

FOR POSSIBLE CARCINOGENICITY

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Carcinogenesis Testing Program
National Cancer Institute/National Toxicology Program

FOREWORD

This report presents the results of the bioassay of phenol conducted for the Carcinogenesis Testing Program, National Cancer Institute (NCI)/National Toxicology Program (NTP). This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. A positive result demonstrates that the test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS

This bioassay of phenol was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the NCI Carcinogenesis Testing Program.

The persons responsible for selecting the protocols used in this bioassay were Drs. O. G. Fitzhugh (1,2), J. F. Robens (1,3), and M. B. Powers (4,5). The principal investigators were Drs. M. B. Powers (4,5) and R. W. Voelker (4). Ms. K. J. Petrovics (4) was responsible for data management, and Mr. G. Najarian (4,1) was the supervisor of animal care. Histopathologic examinations were performed by Drs. D. A. Banas (4), R. W. Voelker (4), and S. V. Machotka (4). The pathology report and slides were reviewed by the NCI Pathology Working Group as described in Ward et al. (1978).

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (6). Statistical analyses were performed by Dr. J. R. Joiner (1) and Ms. S. Vatsan (1), using methods selected for the bioassay program by Dr. J. J. Gart (7).

Chemicals used in this bioassay were analyzed at Midwest Research Institute (8), and dose solutions containing the test chemical were analyzed at Hazleton Laboratories by Dr. R. P. Stanovick (4), Mr. E. Missaghi (4), and Ms. J. Rogers (4). The results of these analyses were reviewed by Dr. S. S. Olin (1).

This report was prepared at Tracor Jitco in collaboration with Hazleton Laboratories and NCI. Those responsible for the report at Tracor Jitco (1) were Dr. L. A. Campbell, Acting Director of the Bioassay Program; Dr. S. S. Olin, Associate Director; Dr. R. L. Schueler, pathologist; Dr. D. J. Beach, reports manager; Dr. A. C. Jacobs, bioscience writer; and Dr. W. D. Theriault and Ms. M. W. Glasser, technical editors.

The following scientists at NCI (9) were responsible for evaluating the bioassay, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Michael P. Dieter, Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Charles K. Grieshaber, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. C. W. Jameson, Dr. Y. Jack Lee, Dr. Harry Mahar, Dr. James McCoy, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Marcelina B. Powers, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

Phenol has been ranked 38th in production among U. S. chemicals with production of 2.38 billion pounds in 1978. A bioassay of phenol to test for possible carcinogenicity was conducted by providing this substance in drinking water to F344 rats and B6C3F1 mice. Groups of 50 rats and 50 mice of each sex were given drinking water containing 2,500 or 5,000 ppm phenol for 103 weeks. As matched controls, groups of 50 rats and 50 mice of each sex received tap water.

A dose-related depression in mean body weight gain occurred in rats and mice of each sex. Rats and mice given water containing phenol drank less than did the corresponding controls. A dose-related decrease in water consumption was observed for mice.

An increased incidence of leukemia or lymphomas was detected in male rats and may have been associated with the administration of phenol. Although the incidence of these tumors in the low-dose group was significantly higher than that in controls, the incidence in the high-dose group was not. Thus an association with administration of phenol was not established.

Under the conditions of this bioassay, phenol was not carcinogenic for either male or female F344 rats or male and female B6C3F1 mice.

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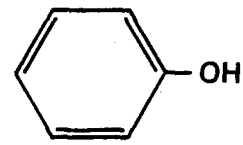
I. INTRODUCTION



PHENOL

Phenol (CAS 108-95-2; NCI C50124) ranked 38th in production among U. S. Chemicals in 1978 (Chemical & Engineering News, 1979) with annual production of 2.38 billion pounds (United States International Trade Commission, 1978). Approximately 90% of the phenol produced is used in the manufacture of phenolic (phenol formaldehyde) resins, caprolactam, bisphenol A, alkyl phenols, and adipic acid (NIOSH, 1976). The remainder of the phenol is used to produce an assortment of end products, including salicylic acid, phenacetin, dyes, metal cleaners, disinfectants, antiseptics, photographic chemicals, wood preservatives (pentachlorophenol), paints, paint and varnish removers, and agricultural chemicals (2,4-D and parathion) (Noller, 1965, NIOSH, 1976).

In 1865, Lister established the use of 5% to 10% aqueous phenol as an antiseptic (Gleason et al., 1969); today phenol is used as a disinfectant on medical instruments (AMA Department of Drugs, 1977) and is occasionally used therapeutically as a chemical cauterizer (Baker and Gordon, 1971; DuPont et al., 1972) as well as to relieve severe chronic pain (Mark et al., 1962). In dentistry, liquified phenol (80% phenol in water) has been used as an analgesic for sensitive dentine, and 5% solutions of phenol have been used to devitalize deciduous tooth pulp (Blacow, 1972). Some over-the-counter products such as antiseptics, lip balms, throat lozenges, poison ivy lotions, and mouthwashes contain varying concentrations (0.1%-1.0%) of phenol as an antipruritic, anaesthetic, or antibacterial agent (Rosenthal, 1972; Harvey, 1975; AMA Department of Drugs, 1977; Physicians' Desk Reference, 1978).

Phenol has also been measured in the smoke of 19 different commercial brands of cigarettes in amounts varying from 9 to 108 μg per cigarette (Spears, 1963).

Phenol may be formed by the metabolism of salicylic acid (Bakke, 1969; and Fishbeck et al., 1975). Benzene is also metabolized to phenol, and urinary phenol levels are used as an index of benzene exposure (Van Haaften and Sie, 1965; and Docter and Zielhuis, 1967).

Acute oral and acute dermal toxicities of phenol to laboratory animals are summarized in Table 1. Rats (unspecified strain and sex) exposed to phenol vapor at concentrations of 100 to 200 mg/m^3 for 53 days showed no toxic signs and no gross or microscopic lesions (Deichmann et al., 1944). Exposure to phenol vapors (900 mg/m^3 for 8 hours) induced ocular and nasal irritation, slight loss of coordination, tremors, and prostration in rats (Flickinger, 1976). The recommended 8-hour, time-weighted average for exposure of chemical plant workers to phenol vapors is 19 mg/m^3 or 5 ppm (ACGIH, 1978; OSHA, 1979).

Phenol has been reported to be mutagenic (without metabolic activation) in Escherichia coli B/sd-4 (Demerec et al., 1951) but not mutagenic (with or without metabolic activation) in six mutant strains of Salmonella typhimurium (Cotruvo et al., 1970).

Salaman and Glendenning (1957), Boutwell and Bosch (1959), Wynder and Hoffmann (1961), and Van Duuren et al. (1968) have shown that phenol in acetone or benzene promotes skin cancer in mice pretreated with 7,12-dimethylbenz(a)anthracene (DMBA) or 3,4-benzo(a)pyrene (BaP).

Phenol was assigned for testing by the NCI Carcinogenesis Testing Program because of its large annual production, significant industrial and consumer exposure, and tumor-promoting effects identified in previous studies.

Table 1. Acute Toxicities of Phenol

Sex/Strain/Species	LD_{50}	Reference
ORAL		
Male white mice (unspecified strain)	300 mg/kg	von Oettingen and Sharpless (1946)
Albino rats	550 mg/kg	Deichmann and Oesper (1940)
Wistar rats	530 mg/kg (2, 5, or 10% aqueous solutions)	
	340 mg/kg (20% aqueous solutions)	Deichmann and Witherup (1944)
Male albino rats (unspecified strain)	650 mg/kg	Flickinger (1976)
DERMAL		
Rabbits	1,400 mg/kg	Vernot et al. (1977)
Alderley Park rats	0.625 ml (undiluted)/kg	Conning and Hayes (1970)

II. MATERIALS AND METHODS

A. Chemical

Phenol was obtained in three batches: U.S.P. grade Lots No. A4X and B4A from Eastman Kodak Company, Rochester, N. Y., were used for all subchronic studies and for the chronic study of mice from week 0 to week 24; and reagent grade Lot No. 79380 from Textile Chemical Company, Reading, Pa., was used for the chronic studies of mice from week 25 to week 103 and for all of the chronic studies of rats. Purity and identity analyses were performed at Midwest Research Institute, Kansas City, Missouri (Appendixes E, F, and G). For all batches, the melting point and elemental analyses were in close agreement with the literature (Dictionary of Organic Compounds, 1965; and Merck, 1968) and with theoretical values. The infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with those in Sadtler Standard Spectra. Lot No. 79380 contained 98.47% phenol using the U.S.P. titration (U. S. Pharmacopeia, 1975) method. A single component in Lot No. 79380 was found by vapor-phase chromatography and thin-layer chromatography. In Lot No. B4A, two impurities (1.36% relative area) were detected by vapor-phase chromatography, and a trace impurity was detected at the origin by thin-layer chromatography. In Lot No. A4X, one homogeneous component was indicated by vapor-phase chromatography and an impurity at the origin by thin-layer chromatography.

All batches were stored at room temperature in their original containers, Lots A4X and B4A in dark-brown glass bottles and Lot No. 79380 in a pasteboard drum.

B. Dosage Preparation and Analysis

The aqueous test solutions of phenol were prepared by completely dissolving a weighed amount of phenol in a measured volume of tap water and then diluting the solution to the desired final volume calculated to achieve the proper concentrations.

Selected samples of the test solutions were analyzed by gas chromatography. The mean concentration of eight samples containing a theoretical level of 5,000 ppm was 5,237 (±509 ppm) (Appendix H).

C. Animals

F344 rats and B6C3F1 mice 3 to 4 weeks of age were obtained from the NCI Frederick Cancer Research Center (Frederick, Maryland). Following a 2-week isolation and observation period, animals were assigned to dosed or control groups so that the mean animal weights for each group of the same sex and species were approximately the same.

D. Animal Maintenance

The rats and mice were housed in solid-bottom polycarbonate cages (Maryland Plastic, Federalsburg, Md.) covered with stainless steel wire mesh cage lids and nonwoven, spun-bonded Filtek fiber filter bonnets (Lab Products, Garfield, N. J.). Rats were housed three per cage and mice were housed five per cage. All cages were changed twice per week and were furnished with heat-treated hardwood chip bedding (Sani-chips®, P. J. Murphy, Moonachie, N. J.). Diets consisting of Wayne® Lab Blox Chow Meal (Allied Mills, Chicago, Ill.) were provided ad libitum, as well as dosed water for test animals and tap water for controls. Cages and water bottles were changed twice weekly and feed hoppers were changed once a week.

Animal rooms were maintained at 21° to 23°C, and the relative humidity was 40% to 50%. A single-pass system filtered incoming air through 2-inch-thick disposable fiberglass filters at a rate that allowed 12 changes of room air per hour. Fluorescent lighting was provided on a 12-hour-per-day cycle. Rats and mice were housed in separate rooms, and control animals were housed in the same room as the respective dosed animals.

For the first 18 weeks of the chronic study, rats were housed in the same room as rats used in the following studies:

(CAS 108-60-1) bis(2-chloro-1-methylethyl)ether (Gavage Study)
(CAS 120-61-6) dimethyl terephthalate (Feed Study)
(CAS 119-53-9) benzoin (Feed study)

For the first 18 weeks of the chronic study, mice were housed in the same room as mice on the following studies:

(CAS 108-60-1) bis(2-chloro-1-methylethyl)ether (Gavage Study)
(CAS 120-61-6) dimethyl terephthalate (Feed Study)
(CAS 119-53-9) benzoin (Feed study)

Beginning with week 19, the rats were housed alone in one room and the mice were housed alone in another room.

E. Subchronic Studies

Subchronic studies were conducted to determine the concentrations of phenol to be used in the subsequent 2-year study. Groups of 10 rats and 10 mice of each sex were provided with tap water containing 100, 300, 1,000, 3,000, or 10,000 ppm phenol for 13 weeks. Control groups consisting of 10 males and 10 females of each species received tap water. Body weights, appearance, behavior, and food and water consumption were recorded weekly. After 13 weeks, all rats and mice were killed by intraperitoneal injections of sodium pentobarbital (Diabutal®; Diamond Laboratories, Inc., Des Moines, Iowa).

Representative tissues were examined microscopically, as described in the section on chronic studies. The doses administered, the survival of animals in each dosed group at the end of the study, and the mean body weights of dosed groups at week 13 are shown in Tables 2 and 3.

Rats

Mean body weight gains for rats receiving 10,000 ppm phenol were depressed (16% for males and 26% for females). Mean body weight gains for all other treated groups were comparable with those of the controls. Survival was 100% for all groups.

No tissue or organ changes attributable to the administration of the test material were detected at necropsy. No histomorphologic alterations attributable to compound administration were observed.

Because the rats rejected water and had decreased mean weight gains at 10,000 ppm in the subchronic studies, low and high doses for the chronic

Table 2. Dose, Survival, and Mean Body Weights of Rats Administered Phenol in Drinking Water in the 90-Day Subchronic Study

Dose(a,b)	Survival(c)	Mean Body Weight (grams) Initial	Final	Gain	Weight Change Relative to Controls(d) (Percent)
MALE					
0(e)	10/10	109	325	216	
100	10/10	109	322	213	-1.4
300	10/10	109	323	214	-0.9
1,000	10/10	109	323	214	-0.9
3,000	10/10	108	313	205	-4.0
10,000	10/10	107	288	181	-16.0
FEMALE					
0(e)	10/10	91	184(f)	93	
100	10/10	92	185(f)	93	0
300	10/10	91	185(f)	94	+1.0
1,000	10/10	92	183(f)	91	-2.0
3,000	10/10	92	181(f)	89	-4.0
10,000	10/10	90	159(f)	69	-26.0

(a) ppm phenol in drinking water.
(b) Feed consumption among all treated groups of males and females was comparable with the controls, but water consumption among males or females treated with 10,000 ppm was 50% or 67%, respectively, that of the controls.
(c) Number surviving/number per group.
(d) Weight Change Relative to Controls =

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

(e) Controls received drinking water without phenol.
(f) Weight at 12 weeks.

Table 3. Dose, Survival, and Mean Body Weights of Mice Administered Phenol in Drinking Water in the 90-Day Subchronic Study

Dose(a,b)	Survival(c)	Mean Body Weights (grams)			Weight Change Relative to Controls(d) (Percent)
		Initial	Final	Gain	
MALE					
0(e)	10/10	21	26	5	
100	10/10	22	29	7	+40
300	10/10	22	28	6	+20
1,000	10/10	22	29	7	+40
3,000	10/10	22	27	5	0
10,000	10/10	22	23	1	-80
FEMALE					
0(e)	10/10	18	21	3	
100	10/10	17	22	5	+67
300	10/10	18	22	4	+33
1,000	10/10	18	23	5	+67
3,000	10/10	17	23	6	+100
10,000	10/10	18	20	2	-33

(a) ppm phenol in drinking water.
(b) Feed consumption among all treated groups of males and females was comparable with the controls, but water consumption among males or females treated with 3,000 or 10,000 ppm was 60% and 20%, respectively, that of the controls.
(c) Number surviving/number per group.
(d) Weight Change Relative to Controls =

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

(e) Controls received drinking water without phenol.

studies were set at 2,500 and 5,000 ppm in drinking water for rats of each sex.

