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BIOASSAY OF

STYRENE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

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REPORT ON THE BIOASSAY OF STYRENE
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of styrene conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of styrene was conducted by Litton Bionetics, Inc., Kensington, Maryland, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. N. P. Page (1,2), Dr. E. K. Weisburger (1) and Dr. J. H. Weisburger (1,3). The principal investigators for the contract were Dr. F. M. Garner (4) and Dr. B. M. Ulland (4,5). Mr. S. Johnson (4) was the coprincipal investigator for the contract. Animal treatment and observation were supervised by Mr. R. Cypher (4), Mr. D. S. Howard (4) and Mr. H. D. Thornett (4); Mr. H. Paulin (4) analyzed dosed feed mixtures. Ms. J. Blalock (4) was responsible for data collection and assembly. Chemical analyses were performed by Litton Bionetics, Inc. (4) and Midwest Research Institute (6) and the analytical results were reviewed by Dr. N. Zimmerman (7).

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Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (10); the statistical analysis was performed by Mr. R. M. Helfand (7) and Dr. J. P. Dirkse, III (11), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (12).

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SUMMARY

A bioassay for the possible carcinogenicity of styrene was conducted using Fischer 344 rats and B6C3F1 mice. Styrene was administered by gavage to groups of 50 male and 50 female animals of each species. Forty rats of each sex and twenty mice of each sex were placed on test as vehicle controls. The high, medium, and low dosages of styrene administered to rats were, respectively, 2000, 1000 and 500 mg/kg. The high and low dosages administered to mice were 300 and 150 mg/kg, respectively. The compound was administered for 78 weeks to high and medium dose rats, for 103 weeks to low dose rats, and for 78 weeks to mice. The period of compound administration was followed by an observation period of 27 weeks for high and medium dose rats, 1 week for low dose rats, and 13 weeks for mice.

Mortality among male and female high dose rats was significantly higher than that among their respective vehicle controls. In response to this elevated and early mortality, an additional dosed group of each sex was included in the chronic bioassay. No significant positive association was apparent between dosage and mortality among any other dosed rat groups. For mice, there was a significant positive association between mortality and the dosages of styrene administered to males, but not to females. Adequate numbers of animals in all groups, except for the high dose male and female rats, survived sufficiently long to be at risk from late-developing tumors. Slight dose-related mean body weight depression was apparent when male rats and female mice were compared to their respective vehicle controls, indicating that the dosages administered to these animals during the chronic bioassay may have approximated the maximum tolerated dosages. There was no distinct depression in mean body weight when dosed female rats and dosed male mice were compared to their respective vehicles controls. However, since there was significant accelerated mortality among high dose female rats, it is possible that the dosage administered to the medium dose female rats may have exceeded the maximum tolerated dosage.

In male mice, there was a significant positive association between styrene dosage and the incidences of a combination of adenomas and carcinomas of the lung. This finding was supported by the high dose to control Fisher exact comparison. However, the variation of the incidence of these neoplasms in historical control male mice at this laboratory does not permit a firm conclusion of carcinogenicity. There was no significant difference between tumor incidence at any other site in male mice, or at any site in rats or female mice, when dosed groups were compared to vehicle controls.

The findings of an increased incidence of a combination of adenomas and carcinomas of the lung provided suggestive evidence for the carcinogenicity of styrene in male B6C3F1 mice. However, it is concluded that, under the conditions of this bioassay, no convincing evidence for the carcinogenicity of the compound was obtained in Fischer 344 rats or B6C3F1 mice of either sex.

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I. INTRODUCTION

Styrene (Figure 1) (NCI No. C02200), a widely used intermediate in the manufacture of plastics, elastomers, and resins, was selected for bioassay by the National Cancer Institute because of the widespread use of this compound and a lack of adequate carcinogenicity data.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is ethenylbenzene.* It is also called vinylbenzene, vinylbenzol, styrolene, styrol, styrole, styropol, styropor, styron, cinnamene, cinnamol, phenethylene, phenylethylene, and phenylethene.

Styrene is used in the manufacture of high impact or rubber-modified polystyrene (32.9 percent of total U.S. styrene use), polystyrene (25.9 percent), styrene-butadiene rubber (10.2 percent), acrylonitrile-butadiene-styrene resins (9.3 percent), styrene-butadiene resins (6.2 percent), unsaturated polyester resins (6.7 percent), and styrene-acrylonitrile resins (1.4 percent) (Chemical Marketing Reporter, 1977).

Styrene is currently manufactured in commercial quantities (in excess of 1000 pounds or $1000 in value annually) by 12 U.S. companies at 14 production facilities having a combined capacity of 9.18 x 10^9 pounds per year (Chemical Marketing Reporter, 1977). U.S. production of styrene was approximately 4.67 x 10^9 pounds in 1975 (U.S.

*The CAS registry number is 100-42-5.

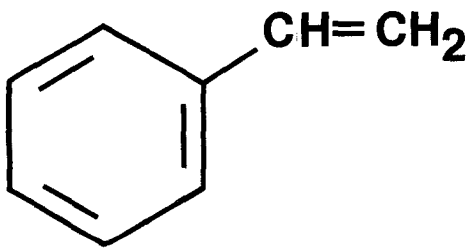


FIGURE 1
CHEMICAL STRUCTURE OF STYRENE

International Trade Commission, 1977); 6.3×10^9 pounds in 1976; and 6.62×10^9 pounds in 1977 (Chemical Marketing Reporter, 1977). Sales of styrene by U.S. producers totaled 1.96×10^9 pounds in 1975 (U.S. International Trade Commission, 1977). U.S. imports of styrene in 1974 amounted to 6.09×10^7 pounds (U.S. International Trade Commission, 1976), and 15 percent of the annual U.S. production (presumably 9.93×10^7 pounds in 1977) is reportedly for export (Chemical Marketing Reporter, 1977).

A potential for exposure exists for a large number of workers in several industries, most notably the styrene producing, plastics, resins, and synthetic rubber industries. Of the 14 facilities which produce styrene, production is captive* in at least 3, mostly captive in at least 1, and partly captive in at least 4 (Stanford Research Institute, 1977); consequently, the potential for exposure to styrene at these sites may be less than that at facilities which produce the compound for other than captive uses.

Numerous cases of "styrene sickness" have been reported among industrial workers following exposure to styrene vapors or mists. Symptoms include headache, fatigue, weakness, depression, and unsteadiness or narcosis. At least one case of toxic retrobulbar neuritis has been reported, and many exposed workers have exhibited abnormal electroencephalograms. Dermal contact with liquid styrene

*That is, the styrene remains in a closed system after production and is directly employed as an intermediate in the synthesis of other materials.

produces drying and cracking of the skin, and styrene vapor in concentrations above 200 ppm is a primary irritant to mucosal surfaces. In the body, styrene is largely metabolized to hippuric acid (Gosselin et al., 1976).

II. MATERIALS AND METHODS

A. Chemicals

Six batches of styrene, containing t-butylcatechol as an inhibitor, were purchased for the bioassay. One batch of styrene was purchased from Dow Chemical Company, Midland, Michigan. Chemical analysis was performed by Litton Bionetics, Inc., Kensington, Maryland. The experimentally determined refractive index, $n_D^{20} = 1.5740$, was compared with a literature value of $n_D^{20} = 1.5463$ (Windholtz, 1976). The results of nuclear magnetic resonance (NMR) analysis were consistent with those expected based on the structure of the compound. Ultraviolet/visible (UV/VIS) analysis revealed λ_{max} of 250 nm with a molar extinction coefficient (ϵ) of 1.48×10^4.

Chemical analysis data are not available for the four batches of styrene purchased after this first batch.

The sixth batch of styrene was purchased from Amoco Chemicals Corporation, Chicago, Illinois. Chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. The experimentally determined range in boiling point, 142.6° to 142.7°C, was compared to the literature value of 145.2°C (Boundy and Boyer, 1952). Elemental analysis was within 1 percent of that expected based on the molecular formula of the chemical, C_8H_8. Vapor-phase chromatography indicated the major peak and one impurity that was 0.3 percent of the total area. The results of infrared (IR) and NMR analyses were

consistent with those reported in the literature (Sadtler Standard Spectra). UV/VIS analysis revealed the following:

Amoco Chemicals Corp. Sample		Sadtler Standard Spectra	
λ_{max} (nm)	ϵ	λ_{max} (nm)	ϵ
247	14.93×10^3	245.5	15.3×10^3
273.5	7.89×10^2	272.5	9.19×10^2
282	7.78×10^2	281	9.32×10^2
291	5.82×10^2	289	6.69×10^2

Throughout this report, the term styrene is used to represent these materials.

B. Dosage Preparation

The inhibitor, t-butylcatechol, was removed from the test chemical with anhydrous calcium sulfate, white Drierite®, 2 to 4 weeks prior to dosage preparation. Drierite® crystals were placed in the styrene and refrigerated at 4°C for a 2- to 4-week period. The treated styrene was mixed with corn oil (Great Atlantic & Pacific Tea Company, New Baltimore, Maryland) and used within 2 hours. Excess portions of the corn oil and styrene mixtures were disposed of rather than stored. The concentrations of styrene in corn oil ranged from 21.5 to 43 percent for rats and from 3.2 to 6.4 percent for mice.

C. Animals

The two animal species, Fischer 344 rats and B6C3F1 mice, used in the carcinogenicity bioassay were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. Rats were supplied by A. R. Schmidt, Madison, Wisconsin, and Charles River

Breeding Laboratories, Inc., Wilmington, Massachusetts. Mice were supplied by Charles River Breeding Laboratories, Inc.