Mice

Survival of mice was 100% during the study. Except for the groups receiving 10,000 ppm, gains in mean body weight in all treated groups were comparable with or greater than those in the controls. In mice receiving 10,000 ppm, weight gain was 80% less than the control values for the males and 33% less for the females. Body weight loss occurred in male and female mice at the highest concentration (10,000 ppm) during the first 7 weeks followed by lower weight gains for the remaining weeks of the study.

Microscopic examination failed to reveal any compound-related histomorphologic alterations.

Since the animals that rejected the water had a decreased mean weight gain at 10,000 ppm in the subchronic studies, low and high doses for the chronic studies were set at 2,500 and 5,000 ppm in drinking water for mice of each sex.

F. Chronic Studies

The number of animals in test groups, doses administered, and times on study of the chronic studies in rats and mice are shown in Table 4.

G. Clinical Examinations and Pathology

Observations of the animals were recorded twice daily, and examinations for clinical signs and the presence of palpable masses were recorded weekly. Mean body weights and food consumption were recorded every 2 weeks for the first 12 weeks and then monthly thereafter. Water consumption was recorded weekly.

Moribund animals and those that survived to the termination of the study were killed by intraperitoneal injections of sodium pentobarbital (Diabutal®, Diamond Laboratories, Inc., Des Moines, Iowa) and necropsied.

Table 4. Experimental Design for Chronic Studies of Rats and Mice Receiving Phenol in Drinking Water

Species, Sex and Test Group	Initial Number of Animals	Phenol Dose(a)	Time on Study	
			Dosed (weeks)	Observed (weeks)
RATS				
Male				
Matched-Control	50	0		105
Low-Dose	50	2,500	103	1-2
High-Dose	50	5,000	103	1-2
Female				
Matched-Control	50	0		105
Low-Dose	50	2,500	103	1-2
High-Dose	50	5,000	103	1-2
MICE				
Male				
Matched-Control	50	0		105
Low-Dose	50	2,500	103	1-2
High-Dose	50	5,000	103	1-2
Female				
Matched-Control	50	0		105
Low-Dose	50	2,500	103	1-2
High-Dose	50	5,000	103	1-2

(a)ppm phenol administered in drinking water.

Gross and microscopic examinations were performed on major tissues, major organs, and all gross lesions from animals found dead or killed. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, pancreas, stomach, small intestine, large intestine, gall bladder (mice), kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Occasionally, additional tissues were also examined microscopically. Special staining techniques were utilized as necessary.

Since necropsies of animals found dead sometimes were precluded in whole or in part by autolysis or cannibalization, 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.

H. Data Recording and Statistical Analyses

Data on this experiment were recorded for processing 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 were performed using 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 for 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 prior to histologic sampling (e.g., skin or mammary tumors) or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

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 for 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 test for inequality (Miller, 1966) requires that the P value 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 a linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance.

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 interval is greater than one, it can be inferred that a statistically significant result has occurred (i.e., P is less than the 0.025

one-tailed test when the control incidence is not zero, and P is less than the 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; 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)

After being on the study approximately 20 weeks, rats in both the male and female high-dose groups had mean body weights lower than those of the respective controls (Figure 1). Food consumption among treated groups was comparable with controls, but water consumption of the low- and high-dose groups was 80% and 90%, respectively, that of the controls. No other clinical signs related to the consumption of phenol in drinking water were observed throughout the study.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female control rats, and for those consuming phenol in the drinking water at the doses of this bioassay, are shown by the Kaplan and Meier curves in Figure 2. The Tarone test for a positive dose-related trend in mortality is not significant in either sex.

In male rats, 26/50 (52%) of the matched-control group, 22/50 (44%) of the low-dose group, and 30/50 (60%) of the high-dose group lived to the end of the bioassay (104-105 weeks). In females, 38/50 (76%) of the control group, 39/50 (78%) of the low-dose group, and 37/50 (74%) of the high-dose group lived to the end of the bioassay at 104 to 105 weeks.

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.

Various neoplasms were observed in both control and dosed rats. Each type of tumor has been encountered previously and occurred with no appreciable difference in frequency between control and dosed rats with the exception of a few types of tumors which were seen in increased incidences

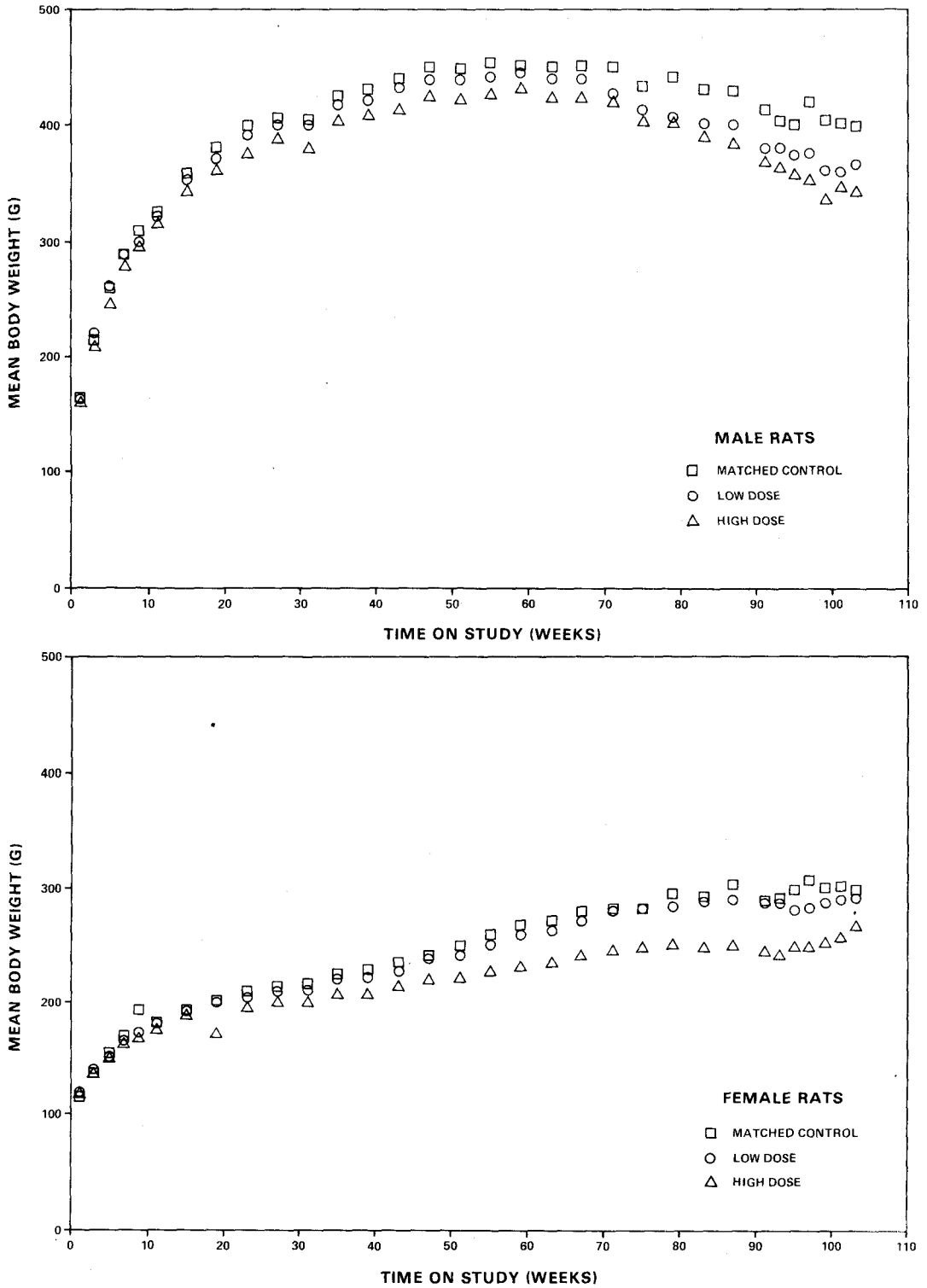


Figure 1. Growth Curves for Rats Administered Phenol in the Drinking Water

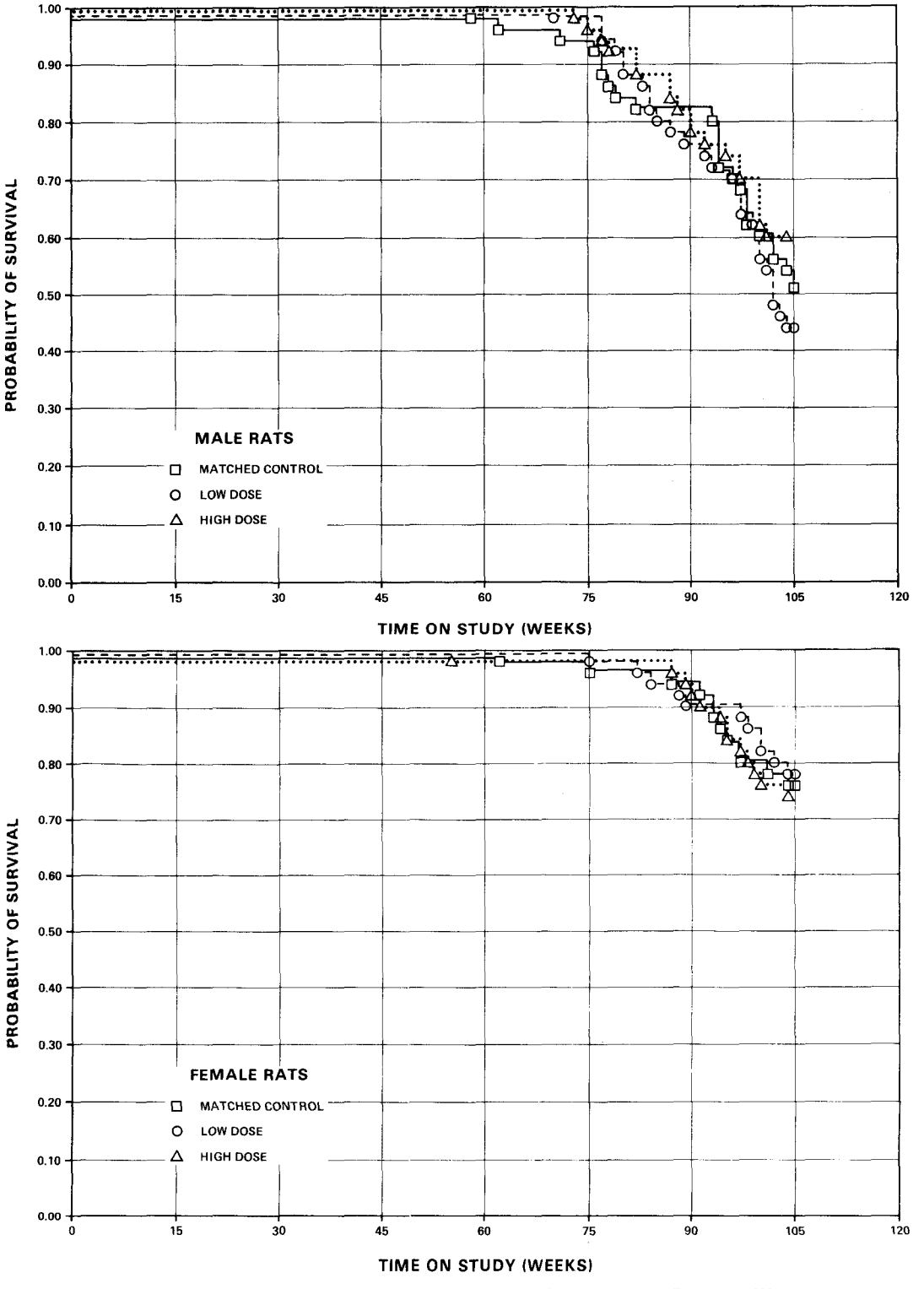


Figure 2. Survival Curves for Rats Administered Phenol in the Drinking Water

in low-dose male rats. Pheochromocytomas of the adrenal medulla were observed with greater frequency in the low-dose male rats than in the controls (control 13/50, low-dose 22/50, high-dose 9/50). Leukemias or lymphomas were seen in 18/50 control males, 31/50 low-dose males, and 25/50 high-dose males. The leukemias in dosed rats were of the type usually seen in untreated F344 rats; and they involved most commonly the spleen, liver, and lung and occasionally the bone marrow.

The inflammatory, degenerative, and hyperplastic lesions were similar in number and kind to those that naturally occur in aged F344 rats.

The results of the histopathologic examination suggest that administration of phenol may have increased the incidences of pheochromocytomas and leukemias or lymphomas in low-dose male F344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables 5 and 6 contain the statistical analysis 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.

In male rats, the incidence of animals with either leukemias or lymphomas is significantly higher (P=0.008) in the low-dose group than in the control group. The Cochran-Armitage test indicates a departure (P=0.028) from linear trend due to the higher incidence in the low-dose group (31/50, 62%) than in the high-dose group (25/50, 50%). The historical incidence of these types of tumors accumulated to date in untreated control male rats from all bioassay laboratories is 319/2130 (15%).

The incidences of control male F344 rats with leukemias or lymphomas in other bioassays conducted under this contract were 8/50 (16%) for benzoin (CAS 119-53-9), 14/49 (29%) for titanium dioxide (CAS 1309-63-3), and 14/49 (29%) for dl-menthol (CAS 89-78-1). In the same room with the test animals were male control rats matched to studies of bis(2-chloro-1-methylethyl) ether and dimethyl terephthalate with incidences of 16/50 (32%) and 13/50 (26%), respectively. The combined incidence of lymphomas or leukemia in these five groups was 65/248 (26%). This value is higher than the overall bioassay results of 15% but is still lower than the 18/50 (36%) observed in

the matched male control group in this study. The association of the administration of phenol in drinking water with lymphomas or leukemias is not clearly established because of the lack of a significant result in the high-dose group (when compared with matched controls) and by the lack of a positive dose response in the female dosed groups.

The incidence of interstitial-cell tumors in the testis of males is higher in the low-dose group (49/50, 98%) than in the control group (42/48, 88%), but the P=0.050 observed in the low-dose group does not meet the significance level of 0.025 required by the Bonferroni inequality criterion, and the Fisher exact test does not indicate a significant result for the high-dose group. The historical incidence of male F344 rats in the bioassay program with this type of tumor is 1,696/2,230 (76%).

In male rats, the incidences of pheochromocytomas in the adrenal and C-cell carcinomas in the thyroid are higher in the low-dose group than in the control groups (P=0.046 and P=0.027, respectively), but the probability level in either instance is above the level of 0.025 required when the Bonferroni inequality criterion is used in the comparison of two dosed groups with a single control group. The Cochran-Armitage test in either instance is not significant because of departures from linear trend (P=0.006 and 0.008) caused by the higher incidence of these tumors in the low-dose group than in the high-dose group. The historical incidences of male F344 rats in the bioassay program with pheochromocytomas in the adrenal and C-cell carcinomas in the thyroid are 200/2,230 (9%) and 42/2,230 (2%), respectively.

A significant negative trend (P=0.038) is found in the incidence of male rats with C-cell adenomas in the thyroid.

The Cochran-Armitage test indicates a negative dose-related trend (P=0.026) in the incidence of female rats with either neoplastic nodules or hepatocellular carcinomas in the liver. The analysis indicates a negative trend (P=0.011) and a significantly lower incidence (P=0.030) of animals with either adenoma or carcinoma in the thyroid in each of the dosed groups of female rats. The historical incidence from all laboratories for these thyroid tumors in F344 female rats is 125/2,094 (6%), which is lower than the control group incidence of 7/50 (14%). This higher incidence in the control group compared with the historical controls cannot be explained.

No tumor at any site can be clearly associated with the administration of phenol in this bioassay.

Except for hematopoietic tumors and C-cell tumors, a numerical value of one is included in each of the 95% confidence intervals for relative risk shown in the tables, and this value 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 phenol, which could not be detected under the conditions of this test.

Table 5. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phenol in the Drinking Water (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Skin: Keratoacanthoma (b)	1/50 (2)	3/50 (6)	2/50 (4)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		3.000	2.000
Lower Limit		0.251	0.108
Upper Limit		154.276	115.621
Weeks to First Observed Tumor	82	105	104
Hematopoietic System: Monocytic Leukemia (b)	18/50 (36)	30/50 (60)	24/50 (48)
P Value (c,d)	N.S.	P=0.014	N.S.
Departure from Linear Trend (f)	P=0.037		
Relative Risk (Matched Control) (e)		1.667	1.333
Lower Limit		1.053	0.802
Upper Limit		2.659	2.239
Weeks to First Observed Tumor	77	70	73
Hematopoietic System: All Leukemias (b)	18/50 (36)	30/50 (60)	25/50 (50)
P Value (c,d)	N.S.	P=0.014	N.S.
Departure from Linear Trend (f)	P=0.049		
Relative Risk (Matched Control) (e)		1.667	1.389
Lower Limit		1.053	0.843
Upper Limit		2.659	2.312
Weeks to First Observed Tumor	77	70	73
Hematopoietic System: Leukemia or Lymphoma (b)	18/50 (36)	31/50 (62)	25/50 (50)
P Value (c,d)	N.S.	P=0.008	N.S.
Departure from Linear Trend (f)	P=0.028		
Relative Risk (Matched Control) (e)		1.722	1.389
Lower Limit		1.096	0.843
Upper Limit		2.723	2.312
Weeks to First Observed Tumor	77	70	73

Table 5. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phenol in the Drinking Water (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Neoplastic Nodule (b)	5/50 (10)	3/50 (6)	2/50 (4)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.600	0.400
Lower Limit		0.098	0.040
Upper Limit		2.910	2.313
Weeks to First Observed Tumor	96	89	104
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	5/50 (10)	4/50 (8)	4/50 (8)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.800	0.800
Lower Limit		0.168	0.168
Upper Limit		3.499	3.499
Weeks to First Observed Tumor	96	89	87
Pituitary: Adenoma, NOS (b)	7/36 (19)	4/45 (9)	6/50 (12)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.457	0.617
Lower Limit		0.107	0.188
Upper Limit		1.655	1.972
Weeks to First Observed Tumor	94	84	87
Adrenal: Pheochromocytoma (b)	13/50 (26)	22/50 (44)	9/50 (18)
P Value (c,d)	N.S.	P=0.046	N.S.
Departure from Linear Trend (f)	P=0.006		
Relative Risk (Matched Control) (e)		1.692	0.692
Lower Limit		0.927	0.288
Upper Limit		3.197	1.585
Weeks to First Observed Tumor	77	77	90

Table 5. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phenol in the Drinking Water (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma (b)	4/50 (8)	2/49 (4)	0/50 (0)
P Value (c,d)	P=0.038(N)	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.510	0.000
Lower Limit		0.048	0.000
Upper Limit		3.383	1.079
Weeks to First Observed Tumor	105	104	--
Thyroid: C-cell Carcinoma (b)	0/50 (0)	5/49 (10)	1/50 (2)
P Value (c,d)	N.S.	P=0.027	N.S.
Departure from Linear Trend (f)	P=0.008		
Relative Risk (Matched Control) (e)		Infinite	Infinite
Lower Limit		1.287	0.054
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	100	104
Thyroid: C-cell Adenoma or Carcinoma (b)	4/50 (8)	7/49 (14)	1/50 (2)
P Value (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.050		
Relative Risk (Matched Control) (e)		1.786	0.250
Lower Limit		0.486	0.005
Upper Limit		7.830	2.411
Weeks to First Observed Tumor	105	100	104
Pancreatic Islets: Islet-cell Adenoma (b)	3/50 (6)	0/49 (0)	2/50 (4)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.000	0.667
Lower Limit		0.000	0.058
Upper Limit		1.696	5.570
Weeks to First Observed Tumor	104	--	87

Table 5. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phenol in the Drinking Water (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Preputial Gland:			
Carcinoma, NOS (b)	4/50 (8)	1/50 (2)	2/50 (4)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.250	0.500
Lower Limit		0.005	0.047
Upper Limit		2.411	3.318
Weeks to First Observed Tumor	98	105	100
Testis: Interstitial-cell			
Tumor (b)	42/48 (88)	49/50 (98)	47/50 (94)
P Value (c,d)	N.S.	P=0.050	N.S.
Relative Risk (Matched Control) (e)		1.120	1.074
Lower Limit		0.983	0.931
Upper Limit		1.169	1.192
Weeks to First Observed Tumor	76	70	73

(a) Dosed groups received doses of 2,500 ppm or 5,000 ppm in the drinking water.
(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 matched 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 the control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the matched control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phenol in the Drinking Water (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Monocytic Leukemia (b)	15/50 (30)	14/50 (28)	12/50 (24)
P Values (c,d)	N.S	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.933	0.800
Lower Limit		0.469	0.382
Upper Limit		1.845	1.637
Weeks to First Observed Tumor	91	97	87
Hematopoietic System: All Leukemias (b)	15/50 (30)	15/50 (30)	12/50 (24)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.000	0.800
Lower Limit		0.513	0.382
Upper Limit		1.948	1.637
Weeks to First Observed Tumor	91	97	87
Hematopoietic System: Leukemia or Lymphoma (b)	16/50 (32)	15/50 (30)	12/50 (24)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.938	0.750
Lower Limit		0.488	0.363
Upper Limit		1.793	1.508
Weeks to First Observed Tumor	91	97	87
Liver: Neoplastic Nodule (b)	3/50 (6)	1/50 (2)	0/50 (0)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.333	0.000
Lower Limit		0.006	0.000
Upper Limit		3.983	1.663
Weeks to First Observed Tumor	105	105	—

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phenol in the Drinking Water (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	4/50 (8)	1/50 (2)	0/50 (0)
P Value (c,d)	P=0.026 (N)	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.250	0.000
Lower Limit		0.005	0.000
Upper Limit		2.411	1.079
Weeks to First Observed Tumor	105	105	--
Pituitary: Adenoma, NOS (b)	24/48 (50)	26/50 (52)	24/49 (49)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.040	0.980
Lower Limit		0.682	0.631
Upper Limit		1.593	1.523
Weeks to First Observed Tumor	91	88	91
Adrenal: Cortical Adenoma (b)	4/50 (8)	4/50 (8)	2/50 (4)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.000	0.500
Lower Limit		0.197	0.047
Upper Limit		5.083	3.318
Weeks to First Observed Tumor	105	98	104
Adrenal: Pheochromocytoma (b)	4/50 (8)	1/50 (2)	3/50 (6)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.250	0.750
Lower Limit		0.005	0.115
Upper Limit		2.411	4.206
Weeks to First Observed Tumor	97	102	100

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phenol in the Drinking Water (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma (b)	3/50 (6)	0/50 (0)	1/50 (2)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.000	0.333
Lower Limit		0.000	0.006
Upper Limit		1.663	3.983
Weeks to First Observed Tumor	94	—	104
Thyroid: C-cell Carcinoma (b)	4/50 (8)	1/50 (2)	0/50 (0)
P Value (c,d)	P=0.026(N)	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.250	0.000
Lower Limit		0.005	0.000
Upper Limit		2.411	1.079
Weeks to First Observed Tumor	105	105	--
Thyroid: C-cell Adenoma or Carcinoma (b)	7/50 (14)	1/50 (2)	1/50 (2)
P Value (c,d)	P=0.011(N)	P=0.030(N)	P=0.030(N)
Relative Risk (Matched Control) (e)		0.143	0.143
Lower Limit		0.003	0.003
Upper Limit		1.052	1.052
Weeks to First Observed Tumor	94	105	104
Mammary Gland: Fibroadenoma (b)	7/50 (14)	5/50 (10)	8/50 (16)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.714	1.143
Lower Limit		0.191	0.392
Upper Limit		2.434	3.423
Weeks to First Observed Tumor	95	105	99

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phenol in the Drinking Water (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Clitoral Gland: Carcinoma, NOS (b)	6/50 (12)	3/50 (6)	2/50 (4)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.500	0.333
Lower Limit		0.085	0.034
Upper Limit		2.200	1.758
Weeks to First Observed Tumor	97	105	104
Uterus: Endometrial Stromal Polyp (b)	6/49 (12)	10/49 (20)	7/49 (14)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.667	1.167
Lower Limit		0.598	0.362
Upper Limit		5.155	3.905
Weeks to First Observed Tumor	75	97	89

(a) Dosed groups received doses of 2,500 ppm or 5,000 ppm in the drinking water.
(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 matched 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 the control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the control group.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

The mean body weights of the high- and low-dose groups of either sex were lower than the weights of the respective control groups throughout most of the test (Figure 3). Throughout the study, food consumption among treated groups was comparable with controls, but water consumption of the low- and high-dose groups was depressed to 75% and 50%-60%, respectively, that of the controls. A reduced tendency to fight was observed among treated male mice beginning at week 80. No other clinical signs related to the consumption of phenol were observed.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered phenol in the drinking water at the doses of this bioassay, together with those for the controls, are shown by the Kaplan and Meier curves in Figure 4. The result of the Tarone test of the mortality in male mice does not indicate shortened survival in dosed groups.

In male mice, 42/50 (84%) of the control group, 45/50 (90%) of the low-dose group, and 48/50 (96%) of the high-dose group lived to the end of the bioassay at 104 to 106 weeks. In females, 41/50 (82%) of the control group, 40/50 (80%) of the low-dose group, and 42/50 (84%) of the high-dose group lived to the end of the bioassay at 105 to 106 weeks.

Sufficient numbers of animals were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