Rats and mice, approximately 4 weeks old when received, were examined and any obviously ill or runted animals were killed. Animals which did not manifest clinical signs of disease after 2 weeks of quarantine were assigned to groups and distributed among cages so that the average body weight per cage was approximately equal for a given species and sex. The animals were then placed on test.

D. Animal Maintenance

Animals were housed by species in rooms maintained at 22° to 26°C and 45 to 55 percent relative humidity. Incoming air was filtered through HEPA filters (Flanders Filters, McLean, Virginia) at a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided 8 hours per day (9:00 a.m. to 5:00 p.m.).

Rats were housed four per cage by sex and mice were housed five per cage by sex. Throughout the study dosed and vehicle control animals of both species were housed in polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) suspended from aluminum racks. Racks were fitted with a continuous piece of stainless steel mesh over which a sheet of filter paper was firmly secured. Filter paper was changed at 2-week intervals, when the racks were sanitized. Clean cages and bedding (Ab-sorb-dri® hardwood chip bedding, Wilner Wood Products Company, Norway, Maine) were provided twice weekly.

Acidulated water (pH 2.5) was supplied to animals in water bottles which were changed and washed twice weekly. Sipper tubes were washed at weekly intervals. All animals were supplied with Wayne Lab-Blox® meal in hanging stainless steel hoppers which were refilled three times per week and sanitized weekly. Food and water were available ad libitum for both species.

All dosed and control rats were housed in a room with other rats receiving diets containing* 4,4'-methylenebis(N,N-dimethyl)-benzenamine (101-61-1); p-quinone dioxime (105-11-3); and NTA trisodium salt (5064-31-3).

All dosed and control mice were housed in a room with mice receiving diets containing nitrofen (1836-75-5); p-nitrosodiphenylamine (156-10-5); acetylaminofluorene (53-96-3); amitrole (61-82-5); nitrilotriacetic acid (139-13-9); and NTA trisodium salt (5064-31-3).

E. Gastric Intubation

Animals were intubated five days per week. Animals of each sex within a dosed group received the same dosage. All animals were weighed and dosages adjusted once monthly, based on group mean body weight. Thus, although the ratio of dose to weight remained constant, the total dosage administered fluctuated with an increase or decrease in group mean body weight.

*CAS registry numbers are given in parentheses.

F. Selection of Initial Dose Levels

To establish the concentrations of styrene for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. Styrene mixed with corn oil was introduced by gavage to five of the six rat groups at dosages of 681, 1000, 1470, 2150 and 3160 mg styrene/kg body weight and to five of the six mouse groups at dosages of 147, 215, 316, 464 and 681 mg/kg. The sixth group of each species served as a vehicle control group, receiving only corn oil by gavage.

Animals were intubated 5 days per week for 7 weeks, followed by a 1-week observation period. Individual body weights were recorded weekly throughout the study. Upon termination of the study all survivors were euthanized and necropsied.

The following table indicates the mean body weight gain, relative to controls, and survival observed in each of the rat groups at the end of the subchronic test.

RAT SUBCHRONIC STUDY RESULTS

mg/kg	Mean Body Weight Gain (%)* Males	Females	Survival** Males	Females
3160	-16	+3	3/5	4/5
2150	-15	+8	5/5	4/5
1470	+ 4	+6	5/5	4/5
1000	+10	+1	4/5	5/5
681	+ 6	+2	5/5	5/5
0	--	--	5/5	5/5

No other clinical abnormalities, which could be attributed to administration of the compound, were observed. The high dosage selected for administration to dosed rats in the chronic bioassay was 2000 mg/kg.

The following table indicates the mean body weight gain, relative to controls, and survival observed in each of the mouse groups at the end of the subchronic test.

MOUSE SUBCHRONIC STUDY RESULTS

mg/kg	Mean Body Weight Gain (%)* Males	Females	Survival** Males	Females
681	0	+ 4	1/5	1/5
464	- 5	- 9	4/5	5/5
316	- 8	- 9	5/5	4/5
215	+ 4	- 1	4/5	5/5
147	- 5	- 7	5/5	5/5
0	--	--	5/5	5/5

*+ is indicative of mean body weight gain greater than that of controls.
- is indicative of mean body weight gain less than that of controls.

**Number of animals observed/number of animals originally in group.

No other clinical abnormalities, which could be attributed to administration of the compound, were observed. The high dosage selected for administration to dosed mice in the chronic bioassay was 300 mg/kg.

G. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, dosages administered, and duration of treated and untreated observation periods) are summarized in Tables 1 and 2.

All rats were approximately 6 weeks old at the time the test was initiated and were placed on test on the same day. These dosed rats were intubated with styrene at a level of 2000 and 1000 mg/kg for 78 weeks followed by a 27-week observation period, when no test chemicals were used. Throughout this report those rats receiving the former dosage are referred to as the high dose groups and those receiving the latter dosage are referred to as the medium dose groups.*

Due to excessive mortality in the high and medium dose groups, an additional group of male and female rats were placed on test in week 23. These dosed rats were intubated with styrene at a level of 500 mg/kg for 103 weeks, followed by a 1-week observation period, when no test chemicals were used. Separate vehicle controls were also started for this group. Throughout this report, those rats

*The initial number of animals assigned to these groups was 60; however, in week 8 the number of animals in each group was reduced to 50.

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
STYRENE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	STYRENE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
LOW DOSE VEHICLE CONTROL	20	0		104
HIGH AND MEDIUM DOSE VEHICLE CONTROL	20	0		105
LOW DOSE	50	500	103	
		0		1
MEDIUM DOSE	50	1000	78	
		0		27
HIGH DOSE	50	2000	78	
		0		27
FEMALE				
LOW DOSE VEHICLE CONTROL	20	0		104
HIGH AND MEDIUM DOSE VEHICLE CONTROL	20	0		105
LOW DOSE	50	500	103	
		0		1
MEDIUM DOSE	50	1000	78	
		0		27
HIGH DOSE	50	2000	78	
		0		27

[a]Dosages, given in mg/kg body weight, were administered by gavage 5 consecutive days per week.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
STYRENE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	STYRENE DOSAGE[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
VEHICLE CONTROL	20	0		91
LOW DOSE	50	150	78	
		0		13
HIGH DOSE	50	300	78	
		0		13
FEMALE				
VEHICLE CONTROL	20	0		91
LOW DOSE	50	150	78	
		0		13
HIGH DOSE	50	300	78	
		0		13

[a]Dosages, given in mg/kg body weight, were administered by gavage 5 consecutive days per week.

receiving 500 mg/kg and their controls are referred to as the low dose and low dose vehicle control groups, respectively.

Mice were approximately 6 weeks old at the time the test was initiated and all were placed on test on the same day. Dosed mice were intubated with styrene at levels of 300 and 150 mg/kg for 78 weeks followed by a 13-week observation period, when no test chemicals were used. Throughout this report those mice receiving the former dosage are referred to as the high dose groups and those receiving the latter dosage are referred to as the low dose groups.*

Vehicle control animals were intubated with corn oil at a level of 10 ml/kg five times per week.

H. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment and body weights of high dose, medium dose, and high and medium dose vehicle control rats and all mice were recorded once a week for the first 6 weeks, every 2 weeks for the next 12 weeks, and at monthly intervals thereafter. Body weights of low dose and low dose vehicle control rats were recorded at monthly intervals throughout the bioassay. All animals were inspected twice daily. Food consumption data were collected at monthly intervals from 20 percent of the animals in each group.

*The initial number of animals assigned to these groups was 60; however, in week 8 the number of animals in each group was reduced to 50.

All moribund animals, animals that developed large, palpable masses that jeopardized their health, or animals that survived until the end of the bioassay were euthanized using carbon dioxide. Necropsies were performed immediately on these animals and on all animals found dead during the bioassay. Gross and microscopic examinations were performed on all major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in a 10 percent neutral buffered formalin solution, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, uterus, mammary gland, and ovary.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were recorded in each group at the time that the test was initiated.

I. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, 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). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported 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 was 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 purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing

these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

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 percent of a large number of identical experiments, the true ratio of the risk in a treated 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 (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

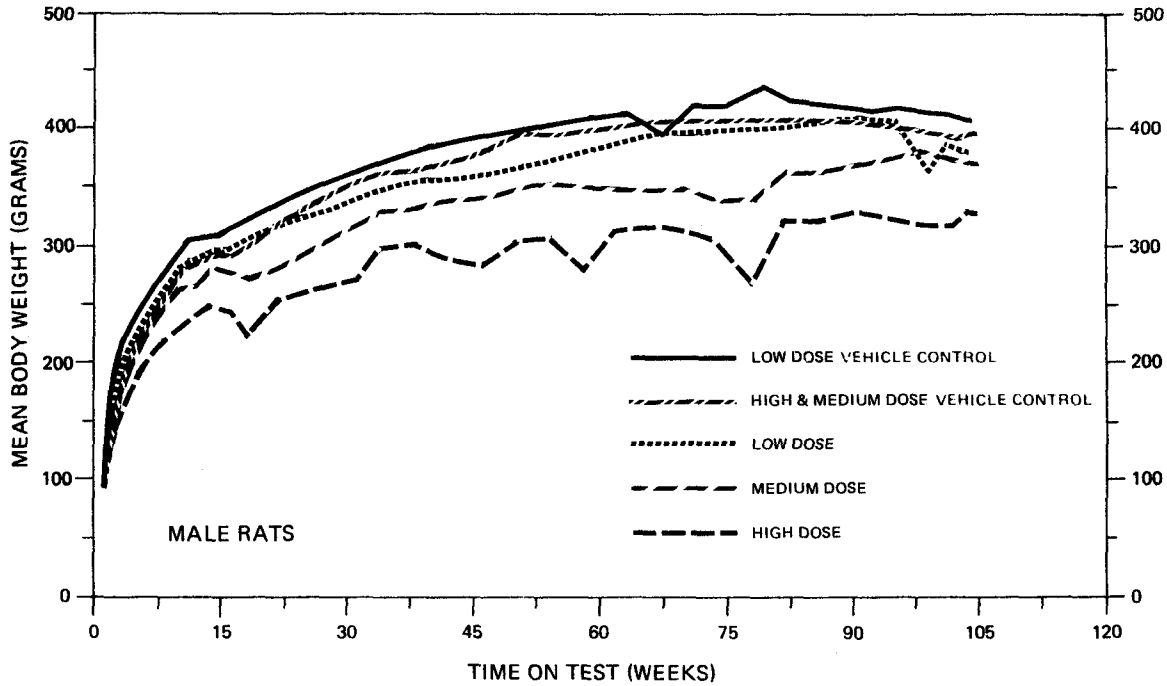
Distinct dose-related mean body weight depression was apparent in male rats. In female rats the mean body weight among the medium dose group was slightly less than that of their vehicle control (Figure 2). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

No other clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female rats in the vehicle control and styrene-dosed groups are shown in Figure 3. The Cox test for comparison of survival of a dosed group relative to its vehicle control was significant for high dose males ($P < 0.001$) and high dose females ($P < 0.001$). However, the Cox test was not significant when comparing each of the other male or female dosed groups with their vehicle controls.

There were inadequate numbers of high dose male rats at risk from late-developing tumors as only 12 percent (6/50) survived on test past week 53. However, survival was adequate in the other rat groups, as 94 percent (47/50) of the medium dose, 88 percent (44/50) of the low dose, 90 percent (18/20) of the high and medium dose vehicle controls and 85 percent (17/20) of the low dose vehicle controls survived on test for at least 90 weeks.



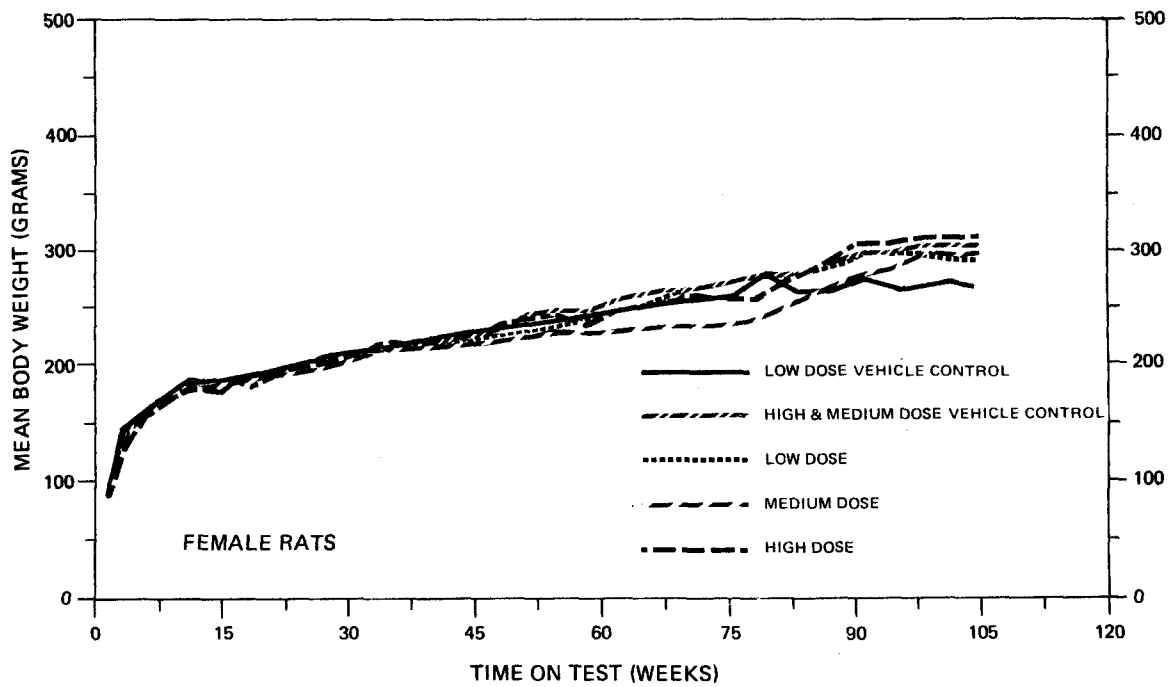
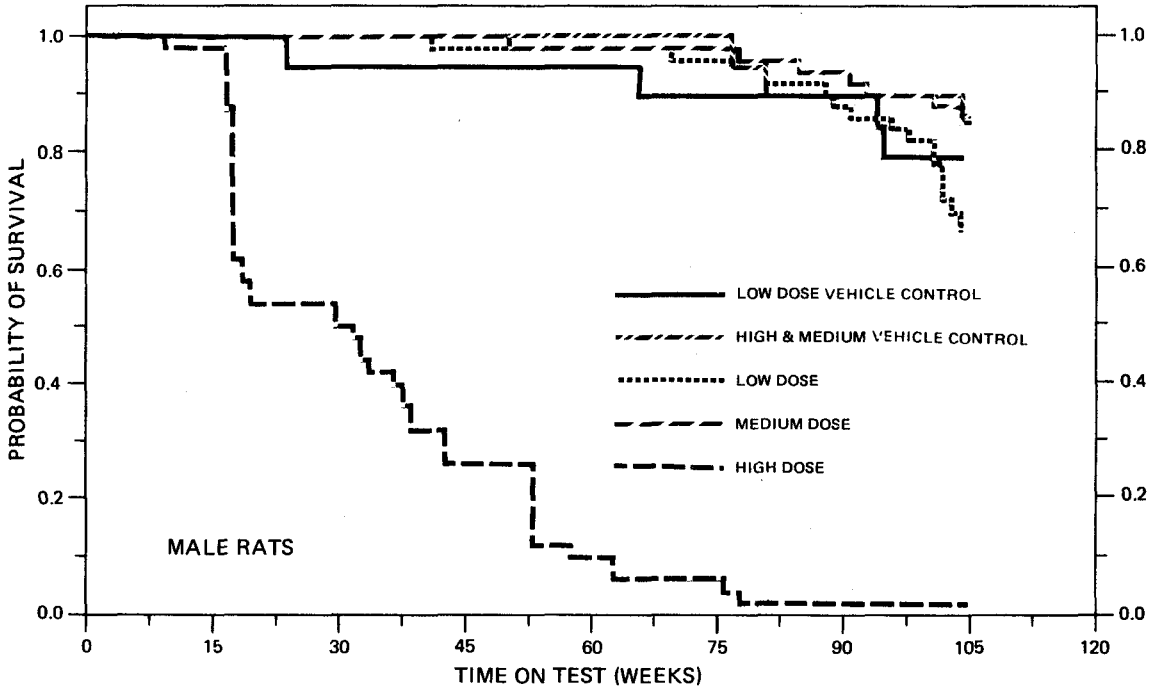


FIGURE 2
GROWTH CURVES FOR STYRENE CHRONIC STUDY RATS



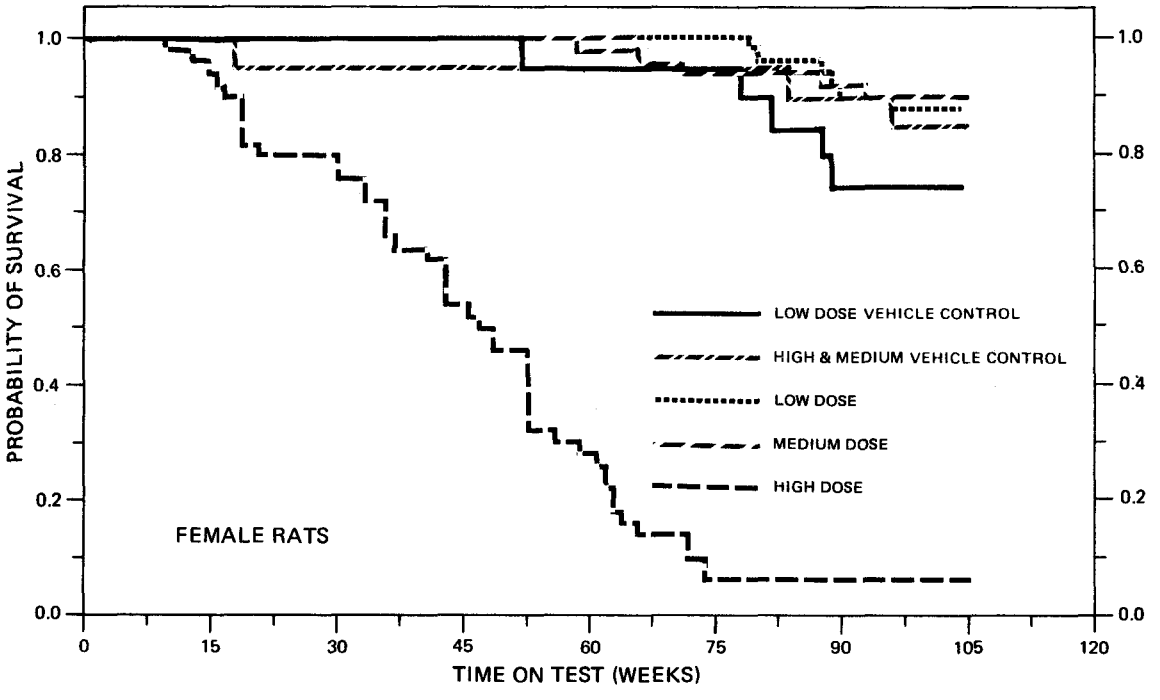


FIGURE 3
SURVIVAL COMPARISONS OF STYRENE CHRONIC STUDY RATS

Survival was poor for high dose female rats as all but 14 percent (7/50) were dead by week 70. However, there were adequate numbers of female rats at risk from late-developing tumors in the remaining four groups, as 92 percent (46/50) of the medium dose, 92 percent (46/50) of the low dose, 90 percent (18/20) of the high and medium dose vehicle controls and 75 percent (15/20) of the low dose vehicle controls survived on test for at least 90 weeks.