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

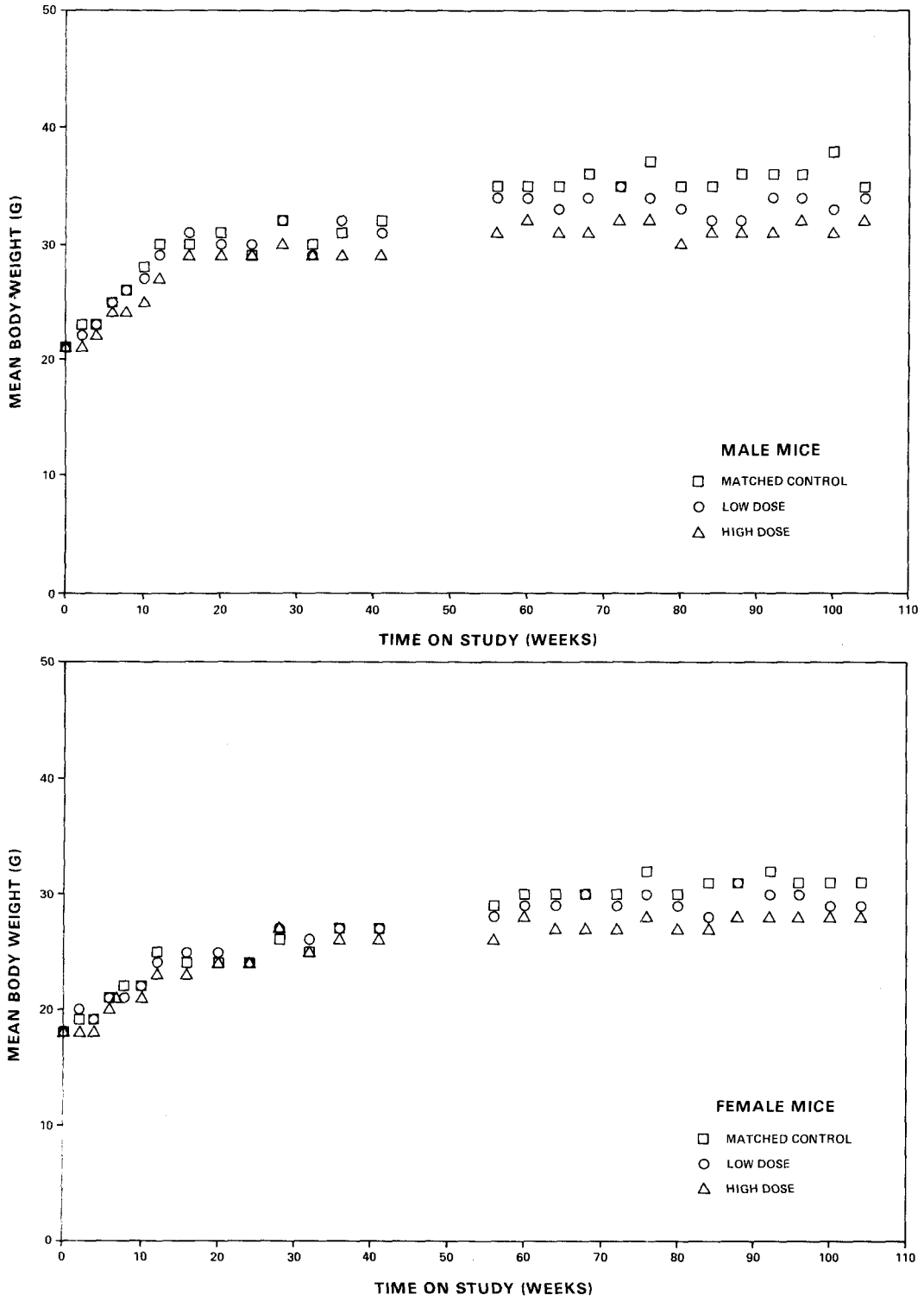


Figure 3. Growth Curves for Mice Administered Phenol in the Drinking Water

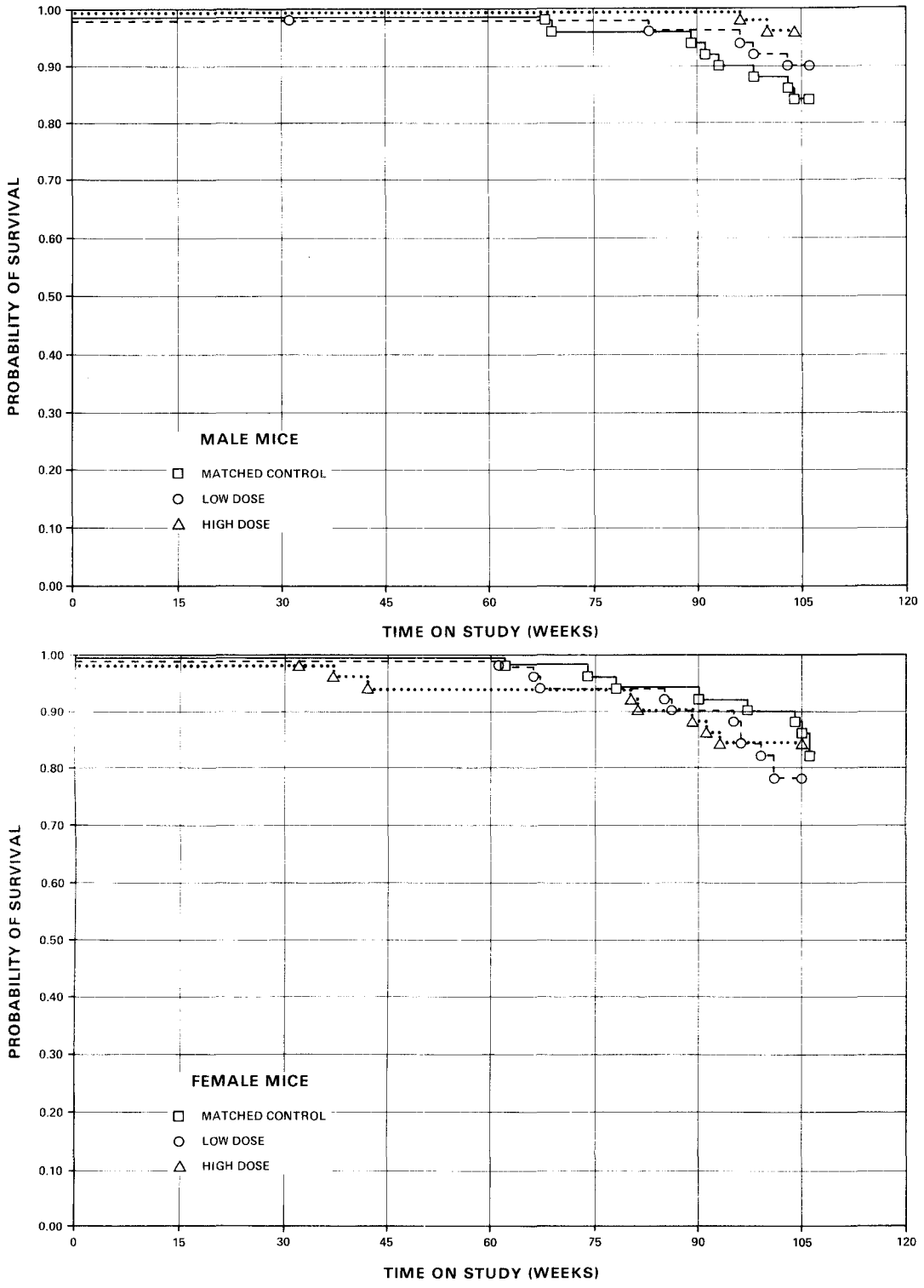


Figure 4. Survival Curves for Mice Administered Phenol in the Drinking Water

Neoplasms observed were of the usual number and type found in mice of this strain and age. An increase in the number of uterine endometrial stromal polyps relative to matched controls was observed in high-dose females (5/48); however, this increase did not appear to exceed that observed in historical control mice of this strain and age.

Other degenerative, proliferative, and inflammatory lesions were of the usual number and kind observed in aged B6C3F1 mice and appeared without relationship to the test chemicals.

According to the histopathologic examination, phenol was neither toxic nor carcinogenic to B6C3F1 mice under the conditions of this experiment.

D. Statistical Analyses of Results (Mice)

Tables 7 and 8 contain the statistical analyses of the incidences 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 Cochran-Armitage test indicates a positive dose-related trend (P=0.034) in female mice with endometrial stromal polyps in the uterus, but the results of the Fisher exact test do not indicate significantly higher incidences in the dosed groups than in the control group.

A departure from linear trend is indicated in the incidence of either hepatocellular adenomas or carcinomas (P=0.036) in males as a result of a sharp increase in the incidence of the low-dose group compared with the high-dose group. Historical records of untreated male mice, in bioassays of 103 weeks or more duration at this laboratory, with hepatocellular adenomas or carcinomas indicate an incidence of 61/212 (29%) compared with 14/50 (28%) in the control group and 19/48 (40%) in the low-dose group.

A significantly lower incidence (P=0.028) of fibrosarcomas in the subcutaneous tissue of male mice in the high-dose group than in the control group, and a negative trend (P=0.011) are indicated. The historical incidence of all male B6C3F1 control mice in the bioassay program is 23/2,843 (0.8%), which is lower than the 5/50 (10%) observed in the matched controls of this study.

The negative trend in the incidence of lymphomas or leukemias in female mice indicates a significant (P=0.023) negative trend which is due to a

significantly lower incidence (P=0.030) in the high-dose group than in the other groups.

No tumor at any site in the mice can be clearly associated with the administration of phenol in this bioassay. In each of the 95% confidence intervals for relative risk shown in the tables, the value of 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 fibrosarcoma in the subcutaneous tissue, in the high-dose group of male mice, has an upper limit greater than one indicating the theoretical possibility of tumor induction in mice by phenol, which could not be detected under the conditions of this test.

Table 7. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phenol in the Drinking Water (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Subcutaneous Tissue: Fibrosarcoma (b)	5/50 (10)	1/50 (2)	0/50 (0)
P Value (c,d)	P=0.011(N)	N.S.	P=0.028(N)
Relative Risk (Matched Control) (e)		0.200	0.000
Lower Limit		0.004	0.000
Upper Limit		1.699	0.793
Weeks to First Observed Tumor	93	105	--
Lung: Alveolar/Bronchiolar Adenomas (b)	5/50 (10)	5/48 (10)	6/50 (12)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.042	1.200
Lower Limit		0.255	0.326
Upper Limit		4.243	4.660
Weeks to First Observed Tumor	104	105	104
Lung: Alveolar/Bronchiolar Carcinoma (b)	1/50 (2)	0/48 (0)	4/50 (8)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.000	4.000
Lower Limit		0.000	0.415
Upper Limit		19.420	192.805
Weeks to First Observed Tumor	98	—	104
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	6/50 (12)	5/48 (10)	10/50 (20)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.868	1.667
Lower Limit		0.224	0.597
Upper Limit		3.185	5.164
Weeks to First Observed Tumor	98	105	104

Table 7. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phenol in the Drinking Water (a)
(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Malignant			
Lymphoma, Lymphocytic Type (b)	3/50 (6)	0/50 (0)	1/50 (2)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.000	0.333
Lower Limit		0.000	0.006
Upper Limit		1.663	3.983
Weeks to First Observed Tumor	91	--	104
Hematopoietic System: Malignant			
Lymphoma, Histiocytic Type (b)	4/50 (8)	6/50 (12)	4/50 (8)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.500	1.000
Lower Limit		0.380	0.197
Upper Limit		6.820	5.083
Weeks to First Observed Tumor	104	105	100
Hematopoietic System:			
All Lymphomas (b)	7/50 (14)	8/50 (16)	5/50 (10)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.143	0.714
Lower Limit		0.392	0.191
Upper Limit		3.423	2.434
Weeks to First Observed Tumor	91	103	100
Hematopoietic System:			
Lymphoma or Leukemia (b)	8/50 (16)	8/50 (16)	5/50 (10)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.000	0.625
Lower Limit		0.355	0.172
Upper Limit		2.815	2.011
Weeks to First Observed Tumor	91	103	100

Table 7. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phenol in the Drinking Water (a)
(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma (b)	2/50 (4)	3/48 (6)	2/50 (4)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.563	1.000
Lower Limit		0.187	0.075
Upper Limit		18.028	13.326
Weeks to First Observed Tumor	106	103	104
Liver: Hepatocellular Carcinoma (b)	12/50 (24)	17/48 (35)	7/50 (14)
P Value (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.029		
Relative Risk (Matched Control) (e)		1.476	0.583
Lower Limit		0.747	0.212
Upper Limit		2.999	1.467
Weeks to First Observed Tumor	69	98	104
Liver: Hepatocellular Adenoma or Carcinoma (b)	14/50 (28)	19/48 (40)	9/50 (18)
P Value (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.036		
Relative Risk (Matched Control) (e)		1.414	0.643
Lower Limit		0.763	0.271
Upper Limit		2.667	1.441
Weeks to First Observed Tumor	69	98	104

(a) Dosed groups received doses of 2,500 ppm or 5,000 ppm in the drinking water.
(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 matched 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 the control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the matched control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 8. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phenol in the Drinking Water (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	1/50 (2)	3/48 (6)	1/48 (2)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		3.125	1.042
Lower Limit		0.262	0.014
Upper Limit		160.536	80.093
Weeks to First Observed Tumor	106	96	105
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	1/50 (2)	3/48 (6)	2/48 (4)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		3.125	2.083
Lower Limit		0.262	0.112
Upper Limit		160.536	120.307
Weeks to First Observed Tumor	106	96	105
Hematopoietic System: Malignant Lymphoma, Undifferentiated Type (b)	4/50 (8)	1/49 (2)	4/48 (8)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.255	1.042
Lower Limit		0.005	0.205
Upper Limit		2.459	5.286
Weeks to First Observed Tumor	78	105	91
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type (b)	2/50 (4)	3/49 (6)	1/48 (2)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.531	0.521
Lower Limit		0.183	0.009
Upper Limit		17.671	9.666
Weeks to First Observed Tumor	106	66	105

Table 8. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phenol in the Drinking Water (a)
(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma, Histiocytic Type (b)	8/50 (16)	5/49 (10)	0/48 (0)
P Value (c,d)	P=0.005(N)	N.S.	P=0.003(N)
Relative Risk (Matched Control) (e)		0.638	0.000
Lower Limit		0.176	0.000
Upper Limit		2.049	0.456
Weeks to First Observed Tumor	104	101	--
Hematopoietic System: All Lymphomas (b)	14/50 (28)	10/49 (20)	6/48 (13)
P Value (c,d)	P=0.038(N)	N.S.	P=0.048(N)
Relative Risk (Matched Control) (e)		0.729	0.446
Lower Limit		0.321	0.153
Upper Limit		1.587	1.125
Weeks to First Observed Tumor	78	66	91
Hematopoietic System: Lymphoma or Leukemia (b)	15/50 (30)	10/49 (20)	6/48 (13)
P Value (c,d)	P=0.023(N)	N.S.	P=0.030(N)
Relative Risk (Matched Control) (e)		0.680	0.417
Lower Limit		0.304	0.145
Upper Limit		1.453	1.032
Weeks to First Observed Tumor	78	66	91
Liver: Hepatocellular Adenoma or Carcinoma (b)	3/50 (6)	1/48 (2)	1/48 (2)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.347	0.347
Lower Limit		0.007	0.007
Upper Limit		4.143	4.143
Weeks to First Observed Tumor	105	105	105

Table 8. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phenol in the Drinking Water (a)
(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe			
Adenoma (b)	3/41 (7)	1/47 (2)	0/44 (0)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.291	0.000
Lower Limit		0.006	0.000
Upper Limit		3.460	1.542
Weeks to First Observed Tumor	105	105	--
Thyroid: Follicular-cell			
Adenoma (b)	3/48 (6)	2/47 (4)	3/43 (7)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.681	1.116
Lower Limit		0.059	0.157
Upper Limit		5.673	7.911
Weeks to First Observed Tumor	104	105	104
Mammary Gland: Adenocarcinoma,			
NOS (b)	3/50 (6)	2/49 (4)	4/48 (8)
P Value (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.680	1.389
Lower Limit		0.059	0.248
Upper Limit		5.680	9.031
Weeks to First Observed Tumor	74	105	89
Uterus: Endometrial Stromal			
Polyp (b)	1/50 (2)	0/48 (0)	5/48 (10)
P Value (c,d)	P=0.034	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.000	5.208
Lower Limit		0.000	0.613
Upper Limit		19.420	240.772
Weeks to First Observed Tumor	106	--	89

Table 8. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phenol in the Drinking Water (a)

(continued)

(a) Dosed groups received doses of 2,500 ppm or 5,000 ppm in the drinking water.
(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 matched 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 the control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the matched control group.

V. DISCUSSION

A dose-related decrease in mean body weight gain was observed in rats and mice of each sex. Rats and mice given water containing phenol drank less than did the corresponding controls. The dose-related decrease in water consumption observed in the chronic studies was an important consideration in selecting doses for the chronic study. Further increasing the concentration of phenol in drinking water in the chronic study probably would not have resulted in an increased uptake of phenol because mice given water containing higher concentrations of phenol drank less. High-dose rats, low-dose rats, high-dose mice, and low-dose mice drank 90%, 80%, 50-60%, and 75%, respectively, that of the corresponding controls. No other clinical signs were associated with administration of phenol.

A significantly higher incidence (P=0.002) of leukemias or lymphomas occurred in low-dose male rats than in control male rats. The incidence in the high-dose group was also higher but not significantly so. The dose response was not significant by the Cochran-Armitage test. The historical incidence in previous 103- to 104-week bioassays (conducted by the NCI testing program) of the control male rats with leukemias and lymphomas is 319/2,130 (15%). The incidence of lymphomas or leukemias in control male rats in five other 103- to 104-week bioassays conducted in the same laboratory is 65/248 (26%) which is still lower than the 18/50 (36%) observed in the matched-controls in this study. Although the increased incidences of leukemias or lymphomas in low-dose male rats is statistically significant when compared with any of the historical controls from 103- to 104-week bioassays conducted by the NCI testing program, the high spontaneous tumor rate observed in the matched controls and the lack of a positive effect in the high-dose group indicate that the association between phenol and the incidence of leukemia or lymphomas is not clearly established.

In low-dose male rats, interstitial-cell tumors in the testes occurred at a significantly higher incidence (P=0.050) when compared with the matched controls. In the high-dose group, the increased incidence observed for this type of tumor was not significant and did not meet the Bonferroni inequality criterion of P=0.025 for multiple comparison of two dosed groups.

In low-dose male rats, pheochromocytomas in the adrenals and C-cell carcinomas in the thyroid occurred at incidences significantly higher (P=0.046 and P=0.027, respectively) than did those in the matched control. Again, in each instance the Bonferroni requirement of P=0.025 was not met.

VI. CONCLUSIONS

Under the conditions of this bioassay, phenol was not carcinogenic for either male or female F344 rats, or for male or female B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED PHENOL IN THE DRINKING WATER

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED PHENOL IN THE DRINKING WATER

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
BASAL-CELL TUMOR		1 (2%)	
SEBACEOUS ADENOMA		1 (2%)	1 (2%)
KERATOACANTHOMA	3 (6%)	2 (4%)	1 (2%)
FIBROMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
FIBROMA	1 (2%)	1 (2%)	2 (4%)
RHABDOMYOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		1 (2%)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MYELOMONOCYTIC LEUKEMIA			1 (2%)
MONOCYTIC LEUKEMIA	18 (36%)	30 (60%)	24 (48%)
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(49)
ACINAR-CELL ADENOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	5 (10%)	3 (6%)	2 (4%)
HEPATOCELLULAR CARCINOMA	1 (2%)	1 (2%)	2 (4%)
#COLON	(50)	(48)	(47)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(36)	(45)	(50)
CARCINOMA,NOS	1 (3%)		
ADENOMA, NOS	7 (19%)	4 (9%)	6 (12%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA		1 (2%)	1 (2%)
PHEOCHROMOCYTOMA	13 (26%)	22 (44%)	9 (18%)
#THYROID	(50)	(49)	(50)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA	4 (8%)	2 (4%)	
C-CELL CARCINOMA		5 (10%)	1 (2%)
#PANCREATIC ISLETS	(50)	(49)	(50)
ISLET-CELL ADENOMA	3 (6%)		2 (4%)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CARCINOMA,NOS			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ADENOMA, NOS	1 (2%)	1 (2%)	
FIBROADENOMA			2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	4 (8%)	1 (2%)	2 (4%)
*SEMINAL VESICLE	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		
#TESTIS	(48)	(50)	(50)
INTERSTITIAL-CELL TUMOR	42 (88%)	49 (98%)	47 (94%)
*EPIDIDYMIS	(50)	(50)	(50)
LIPOSARCOMA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
CARCINOMA, NOS, INVASIVE	1 (2%)		
GLIOMA, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	24	28	20
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	26	22	30
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	50	49
TOTAL PRIMARY TUMORS	113	131	112
TOTAL ANIMALS WITH BENIGN TUMORS	45	50	49
TOTAL BENIGN TUMORS	78	86	73
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	36	29
TOTAL MALIGNANT TUMORS	28	41	36
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	
TOTAL SECONDARY TUMORS	2	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	5	4	3
TOTAL UNCERTAIN TUMORS	7	4	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED PHENOL IN THE DRINKING WATER

	MATCHED 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)
FIBROMA	1 (2%)	1 (2%)	
OSTEOSARCOMA, UNC PRIM OR META	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	1 (2%)
FOLLICULAR-CELL CARCINOMA, METAS			1 (2%)
C-CELL CARCINOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
LEUKEMIA,NOS		1 (2%)	
MONOCYTIC LEUKEMIA	15 (30%)	14 (28%)	12 (24%)
#SPLEEN	(50)	(50)	(50)
FIBROSARCOMA	1 (2%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	3 (6%)	1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA	2 (4%)		
#PANCREAS	(49)	(49)	(50)
NEUROFIBROSARCOMA, UNC PRIM OR M	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(49)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS	24 (50%)	26 (52%)	24 (49%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	4 (8%)	4 (8%)	2 (4%)
PHEOCHROMOCYTOMA	4 (8%)	1 (2%)	3 (6%)
#THYROID	(50)	(50)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)	
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA	3 (6%)		1 (2%)
C-CELL CARCINOMA	4 (8%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	2 (4%)	
ADENOCARCINOMA, NOS	1 (2%)		1 (2%)
FIBROADENOMA	7 (14%)	5 (10%)	8 (16%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	6 (12%)	3 (6%)	2 (4%)
#UTERUS	(49)	(49)	(49)
ENDOMETRIAL STROMAL POLYP	6 (12%)	10 (20%)	7 (14%)
ENDOMETRIAL STROMAL SARCOMA		2 (4%)	
NERVOUS SYSTEM			
#CEREBRUM	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE		1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF LEG	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
NEUROFIBROSARCOMA, UNC PRIM OR M	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA, MET			1 (2%)
ENDOMETRIAL STROMAL SARCOMA, INV		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	12	11	13
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	38	39	37
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	45	38
TOTAL PRIMARY TUMORS	87	76	63
TOTAL ANIMALS WITH BENIGN TUMORS	34	38	34
TOTAL BENIGN TUMORS	50	52	46
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	22	15
TOTAL MALIGNANT TUMORS	31	23	17
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	2
TOTAL SECONDARY TUMORS	1	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	1	
TOTAL UNCERTAIN TUMORS	3	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC	2		
TOTAL UNCERTAIN TUMORS	3		

* 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 ADMINISTERED PHENOL IN THE DRINKING WATER

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED PHENOL IN THE DRINKING WATER

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
FIBROMA	2 (4%)		
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA		2 (4%)	2 (4%)
FIBROSARCOMA	5 (10%)	1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(50)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	5 (10%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE		2 (4%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)		1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)	3 (6%)	1 (2%)
GRANULOCYTIC LEUKEMIA	1 (2%)		
#SPLENIC CAPSULE	(50)	(47)	(50)
SARCOMA, NOS	1 (2%)		
#PANCREATIC L.NODE	(50)	(48)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
#MESENTERIC L. NODE	(50)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	3 (6%)
#PEYER'S PATCH	(49)	(48)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#ILEUM	(49)	(48)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#MESENTERIC L. NODE	(50)	(48)	(48)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(48)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)	3 (6%)	2 (4%)
HEPATOCELLULAR CARCINOMA	12 (24%)	17 (35%)	7 (14%)
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(50)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	
ENDOCRINE SYSTEM			
#THYROID	(47)	(47)	(48)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	1 (2%)
#THYROID FOLLICLE	(47)	(47)	(48)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(50)	(48)	(50)
INTERSTITIAL-CELL TUMOR			2 (4%)
NERVOUS SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	4	2
MORIBUND SACRIFICE		1	
**SCHEDULED SACRIFICE	29		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	45	48
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

** Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	30	28	25
TOTAL PRIMARY TUMORS	40	39	30
TOTAL ANIMALS WITH BENIGN TUMORS	10	9	12
TOTAL BENIGN TUMORS	11	11	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	25	14
TOTAL MALIGNANT TUMORS	29	28	17
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	1	
TOTAL SECONDARY TUMORS	3	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
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 B2.

SUMMARY OF THE INCIDENCE OF NEOPLAMS IN FEMALE MICE ADMINISTERED PHENOL IN THE DRINKING WATER

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	48
INTEGUMENTARY SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(48)
FIBROUS HISTIOCYTOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	3 (6%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE	4 (8%)	1 (2%)	4 (8%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	7 (14%)	4 (8%)	
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
GRANULOCYTIC LEUKEMIA	1 (2%)		
#SPLEEN	(50)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#LIVER	(50)	(48)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#PEYER'S PATCH	(48)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(48)	(47)	(47)
ANGIOSARCOMA			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*PALATE	(50)	(49)	(48)
SQUAMOUS CELL CARCINOMA			1 (2%)
#LIVER	(50)	(48)	(48)
HEPATOCELLULAR ADENOMA	1 (2%)		1 (2%)
HEPATOCELLULAR CARCINOMA	2 (4%)	1 (2%)	
#PANCREATIC DUCT	(49)	(48)	(48)
SARCOMA, NOS	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(47)	(44)
CHROMOPHOBE ADENOMA	3 (7%)	1 (2%)	
#ADRENAL	(49)	(45)	(47)
CORTICAL ADENOMA		1 (2%)	1 (2%)
#THYROID	(48)	(47)	(43)
FOLLICULAR-CELL ADENOMA	3 (6%)	2 (4%)	3 (7%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(48)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	3 (6%)	2 (4%)	4 (8%)
#UTERUS	(50)	(48)	(48)
ENDOMETRIAL STROMAL POLYP	1 (2%)		5 (10%)
#OVARY/OVIDUCT	(50)	(48)	(48)
PAPILLARY ADENOMA	1 (2%)		
#OVARY	(49)	(47)	(46)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
GRANULOSA-CELL TUMOR	1 (2%)		
TERATOMA, MALIGNANT			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(48)
ADENOMA, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*VERTEBRA	(50)	(49)	(48)
OSTEOSARCOMA		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	9	10	8
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	41	40	42
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	27	21	21
TOTAL PRIMARY TUMORS	35	23	25
TOTAL ANIMALS WITH BENIGN TUMORS	11	9	10
TOTAL BENIGN TUMORS	13	9	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	12	14
TOTAL MALIGNANT TUMORS	21	14	14
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
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 ADMINISTERED PHENOL IN THE DRINKING WATER

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED PHENOL IN THE DRINKING WATER

	MATCHED 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)
ABSCESS, NOS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
ABSCESS, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
MINERALIZATION			1 (2%)
PNEUMONIA, ASPIRATION	1 (2%)		
PNEUMONIA, CHRONIC MURINE	48 (96%)	44 (88%)	49 (98%)
GRANULOMA, FOREIGN BODY			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	4 (8%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
FIBROSIS, FOCAL			1 (2%)
HEMOSIDEROSIS	16 (32%)	1 (2%)	7 (14%)
ATROPHY, NOS		6 (12%)	1 (2%)
LYMPHOID DEPLETION	1 (2%)		3 (6%)
HEMATOPOIESIS	24 (48%)	17 (34%)	27 (54%)
#CERVICAL LYMPH NODE	(50)	(49)	(49)
HEMORRHAGE		1 (2%)	
DEGENERATION, RETICULAR			1 (2%)
#MESENTERIC L. NODE	(50)	(49)	(49)
MINERALIZATION			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE	1 (2%)	1 (2%)	
DEGENERATION, RETICULAR			1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (2%)		
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
#HEPATIC SINUSOID	(50)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
#THYMUS	(21)	(26)	(35)
CYST, NOS	1 (5%)		
CIRCULATORY SYSTEM			
#BRAIN	(49)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#CERVICAL LYMPH NODE	(50)	(49)	(49)
LYMPHANGIECTASIS	3 (6%)	2 (4%)	
#MESENTERIC L. NODE	(50)	(49)	(49)
LYMPHANGIECTASIS	1 (2%)		
PERIARTERITIS			1 (2%)
#HEART	(50)	(50)	(50)
MINERALIZATION	2 (4%)		
THROMBOSIS, NOS	1 (2%)		
THROMBUS, FIBRIN	2 (4%)	8 (16%)	6 (12%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, CHRONIC	13 (26%)	13 (26%)	11 (22%)
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*AORTA	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
*ARTERY OF HEAD NECK	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
*JUGULAR VEIN	(50)	(50)	(50)
THROMBUS, FIBRIN		1 (2%)	
#PANCREAS	(50)	(49)	(50)
PERIARTERITIS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*MESENTERY	(50)	(50)	(50)
PERIARTERITIS			2 (4%)
DIGESTIVE SYSTEM			
*ORAL CAVITY	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
#SALIVARY GLAND	(49)	(49)	(49)
NECROSIS, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
HERNIA, NOS	2 (4%)	1 (2%)	
CONGESTION, NOS			1 (2%)
HEMORRHAGE	2 (4%)		
CHOLANGIOFIBROSIS	5 (10%)	5 (10%)	4 (8%)
DEGENERATION, CYSTIC	1 (2%)	3 (6%)	2 (4%)
NECROSIS, NOS	6 (12%)	7 (14%)	1 (2%)
NECROSIS, COAGULATIVE		2 (4%)	
METAMORPHOSIS FATTY	2 (4%)	2 (4%)	7 (14%)
CYTOPLASMIC CHANGE, NOS			1 (2%)
FOCAL CELLULAR CHANGE	5 (10%)	10 (20%)	5 (10%)
ANGIECTASIS		2 (4%)	2 (4%)
REGENERATIVE NODULE		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CONGESTION, NOS			2 (4%)
NECROSIS, COAGULATIVE	1 (2%)		3 (6%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	8 (16%)	17 (34%)	9 (18%)
#PANCREAS	(50)	(49)	(50)
EDEMA, NOS			1 (2%)
INFLAMMATION, CHRONIC	5 (10%)	2 (4%)	6 (12%)
ATROPHY, NOS		2 (4%)	
ATROPHY, FOCAL		1 (2%)	
#PANCREATIC DUCT	(50)	(49)	(50)
HYPERPLASIA, NOS	3 (6%)		1 (2%)
#STOMACH	(50)	(50)	(50)
MINERALIZATION	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ULCER, NOS		5 (10%)	3 (6%)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
ULCER, ACUTE	1 (2%)		
INFLAMMATION, ACUTE FOCAL			2 (4%)
NECROSIS, NOS		4 (8%)	
NECROSIS, FOCAL		1 (2%)	
#GASTRIC SUBMUCOSA	(50)	(50)	(50)
ABSCESS, NOS	1 (2%)		
#SMALL INTESTINE	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
#LARGE INTESTINE	(50)	(48)	(47)
EDEMA, NOS			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
PARASITISM		3 (6%)	8 (17%)
#CECUM	(50)	(48)	(47)
PARASITISM			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION			1 (2%)
CYST, NOS			1 (2%)
CONGESTION, NOS	1 (2%)		2 (4%)
INFLAMMATION, CHRONIC	37 (74%)	37 (74%)	48 (96%)
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS	1 (2%)		1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		1 (2%)	
HYPERPLASIA, PAPILLARY			1 (2%)
#URINARY BLADDER	(49)	(49)	(49)
CONGESTION, NOS			1 (2%)
EDEMA, NOS		2 (4%)	2 (4%)
HEMORRHAGE			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(36)	(45)	(50)
CYST, NOS		2 (4%)	2 (4%)
MULTILOCULAR CYST	1 (3%)		
HYPERPLASIA, FOCAL	1 (3%)		2 (4%)
ANGIECTASIS		1 (2%)	
#ADRENAL	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION			1 (2%)
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION		2 (4%)	5 (10%)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, NOS		3 (6%)	3 (6%)
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#THYROID	(50)	(49)	(50)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
#PARATHYROID	(43)	(37)	(49)
CYST, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	5 (10%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		1 (2%)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)		
CYSTIC DUCTS	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
#PROSTATE	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE SUPPURATIVE	13 (26%)	8 (16%)	8 (16%)
INFLAMMATION ACUTE AND CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE		2 (4%)	
#TESTIS	(48)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
GRANULOMA, SPERMATIC	1 (2%)		1 (2%)
DEGENERATION, NOS		1 (2%)	
ATROPHY, NOS	2 (4%)	1 (2%)	2 (4%)
HYPERPLASIA, INTERSTITIAL CELL	3 (6%)	6 (12%)	3 (6%)
#TESTIS/TUBULE	(48)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
*EPIDIDYMIS	(50)	(50)	(50)
STEATITIS	2 (4%)	3 (6%)	10 (20%)
GRANULOMA, SPERMATIC	4 (8%)	4 (8%)	4 (8%)
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
NECROSIS, NOS		1 (2%)	1 (2%)
NECROSIS, FOCAL	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
CATARACT	1 (2%)	1 (2%)	1 (2%)
*EYE/RETINA	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
DEGENERATION, RETICULAR			1 (2%)
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(50)
DEPLETION			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*SKELETAL MUSCLE	(50)	(50)	(50)
EDEMA, NOS			1 (2%)
HEMATOMA, NOS			1 (2%)
*INTERCOSTAL MUSCLE	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
STEATITIS	1 (2%)	1 (2%)	
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*MESENTERY	(50)	(50)	(50)
STEATITIS		6 (12%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
NECROSIS, FAT		2 (4%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED PHENOL IN THE DRINKING WATER