C. Pathology

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

A variety of neoplastic lesions was seen with approximately equal frequency in the vehicle control and dosed rats. In the high dose rats of both sexes, there was a distinct lack of neoplasia. This was most likely due to a large number of early deaths which occurred in high dose rats.

A variety of inflammatory, degenerative and proliferative lesions commonly seen in aged Fischer 344 rats was observed in dosed and vehicle control animals. Hepatic necrosis, observed in several of the high dose rats, may be related to the high mortality observed in these groups.

Based on the results of this pathology examination, styrene was not carcinogenic in Fischer 344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the vehicle control or styrene-dosed groups and where such tumors were observed in at least 5 percent of the group. There were inadequate numbers of high dose rats at risk from late-developing tumors; therefore, the high dose groups were excluded from the statistical analyses.

None of the statistical tests for any site in rats of either sex indicated a significant positive association between the administration of styrene and an increased tumor incidence.

A significant negative association between dose and the combined incidence of chromophobe adenomas or chromophobe carcinomas was indicated in female rats.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH STYRENE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE VEHICLE CONTROL	MEDIUM DOSE VEHICLE CONTROL	LOW DOSE	MEDIUM DOSE
Skin and Subcutaneous Tissue: Fibroma[b]	0/20(0.00)	0/20(0.00)	3/50(0.06)	0/50(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.250	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	101	---
Pituitary: Chromophobe Adenoma[b]	1/17(0.06)	2/18(0.11)	2/44(0.05)	2/45(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.773	0.400
Lower Limit	---	---	0.044	0.032
Upper Limit	---	---	44.565	5.250
Weeks to First Observed Tumor	95	105	104	105
Adrenal: Pheochromocytoma[b]	2/20(0.10)	1/19(0.05)	1/48(0.02)	4/49(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.208	1.551
Lower Limit	---	---	0.004	0.171
Upper Limit	---	---	3.830	74.767
Weeks to First Observed Tumor	104	105	104	105

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE VEHICLE CONTROL	MEDIUM DOSE VEHICLE CONTROL	LOW DOSE	MEDIUM DOSE
Testis: Interstitial-Cell Tumor[b]	15/20(0.75)	19/20(0.95)	42/47(0.89)	48/50(0.96)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.191	1.011
Lower Limit	---	---	0.924	0.942
Upper Limit	---	---	1.578	1.149
Weeks to First Observed Tumor	94	77	70	85

[a]Treated groups received doses of 500 or 1000 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Fisher exact test for the comparison of a treated group with its control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. A negative designation (N) indicates a lower incidence in the treated group than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH STYRENE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE VEHICLE CONTROL	MEDIUM DOSE VEHICLE CONTROL	LOW DOSE	MEDIUM DOSE
Pituitary: Chromophobe Adenoma or Chromophobe Carcinoma[b]	5/20(0.25)	5/18(0.28)	7/44(0.16)	3/43(0.07)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.636	0.251
Lower Limit	---	---	0.205	0.045
Upper Limit	---	---	2.290	1.169
Weeks to First Observed Tumor	88	84	104	105
Mammary Gland: Fibroadenoma[b]	3/20(0.15)	2/20(0.10)	2/50(0.04)	3/50(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.267	0.600
Lower Limit	---	---	0.024	0.076
Upper Limit	---	---	2.190	6.860
Weeks to First Observed Tumor	88	105	104	105
Mammary Gland: Fibroadenoma or Adenocarcinoma NOS[b]	3/20(0.15)	2/20(0.10)	3/50(0.06)	3/50(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.400	0.600
Lower Limit	---	---	0.060	0.076
Upper Limit	---	---	2.802	6.860
Weeks to First Observed Tumor	88	105	104	105

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE VEHICLE CONTROL	MEDIUM DOSE VEHICLE CONTROL	LOW DOSE	MEDIUM DOSE
Uterus: Endometrial Stromal Polyp[b]	4/18(0.22)	3/20(0.15)	9/48(0.19)	5/50(0.10)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.844	0.667
Lower Limit	---	---	0.281	0.147
Upper Limit	---	---	3.406	4.014
Weeks to First Observed Tumor	104	105	105	105

[a]Treated groups received doses of 500 or 1000 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Fisher exact test for the comparison of a treated group with its control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. A negative designation (N) indicates a lower incidence in the treated group than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

rats by styrene that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Slight dose-related mean body weight depression was observed among female mice but not among male mice (Figure 4).

No other clinical signs were recorded.

B. Survival

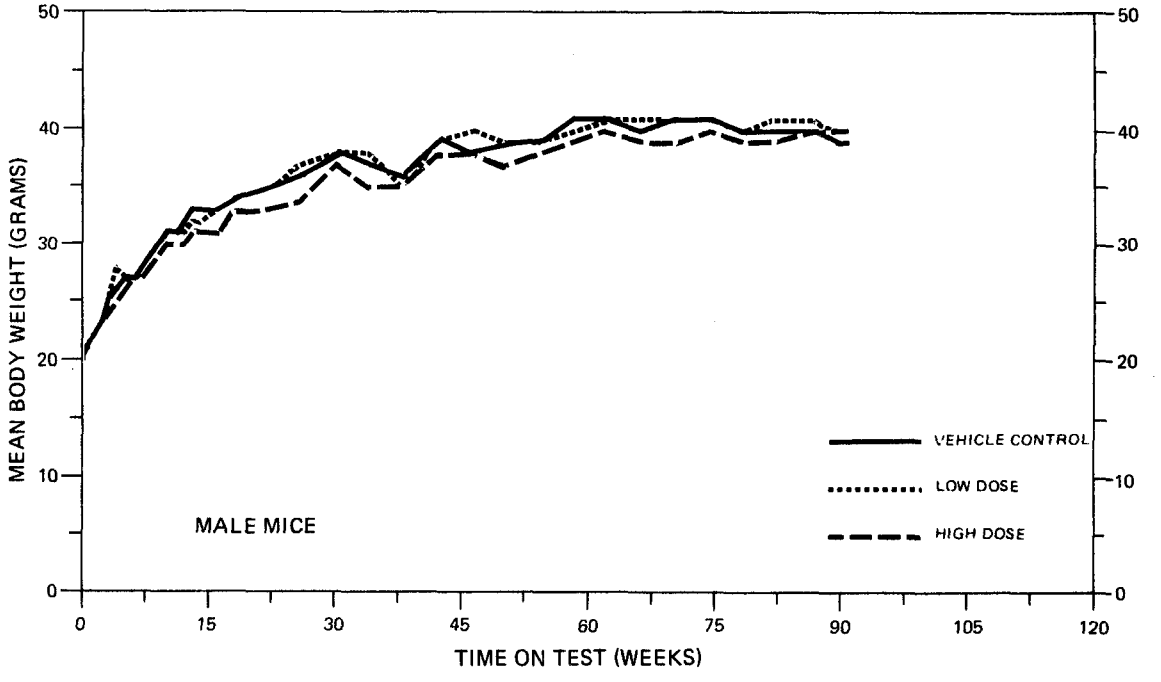
The estimated probabilities of survival for male and female mice in the vehicle control and styrene-dosed groups are shown in Figure 5. The Tarone test for association between dosage and mortality was significant for mice male ($P = 0.003$) but not for female mice.

There were adequate numbers of male mice at risk from late-developing tumors, as 78 percent (39/50) of the high dose, 92 percent (46/50) of the low dose and 100 percent (20/20) of the vehicle controls survived on test until the termination of the study.

There were adequate numbers of female mice at risk from late-developing tumors, as 76 percent (38/50) of the high dose, 80 percent (40/50) of the low dose and 90 percent (18/20) of the vehicle controls survived on test until the termination of the study. Five low dose females were missing, four in week 21 and one in week 74.

C. Pathology

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



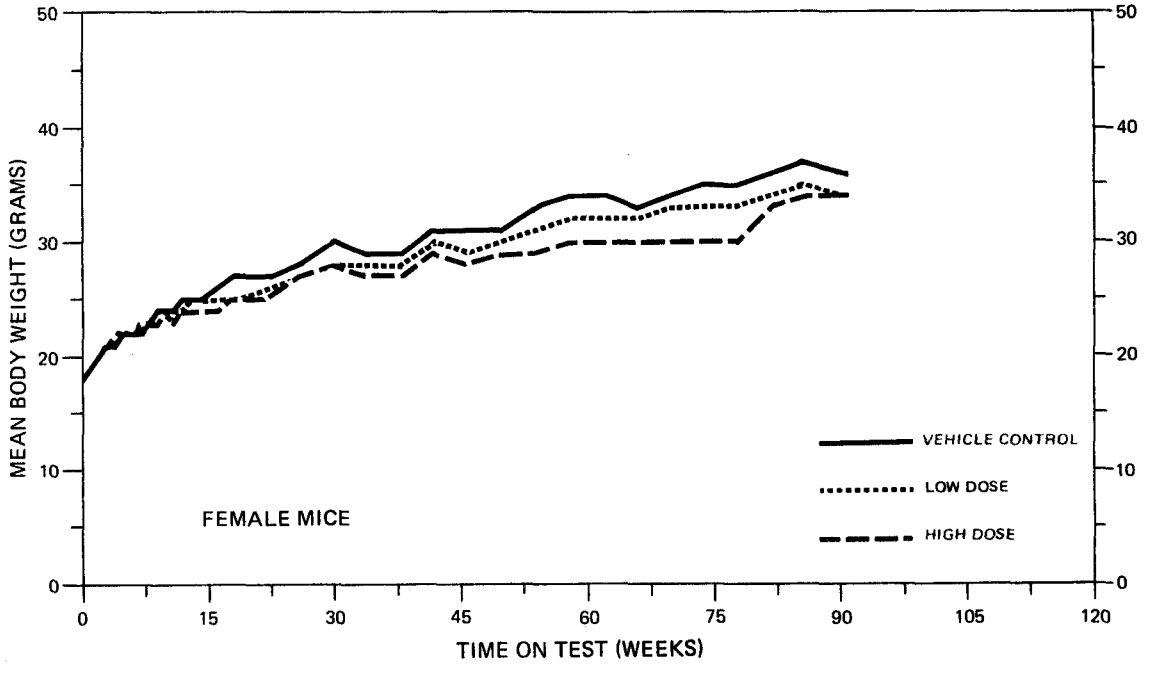
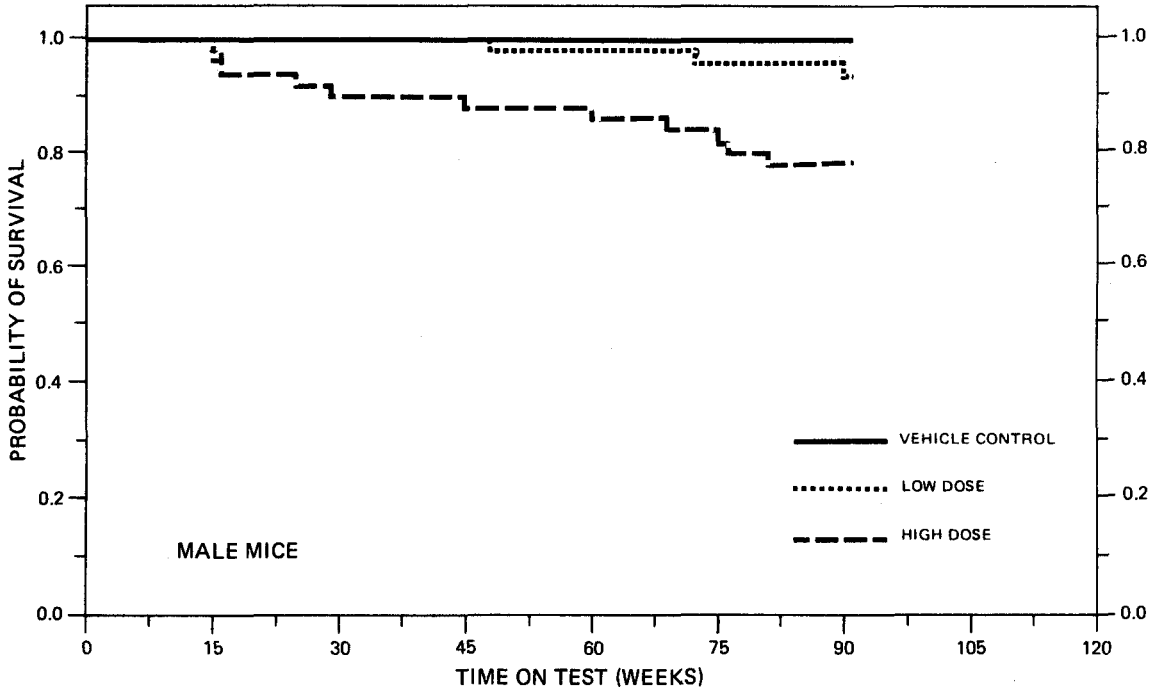


FIGURE 4
GROWTH CURVES FOR STYRENE CHRONIC STUDY MICE



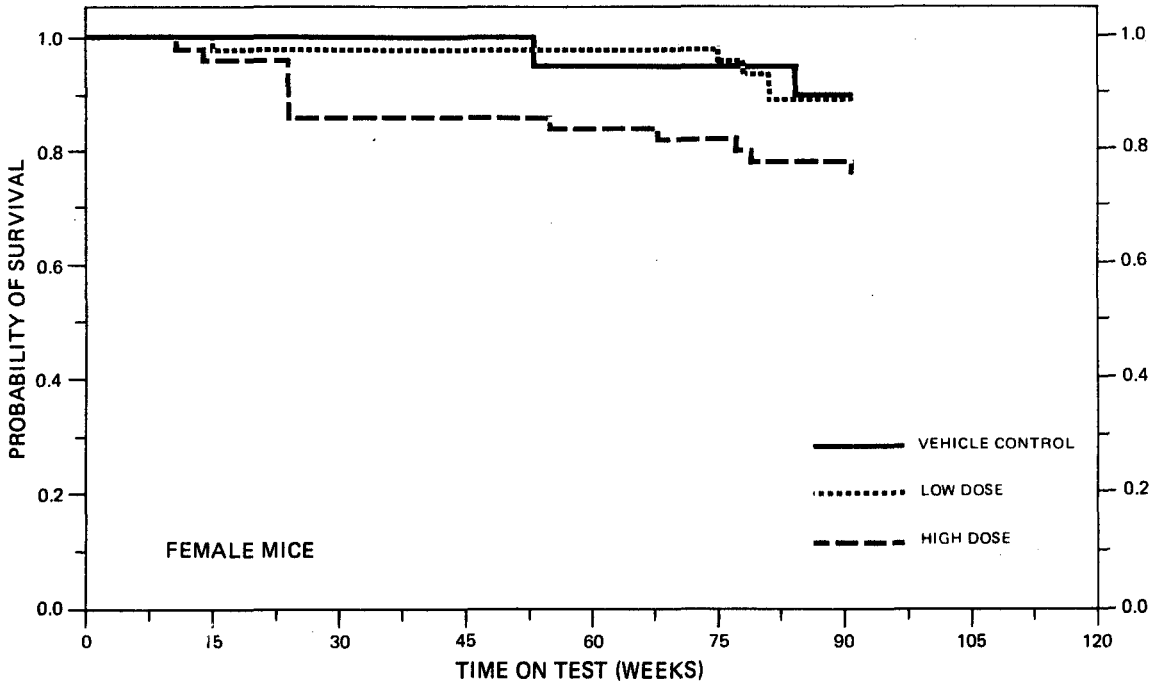


FIGURE 5
SURVIVAL COMPARISONS OF STYRENE CHRONIC STUDY MICE

A variety of neoplastic lesions was present in the dosed and vehicle control groups. Except for the tumors of the lung, the incidences of these neoplasms were apparently not related to compound administration. An increased incidence of alveolar/bronchiolar neoplasms was observed in dosed male mice (i.e., 0/20, 6/45, and 9/49 in the control, low dose and high dose, respectively). The adenomas were small well-circumscribed lesions, while the carcinomas were generally larger and papillary.

A variety of inflammatory and proliferative lesions commonly seen in B6C3F1 mice occurred with approximately equal frequency in dosed and vehicle control mice.

Based on the results of this pathology examination, the increased incidence of alveolar/bronchiolar neoplasms in male mice may have been related to the administration of styrene, under the conditions of this bioassay.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the vehicle control or styrene-dosed groups and where such tumors were observed in at least 5 percent of the group. Due to the early mortality of a number of male and female mice, the analyses for mice have been based solely on those animals surviving at least 52 weeks or, in the event that

TABLE 5

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH STYRENE[a,e]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/20(0.00)	3/44(0.07)	5/43(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.284	0.611
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	91
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	0/20(0.00)	6/44(0.14)	9/43(0.21)
P Values[c]	P = 0.023	N.S.	P = 0.024
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.758	1.276
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	91
Liver: Hepatocellular Carcinoma[b]	4/20(0.20)	3/47(0.06)	6/43(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.319	0.698
Lower Limit	---	0.052	0.192
Upper Limit	---	1.743	3.069
Weeks to First Observed Tumor	91	90	75

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	5/20(0.25)	8/47(0.17)	13/43(0.30)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.681	1.209
Lower Limit	---	0.232	0.486
Upper Limit	---	2.385	3.839
Weeks to First Observed Tumor	91	90	75
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	2/19(0.11)	0/43(0.00)	1/37(0.03)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.257
Lower Limit	---	0.000	0.005
Upper Limit	---	1.480	4.675
Weeks to First Observed Tumor	91	---	91

[a]Treated groups received doses of 150 or 300 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]These analyses were based solely upon animals surviving at least 52 weeks.