	MATCHED 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)
ANASARCA			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
PNEUMONIA, CHRONIC MURINE	42 (84%)	44 (88%)	46 (92%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
HEMOSIDEROSIS	25 (50%)	32 (64%)	31 (62%)
ATROPHY, NOS	2 (4%)		
HEMATOPOIESIS	33 (66%)	29 (58%)	32 (64%)
MYELOPOIESIS	1 (2%)	2 (4%)	
#SPLENIC FOLLICLES	(50)	(50)	(50)
ATROPHY, NOS			1 (2%)
#CERVICAL LYMPH NODE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
HEMOSIDEROSIS	5 (10%)		
#MESENTERIC L. NODE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	5 (10%)	1 (2%)	4 (8%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#HEPATIC SINUSOID	(50)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(50)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)
#HEART	(50)	(50)	(50)
MINERALIZATION			1 (2%)
THROMBUS, FIBRIN	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	17 (34%)	10 (20%)	26 (52%)
*VEIN OF NECK	(50)	(50)	(50)
THROMBUS, FIBRIN	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HERNIA, NOS	5 (10%)	2 (4%)	2 (4%)
CHOLANGIOFIBROSIS	1 (2%)		
NECROSIS, NOS	4 (8%)		3 (6%)
NECROSIS, COAGULATIVE	1 (2%)		
METAMORPHOSIS FATTY	5 (10%)	1 (2%)	2 (4%)
PIGMENTATION, NOS		1 (2%)	
FOCAL CELLULAR CHANGE	31 (62%)	28 (56%)	20 (40%)
HYPERPLASIA, FOCAL			1 (2%)
ANGIECTASIS		1 (2%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	5 (10%)	2 (4%)	4 (8%)
#PANCREAS	(49)	(49)	(50)
ATROPHY, NOS		1 (2%)	3 (6%)
#STOMACH	(50)	(50)	(50)
ULCER, NOS		1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
NECROSIS, NOS	1 (2%)		1 (2%)
HYPERPLASIA, NOS		1 (2%)	
HYPERKERATOSIS		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#GASTRIC MUCOSA	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	
#SMALL INTESTINE	(50)	(47)	(49)
PARASITISM	1 (2%)		1 (2%)
#LARGE INTESTINE	(50)	(49)	(49)
PARASITISM	2 (4%)	3 (6%)	3 (6%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
INFLAMMATION, CHRONIC	7 (14%)	13 (26%)	28 (56%)
METAMORPHOSIS FATTY		1 (2%)	
ANGIECTASIS		1 (2%)	
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS			1 (2%)
ATROPHY, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(49)
CYST, NOS	6 (13%)	6 (12%)	3 (6%)
MULTIPLE CYSTS	2 (4%)		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	2 (4%)
ANGIECTASIS		4 (8%)	1 (2%)
#ADRENAL	(50)	(50)	(50)
DEGENERATION, CYSTIC	5 (10%)	1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION			3 (6%)
ANGIECTASIS	1 (2%)		2 (4%)
#ADRENAL CORTEX	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
DEGENERATION, CYSTIC	2 (4%)	3 (6%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)	3 (6%)	1 (2%)
HYPERPLASIA, NOS	5 (10%)	2 (4%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
#THYROID	(50)	(50)	(50)
HYPERPLASIA, C-CELL	4 (8%)	1 (2%)	2 (4%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	29 (58%)	14 (28%)	14 (28%)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
#UTERUS	(49)	(49)	(49)
CYST, NOS		1 (2%)	
STEATITIS		1 (2%)	2 (4%)
#CERVIX UTERI	(49)	(49)	(49)
HYPERPLASIA, STROMAL			1 (2%)
#UTERUS/ENDOMETRIUM	(49)	(49)	(49)
CYST, NOS	1 (2%)		
HYPERPLASIA, CYSTIC	1 (2%)		
#OVARY	(49)	(49)	(50)
CYST, NOS	1 (2%)		
PAROVARIAN CYST	1 (2%)	4 (8%)	5 (10%)
STEATITIS		2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
INFLAMMATION, CHRONIC			2 (4%)
CATARACT			2 (4%)
*EYE ANTERIOR CHAMBER	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*EYE/IRIS	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
*EYE/RETINA	(50)	(50)	(50)
DEGENERATION, NOS			2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
STEATITIS	1 (2%)	4 (8%)	2 (4%)
*MESENTERY	(50)	(50)	(50)
STEATITIS	2 (4%)	3 (6%)	
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, FAT	1 (2%)		
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, CHRONIC		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 ADMINISTERED PHENOL IN THE DRINKING WATER

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED PHENOL IN THE DRINKING WATER

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)	3 (6%)	1 (2%)
NECROSIS, FOCAL			1 (2%)
ACANTHOSIS		2 (4%)	
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
ABSCESS, NOS	2 (4%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(50)
HEMORRHAGE		4 (8%)	1 (2%)
PNEUMONIA, CHRONIC MURINE	5 (10%)	3 (6%)	4 (8%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(48)	(50)
HYPERPLASIA, NOS			1 (2%)
#SPLEEN	(50)	(47)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
HEMATOPOIESIS	5 (10%)	1 (2%)	
GRANULOPOIESIS			1 (2%)
#SPLENIC FOLLICLES	(50)	(47)	(50)
ATROPHY, NOS	1 (2%)		
#MESENTERIC L. NODE	(50)	(48)	(48)
CONGESTION, NOS	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE	4 (8%)	12 (25%)	3 (6%)
ABSCESS, NOS	1 (2%)		
PIGMENTATION, NOS	1 (2%)		
ATROPHY, NOS	2 (4%)		
HYPERPLASIA, LYMPHOID	7 (14%)	3 (6%)	5 (10%)
HEMATOPOIESIS	2 (4%)		
#LUNG	(50)	(48)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
#LIVER	(50)	(48)	(50)
HEMATOPOIESIS		1 (2%)	
#PEYER'S PATCH	(49)	(48)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(50)	(48)	(48)
LYMPHANGIECTASIS	6 (12%)	12 (25%)	5 (10%)
THROMBOSIS, NOS	1 (2%)		
#HEART	(50)	(48)	(50)
EMBOLUS, SEPTIC	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
#LIVER	(50)	(48)	(50)
THROMBOSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(48)	(50)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL		2 (4%)	1 (2%)
INFARCT, NOS	1 (2%)	1 (2%)	1 (2%)
METAMORPHOSIS FATTY			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)	2 (4%)	1 (2%)
HYPERPLASIA, FOCAL	2 (4%)		
ANGIECTASIS	1 (2%)		
#LIVER/HEPATOCYTES	(50)	(48)	(50)
MEGALOCYTOSIS	1 (2%)		1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#BILE DUCT	(50)	(48)	(50)
CYST, NOS	1 (2%)	1 (2%)	3 (6%)
HYPERPLASIA, FOCAL	1 (2%)		
#PANCREAS	(49)	(48)	(50)
CYSTIC DUCTS	1 (2%)		
HEMORRHAGE	1 (2%)		
ATROPHY, NOS	1 (2%)		
#STOMACH	(49)	(47)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
NECROSIS, FOCAL	2 (4%)		
HYPERKERATOSIS		1 (2%)	1 (2%)
ACANTHOSIS	1 (2%)		
#LARGE INTESTINE	(47)	(48)	(49)
PARASITISM	1 (2%)	1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(50)
HEMORRHAGE	1 (2%)		
INFLAMMATION, CHRONIC	4 (8%)	4 (8%)	3 (6%)
ENDOCRINE SYSTEM			
#THYROID	(47)	(47)	(48)
FOLLICULAR CYST, NOS	1 (2%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)	1 (2%)	1 (2%)
ABSCESS, NOS			1 (2%)
ATROPHY, NOS			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#TESTIS	(50)	(48)	(50)
GRANULOMA, SPERMATIC			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DEGENERATION, NOS			2 (4%)
*EPIDIDYMIS	(50)	(50)	(50)
GRANULOMA, SPERMATIC	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	8	5	12
AUTO/NECROPSY/NO HISTO		2	

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED PHENOL IN THE DRINKING WATER

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(48)
HEMORRHAGE	1 (2%)	2 (4%)	4 (8%)
PNEUMONIA, CHRONIC MURINE	3 (6%)	2 (4%)	5 (10%)
GRANULOMA, NOS			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
METAPLASIA, OSSEOUS	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
#BRAIN/MENINGES	(50)	(48)	(48)
GRANULOPOIESIS			1 (2%)
#BONE MARROW	(48)	(48)	(46)
HYPERPLASIA, NOS			3 (7%)
#SPLEEN	(50)	(48)	(48)
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, NOS			1 (2%)
AMYLOIDOSIS	1 (2%)		
ATROPHY, NOS			2 (4%)
HYPERPLASIA, LYMPHOID	8 (16%)	6 (13%)	1 (2%)
HEMATOPOIESIS		4 (8%)	3 (6%)
GRANULOPOIESIS			1 (2%)
#SPLENIC FOLLICLES	(50)	(48)	(48)
ATROPHY, NOS		3 (6%)	
#MESENTERIC L. NODE	(48)	(47)	(47)
HEMORRHAGE		2 (4%)	2 (4%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ABSCESS, NOS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
ATROPHY, NOS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	3 (6%)	3 (6%)
GRANULOPOIESIS		1 (2%)	1 (2%)
#LUNG	(50)	(48)	(48)
LEUKOCYTOSIS, NOS			1 (2%)
#LIVER	(50)	(48)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)		
#PEYER'S PATCH	(48)	(48)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#KIDNEY	(50)	(48)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
#URINARY BLADDER	(46)	(48)	(48)
HYPERPLASIA, LYMPHOID	3 (7%)		
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(48)	(47)	(47)
LYMPHANGIECTASIS	1 (2%)	7 (15%)	4 (9%)
#MYOCARDIUM	(50)	(48)	(48)
MINERALIZATION			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
CALCIFICATION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(48)	(48)
INFLAMMATION, CHRONIC	1 (2%)		
#LIVER	(50)	(48)	(48)
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, NOS		1 (2%)	2 (4%)
AMYLOIDOSIS	1 (2%)		
FOCAL CELLULAR CHANGE	1 (2%)		
#LIVER/HEPATOCYTES	(50)	(48)	(48)
MEGALOCYTOSIS			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(49)	(48)	(48)
CYSTIC DUCTS	1 (2%)	3 (6%)	2 (4%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
ATROPHY, NOS		1 (2%)	3 (6%)
ATROPHY, FOCAL			1 (2%)
#ESOPHAGUS	(50)	(48)	(48)
HYPERKERATOSIS		1 (2%)	
#STOMACH	(50)	(47)	(48)
CYST, NOS			1 (2%)
HEMORRHAGE		1 (2%)	
ULCER, NOS		1 (2%)	
INFLAMMATION ACUTE PUSTULAR		1 (2%)	
INFLAMMATION, CHRONIC	4 (8%)		
HYPERKERATOSIS	5 (10%)	1 (2%)	3 (6%)
ACANTHOSIS	2 (4%)		1 (2%)
#SMALL INTESTINE	(48)	(48)	(48)
ULCER, NOS		1 (2%)	
#LARGE INTESTINE	(46)	(47)	(47)
PARASITISM	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(48)
MINERALIZATION			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	4 (8%)
CALCIFICATION, NOS		2 (4%)	1 (2%)
METAPLASIA, OSSEOUS	1 (2%)		
#URINARY BLADDER	(46)	(48)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
ANGIECTASIS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(47)	(44)
HYPERPLASIA, FOCAL			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANGIECTASIS		1 (2%)	
#ADRENAL	(49)	(45)	(47)
HEMORRHAGE	1 (2%)	1 (2%)	
NECROSIS, FOCAL			1 (2%)
#ADRENAL CORTEX	(49)	(45)	(47)
DEGENERATION, NOS	3 (6%)		1 (2%)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(48)	(47)	(43)
CYSTIC FOLLICLES			1 (2%)
FOLLICULAR CYST, NOS		1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)	5 (11%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(48)
GALACTOCELE	1 (2%)		1 (2%)
CYSTIC DUCTS	2 (4%)		
HYPERPLASIA, NOS	1 (2%)		
#UTERUS	(50)	(48)	(48)
HYDROMETRA			2 (4%)
ABSCESS, NOS		2 (4%)	
AMYLOIDOSIS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(48)	(48)
ABSCESS, NOS	3 (6%)		
HYPERPLASIA, CYSTIC	39 (78%)	43 (90%)	38 (79%)
#OVARY/OVIDUCT	(50)	(48)	(48)
RETENTION FLUID	1 (2%)		
#OVARY	(49)	(47)	(46)
FOLLICULAR CYST, NOS	8 (16%)	10 (21%)	5 (11%)
PAROVARIAN CYST			1 (2%)
HEMORRHAGE		1 (2%)	4 (9%)
HEMATOMA, NOS		1 (2%)	
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC			2 (4%)
NERVOUS SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE	(50)	(49)	(48)
PHTHISIS BULBI		1 (2%)	
*EYE/CORNEA	(50)	(49)	(48)
INFLAMMATION, CHRONIC		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*CRANIAL AND FACIAL B	(50)	(49)	(48)
EXOSTOSIS	1 (2%)		
*STERNUM	(50)	(49)	(48)
FIBROUS OSTEODYSTROPHY	41 (82%)	42 (86%)	35 (73%)
BODY CAVITIES			
*PERITONEUM	(50)	(49)	(48)
INFLAMMATION, ACUTE	1 (2%)		
*MESENTERY	(50)	(49)	(48)
INFLAMMATION, CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/NO HISTO		1	
AUTOLYSIS/NO NECROPSY		1	2

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

APPENDIX E

ANALYSIS OF PHENOL (LOT A4X) - MIDWEST RESEARCH INSTITUTE

APPENDIX E

Analysis of Phenol (Lot No. A4X)
Midwest Research Institute

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	76.57	6.43	-
Determined	76.40	6.21	
	76.55	6.19	

B. MELTING POINT

Determined	Literature Values
41.8°-42.5°C (Du Pont 900 DTA)	(ultrapure material) 40.85°C (Merck Index, 1968)
41.5° to 43.5°C (visual, capillary)	43°C (Dictionary of Organic Compounds, 1965)

C. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel F-254
Amount Spotted: 100 and 300 μg
Ref. Standard: Phenol
Visualization: Ultraviolet (254 and 366 nm) and Fast Blue B
System 1: Ethyl acetate : Petroleum Ether (10:1)
R_f: 0.762, origin (trace)
R_{st}: 1.00, origin
System 2: Benzene : methanol : acetic acid (80:2:1)
R_f: 0.37
R_{st}: 1.00

D. VAPOR-PHASE CHROMATOGRAPHY

System 1:

Instrument: Tracor MT 220

Detection: Flame Ionization

Column: 1.5% SP2250/1.95% SP2401 on 100/120 Supelcon AW-DMCS 1.8 M x 4 mm (I.D.)