TABLE 6

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH STYRENE[a,e]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	0/20(0.00)	1/43(0.02)	3/43(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.026	0.291
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	91
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/20(0.10)	5/44(0.11)	2/43(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.136	0.465
Lower Limit	---	0.210	0.037
Upper Limit	---	11.319	6.107
Weeks to First Observed Tumor	91	75	77
Liver: Hepatocellular Adenoma[b]	0/20(0.00)	1/44(0.02)	5/43(0.12)
P Values[c]	P = 0.034	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.025	0.611
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	91

TABLE 6 (CONCLUDED)

[a]Treated groups received doses of 150 or 300 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]These analyses were based solely upon animals surviving at least 52 weeks.

the tumor of interest was observed earlier, at least as long as the time at which the first tumor of interest was observed.

The Cochran-Armitage test indicated a significant (P = 0.023) positive association between dose and the combined incidence of alveolar/bronchiolar adenomas or alveolar/bronchiolar carcinomas in male mice. This was supported by a significant (P = 0.024) Fisher exact test comparing the high dose group to the vehicle control group. The historical incidence of a combination of alveolar/bronchiolar adenomas and alveolar/bronchiolar carcinomas in male B6C3F1 mice maintained by this laboratory for the NCI Carcinogenesis Testing Program is 12 percent (32/271) for untreated controls, with the highest incidences in two individual untreated control groups being 4/20 and 4/20. The incidence of these neoplasms in historical vehicle control male mice (i.e., 0/40) is considered to represent too small a number of animals for meaningful use as historical controls.

In female mice the Cochran-Armitage test indicated a significant (P = 0.034) positive association between dose and the incidence of hepatocellular adenomas. However, neither of the Fisher exact tests were significant.

These statistical results suggested that the administration of styrene may have been associated with the increased combined incidence of alveolar/bronchiolar adenomas or alveolar/bronchiolar carcinomas in male mice under the conditions of this bioassay.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by styrene that could not be established under the conditions of this test.

V. DISCUSSION

Mortality among male and female high dose rats was significantly higher than that among their respective vehicle controls. In response to this elevated and early mortality, an additional dosed group of each sex was included in the chronic bioassay. No significant positive association was apparent between dosage and mortality among any other dosed rat groups. For mice, there was a significant positive association between mortality and the dosages of styrene administered to males, but not to females. Adequate numbers of animals in all groups, except for the high dose male and female rats, survived sufficiently long to be at risk from late-developing tumors. Dose-related mean body weight depression was apparent when male rats and female mice were compared to their respective vehicle controls, indicating that the dosages administered to these animals during the chronic bioassay may have approximated the maximum tolerated dosages. There was no distinct depression in mean body weight when dosed female rats and dosed male mice were compared to their respective vehicle controls. However, since there was significant accelerated mortality among high dose female rats, it is possible that the dosage administered to the medium dose female rats closely approximated the maximum tolerated dosage.

In male mice, there was a significant positive association between styrene dosage and the combined incidences of alveolar/

bronchiolar adenomas and alveolar/bronchiolar carcinomas. This finding was supported by the high dose to vehicle control Fisher exact comparison. It should be noted that the untreated control male mice maintained at this laboratory for the NCI Carcinogenesis Testing Program have an historical incidence for these tumors of 32/271 (12 percent). The historical incidence of these neoplasms in vehicle control male mice (i.e., 0/40) is based on too small a number of animals for meaningful use as historical controls. There was no significant difference between tumor incidence at any other site in male mice, or at any site in rats or female mice, when dosed groups were compared to vehicle controls. Therefore, the evidence provided by this bioassay for the carcinogenicity of styrene is limited to an increased incidence of a combination of alveolar/bronchiolar neoplasms in dosed male mice as compared to vehicle controls.

The findings of an increased incidence of a combination of adenomas and carcinomas of the lung provided suggestive evidence for the carcinogenicity of styrene in male B6C3F1 mice. However, it is concluded that, under the conditions of this bioassay, no convincing evidence for the carcinogenicity of the compound was obtained in Fischer 344 rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH STYRENE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH STYRENE

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
ANIMALS NECROPSIED	20	20	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50	50
INTEGUMENTARY SYSTEM					
*SKIN	(20)	(20)	(50)	(50)	(50)
FIBROMA			2 (4%)		
*SUBCUT TISSUE	(20)	(20)	(50)	(50)	(50)
FIBROMA			1 (2%)		1 (2%)
MYXOMA				1 (2%)	
LIPOMA				1 (2%)	
OSTEOSARCOMA			1 (2%)		
RESPIRATORY SYSTEM					
#LUNG	(19)	(20)	(49)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)			1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)		
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)	(50)
LEUKEMIA,NOS	1 (5%)			2 (4%)	
MONOCYTIC LEUKEMIA			2 (4%)		
#MEDIASTINAL L.NODE	(17)	(18)	(49)	(47)	(19)
MESOTHELIOMA, METASTATIC				1 (2%)	
CIRCULATORY SYSTEM					
NONE					
DIGESTIVE SYSTEM					
#LIVER	(20)	(20)	(49)	(50)	(49)
HEPATOCELLULAR CARCINOMA		1 (5%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
#SMALL INTESTINE	(19)	(18)	(39)	(50)	(47)
LEIOMYOMA	1 (5%)				
URINARY SYSTEM					
NONE					
ENDOCRINE SYSTEM					
#PITUITARY	(18)	(17)	(44)	(45)	(39)
CHROMOPHOBE ADENOMA	2 (11%)	1 (6%)	2 (5%)	2 (4%)	1 (3%)
#ADRENAL	(19)	(20)	(48)	(49)	(46)
CORTICAL ADENOMA			1 (2%)		
PHEOCHROMOCYTOMA	1 (5%)	2 (10%)	1 (2%)	4 (8%)	1 (2%)
#THYROID	(20)	(16)	(35)	(46)	(27)
ADENOMA, NOS				1 (2%)	
FOLLICULAR-CELL CARCINOMA			1 (3%)		
#PANCREATIC ISLETS	(20)	(20)	(47)	(49)	(47)
ISLET-CELL ADENOMA		1 (5%)		1 (2%)	
ISLET-CELL CARCINOMA			1 (2%)		
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(20)	(20)	(50)	(50)	(50)
FIBROADENOMA				1 (2%)	
*PREPUTIAL GLAND	(20)	(20)	(50)	(50)	(50)
ADENOMA, NOS	1 (5%)		1 (2%)		
SEBACEOUS ADENOMA				1 (2%)	
#TESTIS	(20)	(20)	(47)	(50)	(49)
CARCINOMA, NOS, METASTATIC				1 (2%)	
INTERSTITIAL-CELL TUMOR	19 (95%)	15 (75%)	42 (89%)	48 (96%)	1 (2%)
NERVOUS SYSTEM					
#BRAIN	(20)	(20)	(50)	(50)	(47)
GLIOMA, NOS			1 (2%)		1 (2%)

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

TABLE A1 (CONTINUED)

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
EPENDYMOMA		1 (5%)			
ASTROCYTOMA			1 (2%)		
SPECIAL SENSE ORGANS					
*ZYMBAL'S GLAND	(20)	(20)	(50)	(50)	(50)
CARCINOMA,NOS				1 (2%)	
MUSCULOSKELETAL SYSTEM					
*SKULL	(20)	(20)	(50)	(50)	(50)
OSTEOMA	1 (5%)				
*KNEE JOINT	(20)	(20)	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)		
BODY CAVITIES					
*TUNICA VAGINALIS	(20)	(20)	(50)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)		
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT				1 (2%)	1 (2%)
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
NATURAL DEATH@	1	4	11	5	39
MORIBUND SACRIFICE	2		5	2	10
SCHEDULED SACRIFICE					
ACCIDENTALLY KILLED		1			
TERMINAL SACRIFICE	17	15	34	43	1
ANIMAL MISSING					

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	17	44	50	4
TOTAL PRIMARY TUMORS	27	21	60	65	6
TOTAL ANIMALS WITH BENIGN TUMORS	19	16	43	48	3
TOTAL BENIGN TUMORS	25	19	51	60	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	2	8	5	2
TOTAL MALIGNANT TUMORS	2	2	8	5	2
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	2	
TOTAL SECONDARY TUMORS			1	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1		
TOTAL UNCERTAIN TUMORS			1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC					
TOTAL UNCERTAIN TUMORS					

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH STYRENE

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
ANIMALS NECROPSIED	20	20	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50	48
INTEGUMENTARY SYSTEM					
*SKIN	(20)	(20)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (5%)				
KERATOACANTHOMA			1 (2%)		
*SUBCUT TISSUE	(20)	(20)	(50)	(50)	(50)
FIBROADENOMA					1 (2%)
RESPIRATORY SYSTEM					
#LUNG	(20)	(19)	(45)	(50)	(48)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)		
MUCOEPIDERMOID CARCINOMA			1 (2%)		
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)	(50)
LEUKEMIA,NOS		1 (5%)			
MONOCYTIC LEUKEMIA	1 (5%)				
CIRCULATORY SYSTEM					
#HEART	(20)	(18)	(45)	(48)	(47)
CARCINOMA, NOS, UNC PRIM OR META			1 (2%)		
DIGESTIVE SYSTEM					
#LIVER	(20)	(19)	(49)	(49)	(48)
HEPATOCELLULAR CARCINOMA				1 (2%)	
URINARY SYSTEM					
NONE					