Oven Temp. Program: 75°C for 5 min; 75° to 250°C at 10°C/minute

Results: One homogeneous peak at 6.4 minutes

System 2:

Instrument: Bendix 2500

Detection: Flame Ionization

Column: Chromosorb 102, 1.8 m x 4 mm (I.D.)

Oven Temp. Program: 100°C for 1 min; 100° to 250°C at 10°C/minute

Results: One homogeneous peak at 16.3 minutes

E. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12

Cell: 2% KBr pellet

Results: See Figure 5

Identical to literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible

Instrument: Cary 118

ϵmax 263.5 = (1.391±0.017(δ)) x 10^3

269.5 = (1.954±0.016(δ)) x 10^3

276.5 = (1.763±0.007(δ)) x 10^3

Calculated from literature spectrum (Sadtler Standard Spectra)

ϵmax 263.5=1,687

269.8=2,693

276.5=2,348

No visible absorbance (350 to 800 nm) Solvent: Cyclohexane at 1 mg/ml

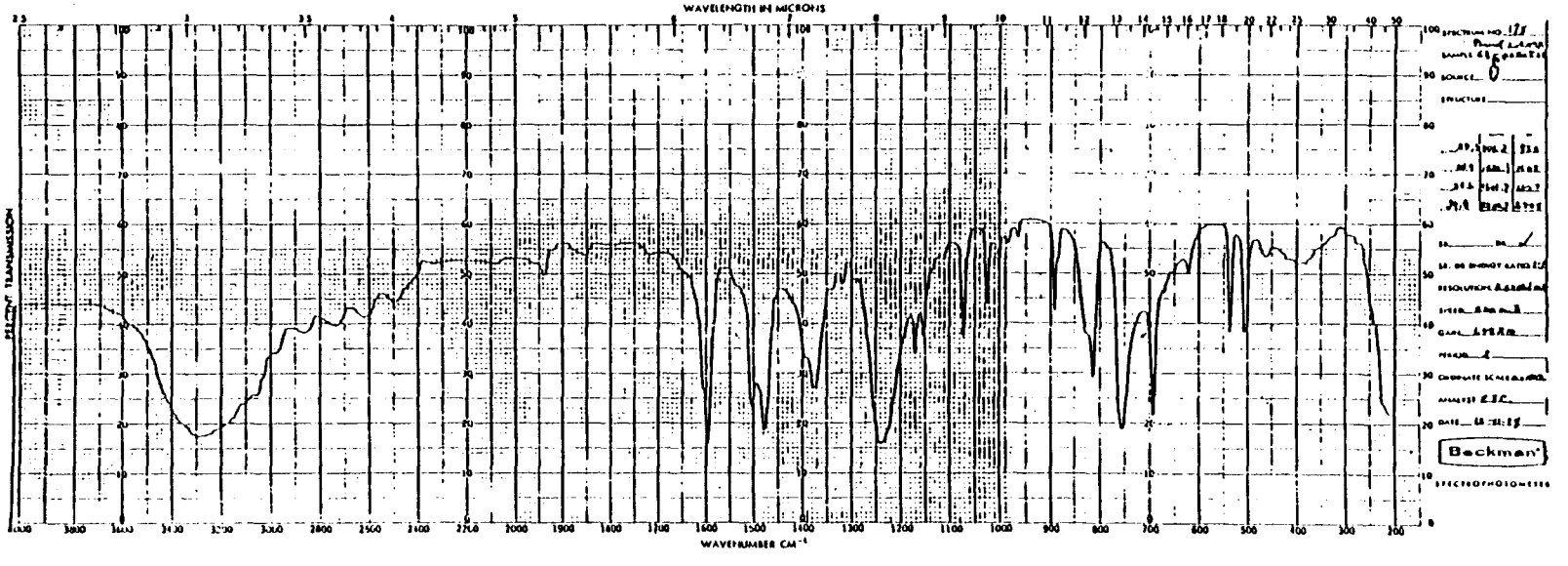

Figure 5. Infrared Absorption Spectrum of Phenol (Lot No. A4X)

3. Nuclear Magnetic Resonance

Instrument: Varian HA-100

Solvent: $CDCl_3$ with internal TMS

Assigments: (Refer to Figure 6)

(a) 6.80 δ

(b) 6.64 to 7.34 δ

(c) 6.36 δ (impurity)

Integration Ratios:

(a) 6.00

(b) 6.00

(c) 0.07

Identical to literature spectrum (Sadtler Standard Spectra)

CONCLUSIONS: The elemental analyses agree with theoretical values. The thin-layer chromatography shows an impurity spot at the origin. Vapor-phase chromatography has one homogeneous peak. The infrared, ultraviolet, and visible spectra are consistent with the structure. The nuclear magnetic resonance spectra show a small impurity (0.07 integration) at 6.36 δ.

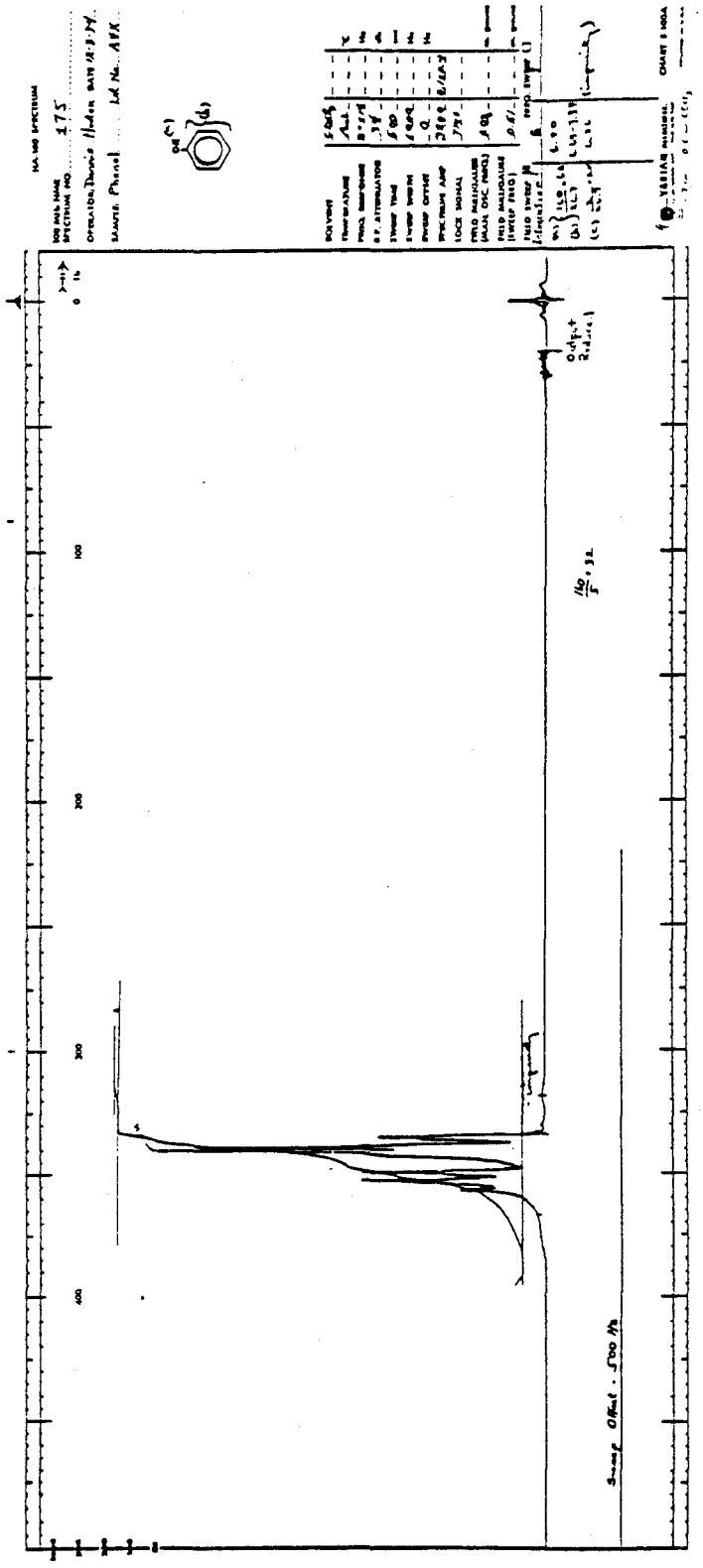

Figure 6. Nuclear Magnetic Resonance of Phenol (Lot No. A4X)

APPENDIX F

ANALYSIS OF PHENOL (LOT B4A) - MIDWEST RESEARCH INSTITUTE

APPENDIX F

Analysis of Phenol (Lot No. B4A)
Midwest Research Institute

A. ELEMENTAL ANALYSIS

Element	C	H
Theory	76.57	6.43
Determined	76.46	6.26
	76.68	6.45

B. MELTING POINT

Determined	Literature Values
41.0°-42.1°C (Du Pont 900 DTA)	(ultrapure material) 40.85°C (Merck Index, 1968)
39-°42°C (visual, capillary)	43°C (Dictionary of Organic Compounds, 1965)

C. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel F-254
Amount Spotted: 100 and 300 μg

System 1: Ethyl acetate : Petroleum Ether (90:10)
R_f: 0.84, origin (trace)
R_{st}: 1.00, origin

Ref. Standard: Phenol
Visualization: Ultraviolet (254 and 366 nm) and ferricyanide-ferric chloride

System 2: Benzene
R_f: 0.18
R_{st}: 1.00

D. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracer MT 220

Detection: Flame Ionization

System 1:

Column: 3% OV-17 on 80/100 mesh Chromosorb WHD; glass, 1.8 M x 4 mm

Oven Temp. Program: 100°C, 5 min; 100°-210°C at 10°C/min

Results: One homogeneous peak at 1.75 minutes

System 2:

Column: Chromosorb 102, 60/80 mesh; glass, 1.8 M x 2 mm

Oven Temp. Program: 100°-250°C at 10°C/minute Results:

Major peak and two impurities

E. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12

Cell: 1.5% KBr pellet

Results: See Figure 7

Identical to literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible

Instrument: Cary 118

Calculated from literature spectrum (Sadtler Standard Spectra)

^{e}max 264.5 nm=(13.94 ± 0.21(δ) x 10^2 ^{e}max 263.5=1,687

270.5 nm=(20.68 ± 0.29(δ) x 10^2 269.8=2,693

277.5 nm=(19.36 ± 0.26(δ)) x 10^2 276.5=2,348

Solvent: Cyclohexane

No visible absorbance (350 to 800 nm)
at 0.1 mg/ml
Solvent: Heptane

3. Nuclear Magnetic Resonance

Instrument: Varian HA-100
Solvent: $CDCl_3$ with internal TMS
Assigments: (See Figure 8)

(a) 6.32δ (b) 6.64-7.40δ

Integration Ratios:
(a) 0.96 (b) 5.04

Identical to literature spectrum (Sadtler Standard Spectra)

CONCLUSIONS: The elemental analyses agree with theoretical values. Thin-layer chromatography shows a trace impurity at the origin. Vapor-phase chromatography indicates two impurities (1.36% relative area). The infrared, ultraviolet, visible, and nuclear magnetic resonance conform to the structure.