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
ENDOCRINE SYSTEM					
#PITUITARY	(20)	(18)	(44)	(43)	(48)
CHROMOPHOBE ADENOMA	4 (20%)	5 (28%)	7 (16%)	3 (7%)	1 (2%)
CHROMOPHOBE CARCINOMA	1 (5%)				
#ADRENAL	(19)	(19)	(49)	(47)	(48)
PHEOCHROMOCYTOMA		1 (5%)			
#THYROID	(15)	(19)	(42)	(49)	(29)
FOLLICULAR-CELL ADENOMA			1 (2%)	1 (2%)	
C-CELL ADENOMA				1 (2%)	
C-CELL CARCINOMA			1 (2%)		
#PANCREATIC ISLETS	(18)	(18)	(46)	(48)	(46)
ISLET-CELL ADENOMA			1 (2%)		
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(20)	(20)	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)		
FIBROADENOMA	3 (15%)	2 (10%)	2 (4%)	3 (6%)	
*CLITORAL GLAND	(20)	(20)	(50)	(50)	(50)
CARCINOMA,NOS			1 (2%)	1 (2%)	
#UTERUS	(18)	(20)	(48)	(50)	(47)
PAPILLARY ADENOMA				1 (2%)	
FIBROMA				1 (2%)	
ENDOMETRIAL STROMAL POLYP	4 (22%)	3 (15%)	9 (19%)	5 (10%)	
#UTERUS/ENDOMETRIUM	(18)	(20)	(48)	(50)	(47)
CARCINOMA,NOS		1 (5%)		1 (2%)	
ADENOCARCINOMA, NOS			2 (4%)		
ADENOCA IN ADENOMATOUS POLYP				1 (2%)	
#OVARY	(17)	(20)	(46)	(50)	(46)
GRANULOSA-CELL TUMOR	1 (6%)				
NERVOUS SYSTEM					
#BRAIN	(20)	(19)	(48)	(48)	(48)
GLIOMA, NOS				1 (2%)	1 (2%)

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
SPECIAL SENSE ORGANS					
NONE					
MUSCULOSKELETAL SYSTEM					
*BONE	(20)	(20)	(50)	(50)	(50)
SARCOMA, NOS		1 (5%)			
BODY CAVITIES					
*MESENTERY	(20)	(20)	(50)	(50)	(50)
LIPOMA			1 (2%)		
ALL OTHER SYSTEMS					
NONE					
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
NATURAL DEATH@	4		3	4	37
MORIBUND SACRIFICE	1	3	3	1	10
SCHEDULED SACRIFICE					
ACCIDENTALLY KILLED					
TERMINAL SACRIFICE	15	17	44	45	3
ANIMAL MISSING					

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	11	25	17	3
TOTAL PRIMARY TUMORS	15	14	30	20	3
TOTAL ANIMALS WITH BENIGN TUMORS	10	10	20	12	2
TOTAL BENIGN TUMORS	11	11	22	15	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	3	6	5	1
TOTAL MALIGNANT TUMORS	3	3	7	5	1
TOTAL ANIMALS WITH SECONDARY TUMORS#					
TOTAL SECONDARY TUMORS					
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1				
TOTAL UNCERTAIN TUMORS	1				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			1		
TOTAL UNCERTAIN TUMORS			1		

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH STYRENE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH STYRENE

	CONTROL(VEH) 22-2075	LOW DOSE 22-2073	HIGH DOSE 22-2071
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(50)
FIBROSARCOMA			1 (2%)
*SUBCUT TISSUE	(20)	(49)	(50)
HEMANGIOSARCOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(45)	(49)
HEPATOCELLULAR CARCINOMA, METAST			2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (7%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		3 (7%)	5 (10%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
LEUKEMIA,NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(49)
HEPATOCELLULAR ADENOMA	1 (5%)	5 (10%)	7 (14%)
HEPATOCELLULAR CARCINOMA	4 (20%)	3 (6%)	6 (12%)
HEMANGIOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL (VEH) 22-2075	LOW DOSE 22-2073	HIGH DOSE 22-2071
ENDOCRINE SYSTEM			
#THYROID	(19)	(44)	(39)
FOLLICULAR-CELL ADENOMA	2 (11%)		
FOLLICULAR-CELL CARCINOMA			1 (3%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(20)	(49)	(50)
FIBROSARCOMA	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL (VEH) 22-2075	LOW DOSE 22-2073	HIGH DOSE 22-2071
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@		3	10
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	20	46	39
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	14	21
TOTAL PRIMARY TUMORS	9	15	26
TOTAL ANIMALS WITH BENIGN TUMORS	3	7	10
TOTAL BENIGN TUMORS	3	8	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	7	13
TOTAL MALIGNANT TUMORS	6	7	15
TOTAL ANIMALS WITH SECONDARY TUMORS#			2
TOTAL SECONDARY TUMORS			2
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 NEOPLASMS IN FEMALE MICE TREATED WITH STYRENE

	CONTROL (VEH) 22-2076	LOW DOSE 22-2074	HIGH DOSE 22-2072
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		5	
ANIMALS NECROPSIED	20	45	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	45	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(44)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(45)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)	3 (7%)	
LEUKEMIA,NOS		1 (2%)	1 (2%)
#SPLEEN	(19)	(42)	(43)
HEMANGIOSARCOMA			1 (2%)
#LYMPH NODE	(17)	(29)	(39)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
#MESENTERIC L. NODE	(17)	(29)	(39)
MALIGNANT LYMPHOMA, NOS	1 (6%)		
#LIVER	(20)	(45)	(48)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(45)	(48)
HEPATOCELLULAR ADENOMA		1 (2%)	5 (10%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL (VEH) 22-2076	LOW DOSE 22-2074	HIGH DOSE 22-2072
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
*ADRENAL	(13)	(40)	(40)
PHEOCHROMOCYTOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(45)	(48)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(45)	(48)
ADENOCARCINOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(45)	(50)
SARCOMA, NOS		1 (2%)	

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

TABLE B2 (CONCLUDED)

	CONTROL (VEH) 22-2076	LOW DOSE 22-2074	HIGH DOSE 22-2072
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	5	10
MORIBUND SACRIFICE			2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	40	38
ANIMAL MISSING		5	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	11	10
TOTAL PRIMARY TUMORS	2	11	11
TOTAL ANIMALS WITH BENIGN TUMORS		4	7
TOTAL BENIGN TUMORS		4	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	7	3
TOTAL MALIGNANT TUMORS	2	7	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
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			

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH STYRENE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH STYRENE

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
ANIMALS NECROPSIED	20	20	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50	50
INTEGUMENTARY SYSTEM					
*SUBCUT TISSUE	(20)	(20)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST				1 (2%)	
RESPIRATORY SYSTEM					
*NASAL CAVITY	(20)	(20)	(50)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV				1 (2%)	
*LARYNX	(20)	(20)	(50)	(50)	(50)
CYST, NOS			1 (2%)		
INFLAMMATION, NOS				1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)		
#TRACHEA	(20)	(20)	(41)	(49)	(45)
INFLAMMATION, NOS					8 (18%)
INFLAMMATION, SUPPURATIVE					1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE					2 (4%)
ABSCESS, NOS			1 (2%)		
INFLAMMATION, CHRONIC		1 (5%)	2 (5%)		
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)		
#LUNG/BRONCHUS	(19)	(20)	(49)	(50)	(50)
BRONCHIECTASIS					1 (2%)
INFLAMMATION, ACUTE					1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE					1 (2%)
INFLAMMATION, CHRONIC	3 (16%)				
#LUNG/BRONCHIOLE	(19)	(20)	(49)	(50)	(50)
FIBROSIS		1 (5%)			
#LUNG	(19)	(20)	(49)	(50)	(50)
ATELECTASIS					8 (16%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
CONGESTION, NOS	1 (5%)				9 (18%)
EDEMA, NOS					2 (4%)
HEMORRHAGE					9 (18%)
INFLAMMATION, FOCAL					1 (2%)
INFLAMMATION, INTERSTITIAL					1 (2%)
BRONCHOPNEUMONIA, ACUTE					3 (6%)
PNEUMONIA, CHRONIC MURINE	7 (37%)	2 (10%)	5 (10%)	29 (58%)	15 (30%)
INFLAMMATION, CHRONIC	3 (16%)				
INFLAMMATION, CHRONIC SUPPURATIV	1 (5%)			1 (2%)	1 (2%)
GRANULOMA, NOS			1 (2%)		1 (2%)
GRANULOMA, FOREIGN BODY		1 (5%)			
INFARCT, NOS					1 (2%)
FOAM-CELL					1 (2%)
HYPERPLASIA, ADENOMATOUS			1 (2%)	1 (2%)	
HISTIOCYTOSIS			1 (2%)		
HEMATOPOIETIC SYSTEM					
#BONE MARROW	(20)	(19)	(48)	(48)	(6)
MYELOSCLEROSIS				1 (2%)	
#SPLEEN	(20)	(20)	(48)	(50)	(48)
CONGESTION, NOS	1 (5%)				
HEMORRHAGE	1 (5%)				
HEMOSIDEROSIS	2 (10%)	8 (40%)	29 (60%)	3 (6%)	3 (6%)
HYPERPLASIA, LYMPHOID		1 (5%)			
HEMATOPOIESIS			2 (4%)	5 (10%)	
#SPLENIC CAPSULE	(20)	(20)	(48)	(50)	(48)
HYPERPLASIA, FOCAL	1 (5%)				
#MESENTERIC L. NODE	(17)	(18)	(49)	(47)	(19)
EDEMA, NOS				1 (2%)	
#THYMUS	(1)	(7)	(6)	(2)	
CYSTIC DUCTS		1 (14%)			
CIRCULATORY SYSTEM					
#MYOCARDIUM	(19)	(20)	(49)	(50)	(48)
INFLAMMATION, FOCAL		1 (5%)		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		5 (25%)	7 (14%)		
FIBROSIS	3 (16%)	3 (15%)	1 (2%)	4 (8%)	1 (2%)