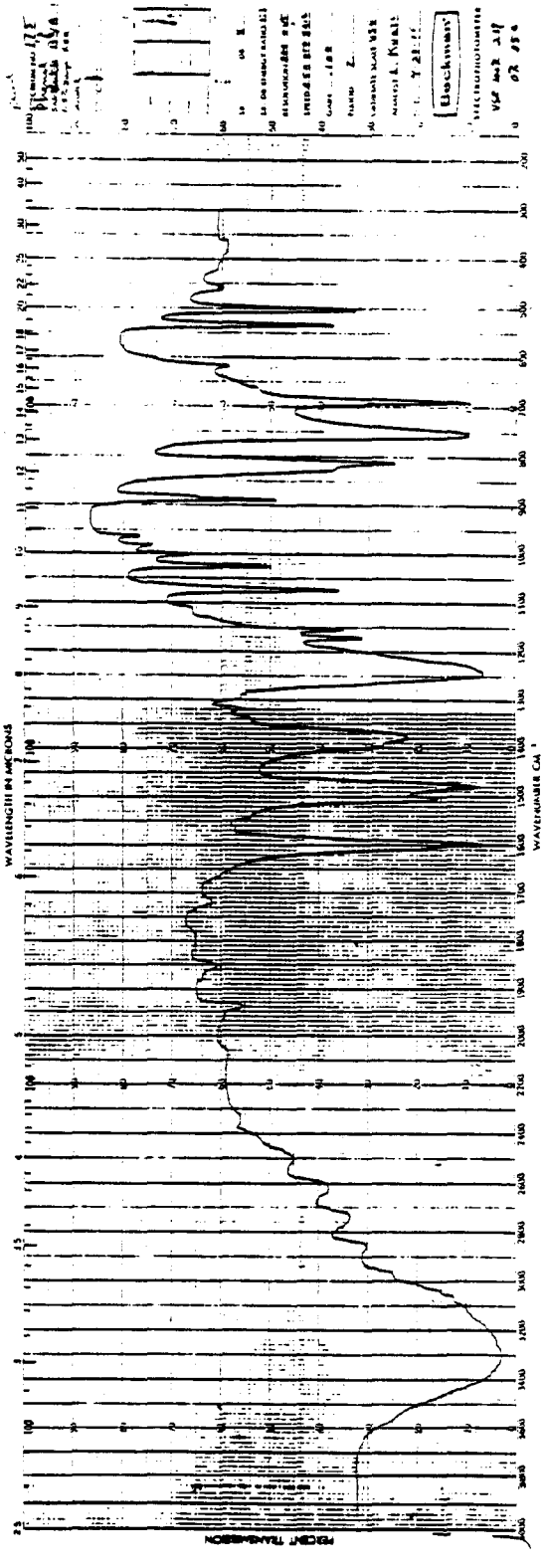

Figure 7. Infrared Absorption Spectrum of Phenol (Lot No. B4A)

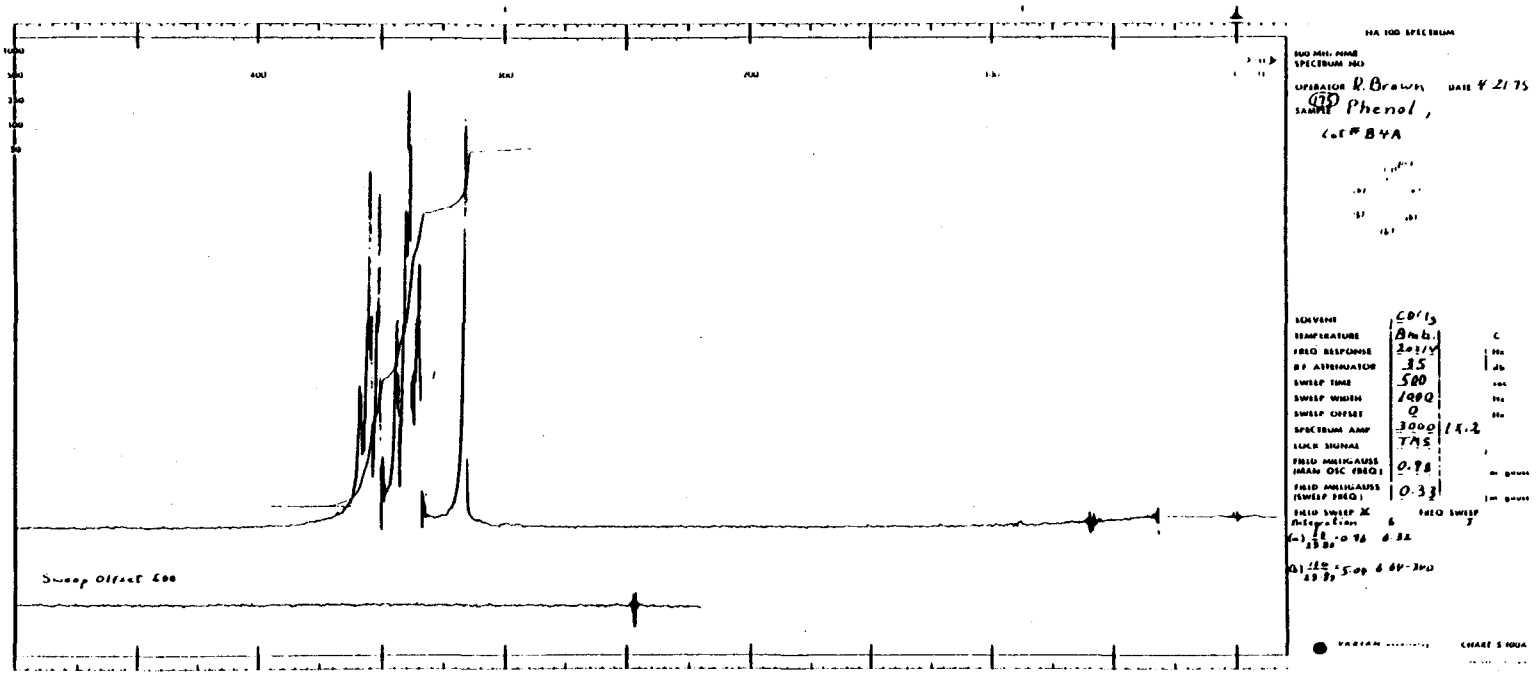

Figure 8. Nuclear Magnetic Resonance Spectrum of Phenol (Lot No. B4A)

APPENDIX G

ANALYSIS OF PHENOL (LOT 79380) - MIDWEST RESEARCH INSTITUTE

APPENDIX G

Analysis of Phenol (Lot No. 79380)
Midwest Research Institute

A. ELEMENTAL ANALYSIS

Element	C	H
Theory	76.57	6.43
Determined	76.53	6.50
	76.62	6.47

B. MELTING POINT

Determined	Literature Values
41.0°-41.7°C (Du Pont 900 DTA)	40.85°C (ultrapure material) (Merck Index, 1968)
39.5°-41.8°C (visual, sealed evacuated capillary)	43°C (Dictionary of Organic Compounds, 1965)

C. U.S.P. TITRATION

98.47°±0.02 (δ)%)
(USP, 1975)

D. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel 60F-254
Amount Spotted: 100 and 300 μg

System 1: Benzene, 100%

R_f: 0.20
R_{st}: 1.00

Ref. Standard: Phenol
Visualization: Iodine vapor and ultraviolet (254 nm)

System 2: Ethyl acetate Petroleum Ether (90:10)

R_f: 0.90
R_{st}: 0.99

E. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracor MT 220

Detection: Flame ionization

Inlet temperature: 245°C

Detector temperature: 275°C

System 1:

Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m x 4 mm I.D.

Oven Temp. Program: 5 min at 100°C, then 100°-210°C at 10°C/minute

Results: One homogeneous peak, retention time 1.8 minutes

System 2:

Column: 100/120 Chromosorb 102, 1.8 m x 4 mm I.D., glass

Oven Temp. Program: 100°-250°C at 10°C/minute

Results: One homogeneous peak, retention time 15.2 minutes

F. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12

Cell: Melt on NaCl plates

Results: See Figure 9

Consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible

Instrument: Cary 118

λ max	$\epsilon \times 10^{-3}$
259 s	0.79±0.01 (δ)
265	1.397±.006 (δ)
268 s	1.365±.008 (δ)
271	2.027±.006 (δ)
278	1.794±.007 (δ)

s - denotes shoulder or inflection point.

Solvent: Cyclohexane

Literature Values (Sadtler Standard Spectra)

λ max (nm)	$\epsilon \times 10^{-3}$
263.5	1.687
269.5	2.693
276.5	2.348

Solvent: Cyclohexane

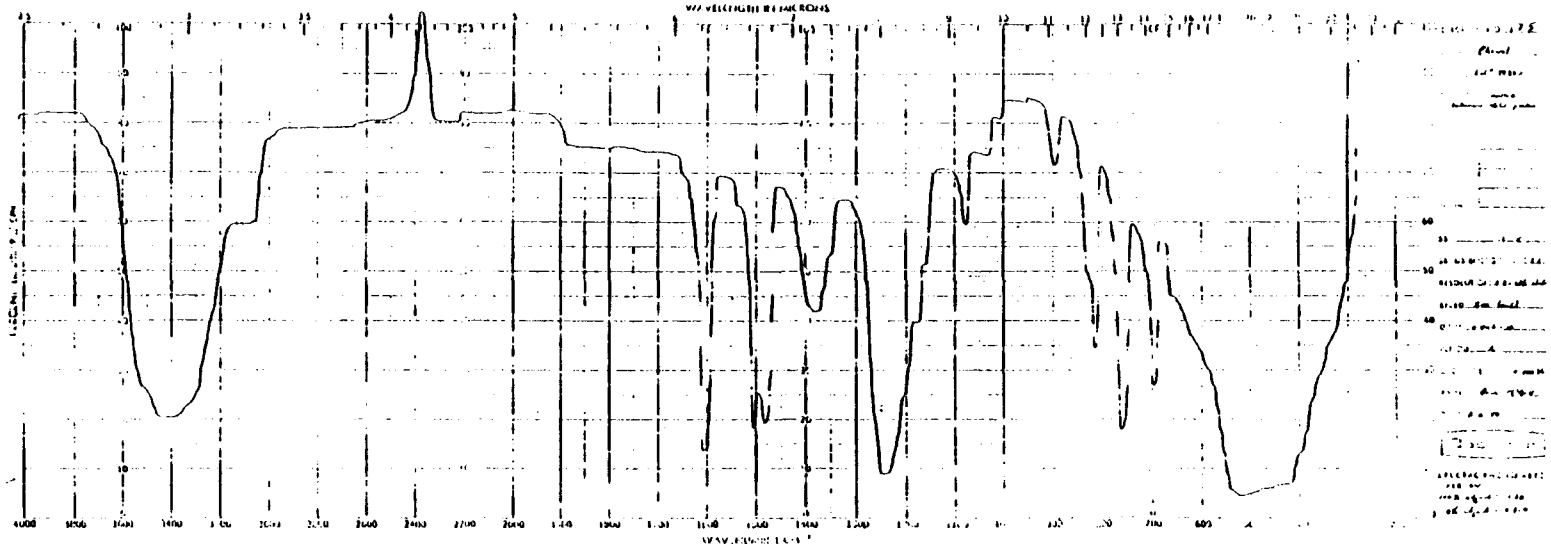

Figure 9. Infrared Absorption Spectrum of Phenol (Lot No. 79380)

3. Nuclear Magnetic Resonance

Instrument: Varian HA-100

Solvent: $CDCl_3$ with internal tetramethylsilane

Assigments: (See Figure 10 and attached spectrum)

(a) δ =6.13 ppm

(b) δ =6.78-7.44 ppm

Integration Ratios:

(a) 1.00

(b) 5.00

Consistent with literature spectrum

CONCLUSIONS: The elemental analyses agree with the theoretical values. Titration using the U.S.P. method indicates 98.47% purity. Thin-layer and vapor-phase chromatography indicate one homogeneous component. The infrared, ultraviolet, and nuclear magnetic resonance spectra are in agreement with the structure of the major component, phenol.

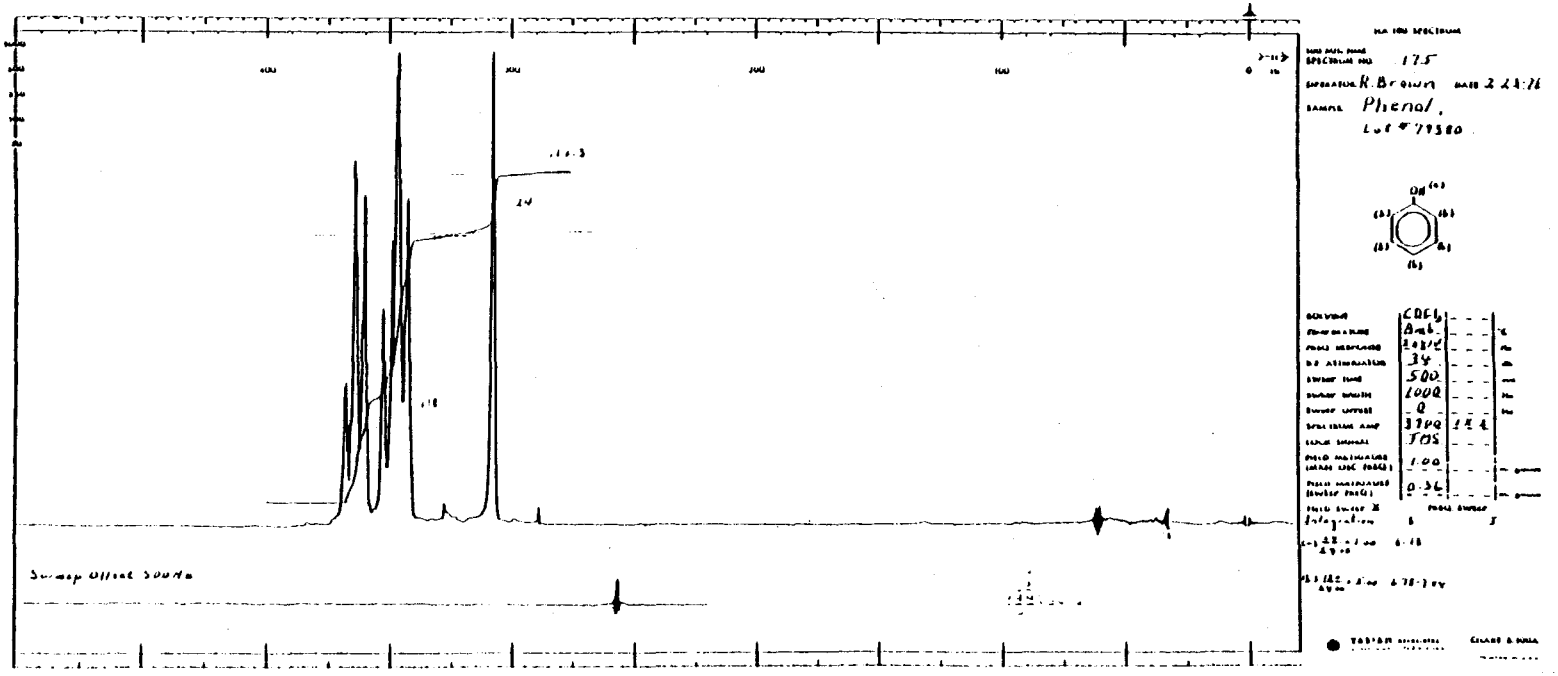

Figure 10. Nuclear Magnetic Resonance Spectrum of Phenol (Lot No. 79380)

APPENDIX H

ANALYSES OF AQUEOUS PHENOL SOLUTIONS

APPENDIX H

Analyses of Aqueous Phenol Solutions

Theoretical Concentration (ppm)	Number of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
5000	8	5237	9.8	4500-6120
2500	1	2800		

Review of the Bioassay of Phenol* for Carcinogenicity
by the Data Ealuation/Risk Assessment Subgroup Subgroup of the
Clearinghouse on Environmental Carcinogens

February 15, 1980

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Phenol for carcinogenicity.

The primary reviewer for the report on the bioassay of phenol indicated that there were no particular shortcomings or other issues to highlight. No evidence was found that phenol was carcinogenic under the conditions of test. The reviewer said that the administration of phenol in the drinking water diminished its chances of acting as an "irritant."

The secondary reviewer pointed out the elevated incidence of leukemias in treated male rats. Because of this finding and the widespread use of phenol, he suggested that it be considered for retest.

The primary reviewer moved that the report on the bioassay of phenol be accepted as written and, further, the chemical be considered for retest because of the elevated incidence of leukemias in male rats. The motion was seconded and approved unanimously.

Members present were:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
David B. Clayson, Eppley Institute for Research in Cancer
Joseph Highland, Environmental Defense Fund
William Lijinsky, Federick Cancer Research Center
Henry C. Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Louise Strong, University of Texas Health Sciences Center

* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

*U S GOVERNMENT PRINTING OFFICE: 311-201/3143

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