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

TABLE C1 (CONTINUED)

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
FIBROSIS, FOCAL		4 (20%)	9 (18%)	1 (2%)	
FIBROSIS, DIFFUSE	2 (11%)				
DEGENERATION, NOS				6 (12%)	5 (10%)
DIGESTIVE SYSTEM					
#LIVER	(20)	(20)	(49)	(50)	(49)
CONGESTION, NOS					1 (2%)
CONGESTION, PASSIVE		1 (5%)	1 (2%)		1 (2%)
INFLAMMATION, ACUTE FOCAL				1 (2%)	
INFLAMMATION, ACUTE NECROTIZING					1 (2%)
DEGENERATION, NOS					3 (6%)
NECROSIS, NOS					1 (2%)
NECROSIS, FOCAL		1 (5%)			
NECROSIS, DIFFUSE					1 (2%)
NECROSIS, COAGULATIVE					2 (4%)
METAMORPHOSIS FATTY		2 (10%)	1 (2%)	1 (2%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)		
BASOPHILIC CYTO CHANGE	1 (5%)	2 (10%)			
HYPERPLASTIC NODULE			1 (2%)		
HEMATOPOIESIS				1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(20)	(49)	(50)	(49)
DEGENERATION, NOS					1 (2%)
NECROSIS, NOS				1 (2%)	2 (4%)
#BILE DUCT	(20)	(20)	(49)	(50)	(49)
HYPERPLASIA, NOS		7 (35%)	8 (16%)		
HYPERPLASIA, FOCAL		2 (10%)	2 (4%)		
#PANCREAS	(20)	(20)	(47)	(49)	(47)
ATROPHY, FOCAL	1 (5%)				
#PANCREATIC ACINUS	(20)	(20)	(47)	(49)	(47)
ATROPHY, NOS				1 (2%)	
ATROPHY, FOCAL		2 (10%)	4 (9%)		
#STOMACH	(19)	(19)	(50)	(48)	(49)
INFLAMMATION, ACUTE FOCAL			1 (2%)		
ULCER, HEALED					1 (2%)
HYPERKERATOSIS	1 (5%)				
#GASTRIC MUCOSA	(19)	(19)	(50)	(48)	(49)
DILATATION, NOS		8 (42%)	29 (58%)		

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

TABLE C1 (CONTINUED)

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
#SMALL INTESTINE	(19)	(18)	(39)	(50)	(47)
HYPERPLASIA, LYMPHOID				1 (2%)	
#ILEUM	(19)	(18)	(39)	(50)	(47)
HYPERPLASIA, LYMPHOID	2 (11%)				
#LARGE INTESTINE	(17)	(19)	(49)	(49)	(47)
NEMATODIASIS				1 (2%)	3 (6%)
#COLON	(17)	(19)	(49)	(49)	(47)
NEMATODIASIS	3 (18%)			3 (6%)	
PARASITISM		2 (11%)	9 (18%)		
URINARY SYSTEM					
#KIDNEY	(19)	(20)	(50)	(50)	(49)
CAST, NOS					2 (4%)
CONGESTION, NOS	1 (5%)				
INFLAMMATION, NOS					1 (2%)
INFLAMMATION, CHRONIC	4 (21%)	11 (55%)	38 (76%)	17 (34%)	14 (29%)
#KIDNEY/GLOMERULUS	(19)	(20)	(50)	(50)	(49)
INFLAMMATION, NOS					1 (2%)
#KIDNEY/TUBULE	(19)	(20)	(50)	(50)	(49)
CAST, NOS					1 (2%)
DEGENERATION, NOS					1 (2%)
*URETER	(20)	(20)	(50)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV					1 (2%)
ENDOCRINE SYSTEM					
#PITUITARY	(18)	(17)	(44)	(45)	(39)
CYST, NOS			2 (5%)		
HYPERPLASIA, CHROMOPHOBE-CELL		1 (6%)	2 (5%)		
#ADRENAL	(19)	(20)	(48)	(49)	(46)
CYST, NOS				1 (2%)	
HEMORRHAGIC CYST				1 (2%)	
GRANULOMA, NOS			1 (2%)		
LIPOIDOSIS				1 (2%)	

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

TABLE C1 (CONTINUED)

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
HEMOSIDEROSIS	2 (11%)				
CYTOPLASMIC VACUOLIZATION		2 (10%)	2 (4%)		
ANGIECTASIS		1 (5%)	6 (13%)		
#ADRENAL CORTEX	(19)	(20)	(48)	(49)	(46)
HEMORRHAGIC CYST	1 (5%)				
#ADRENAL MEDULLA	(19)	(20)	(48)	(49)	(46)
HEMORRHAGIC CYST	1 (5%)				
HYPERPLASIA, FOCAL	1 (5%)				
#THYROID	(20)	(16)	(35)	(46)	(27)
CYSTIC FOLLICLES				2 (4%)	
GOITER COLLOID					2 (7%)
HYPERPLASIA, CYSTIC				1 (2%)	
HYPERPLASIA, C-CELL			1 (3%)	1 (2%)	1 (4%)
REPRODUCTIVE SYSTEM					
#PROSTATE	(17)	(6)	(13)	(40)	(46)
CAST, NOS					1 (2%)
#TESTIS	(20)	(20)	(47)	(50)	(49)
GRANULOMA, NOS		1 (5%)			
ATROPHY, NOS		1 (5%)	1 (2%)		1 (2%)
HYPERPLASIA, INTERSTITIAL CELL			1 (2%)		
NERVOUS SYSTEM					
#BRAIN/MENINGES	(20)	(20)	(50)	(50)	(47)
HEMORRHAGE					1 (2%)
#BRAIN	(20)	(20)	(50)	(50)	(47)
INFARCT, NOS			1 (2%)		
CORPORA AMYLACEA	1 (5%)				
RETICULOCYTOSIS				1 (2%)	
#CEREBELLUM	(20)	(20)	(50)	(50)	(47)
CORPORA AMYLACEA					2 (4%)
SPECIAL SENSE ORGANS					
NONE					

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

TABLE C1 (CONCLUDED)

	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1075	LOW DOSE CONTROL (VEH) 11-1079	LOW DOSE 11-1077	MEDIUM DOSE 11-1073	HIGH DOSE 11-1071
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
*MEDIASTINUM	(20)	(20)	(50)	(50)	(50)
ABSCESS, NOS			2 (4%)		
INFLAMMATION, CHRONIC			1 (2%)		
*PLEURA	(20)	(20)	(50)	(50)	(50)
FOAM-CELL					6 (12%)
*MESENTERY	(20)	(20)	(50)	(50)	(50)
NECROSIS, FAT				1 (2%)	
*TUNICA VAGINALIS	(20)	(20)	(50)	(50)	(50)
HYPERPLASIA, MESOTHELIAL	1 (5%)				
ALL OTHER SYSTEMS					
NONE					
SPECIAL MORPHOLOGY SUMMARY					
NO LESION REPORTED					5
AUTO/NECROPSY/HISTO PERF		1			

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH STYRENE

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
ANIMALS INITIALLY IN STUDY	20	20	50	50	50
ANIMALS NECROPSIED	20	20	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50	48
INTEGUMENTARY SYSTEM					
*SKIN	(20)	(20)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST					1 (2%)
*SUBCUT TISSUE	(20)	(20)	(50)	(50)	(50)
ABSCESS, NOS					1 (2%)
RESPIRATORY SYSTEM					
*NASAL CAVITY	(20)	(20)	(50)	(50)	(50)
CYST, NOS				1 (2%)	
INFLAMMATION, NOS		1 (5%)			
#TRACHEA	(18)	(19)	(44)	(50)	(43)
INFLAMMATION, NOS				1 (2%)	6 (14%)
INFLAMMATION, SUPPURATIVE				1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)	2 (4%)	
#LUNG/BRONCHUS	(20)	(19)	(45)	(50)	(48)
INFLAMMATION, NOS				1 (2%)	
INFLAMMATION, CHRONIC				1 (2%)	
#LUNG/BRONCHIOLE	(20)	(19)	(45)	(50)	(48)
INFLAMMATION, FOCAL	1 (5%)				
#LUNG	(20)	(19)	(45)	(50)	(48)
ATELECTASIS					3 (6%)
CONGESTION, NOS				2 (4%)	6 (13%)
EDEMA, NOS					2 (4%)
HEMORRHAGE					2 (4%)
BRONCHOPNEUMONIA, NOS				1 (2%)	
INFLAMMATION, FOCAL			1 (2%)	1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
PNEUMONIA, LIPID				1 (2%)	
BRONCHOPNEUMONIA, ACUTE					2 (4%)
PNEUMONIA, CHRONIC MURINE	1 (5%)	8 (42%)	5 (11%)	24 (48%)	20 (42%)
INFLAMMATION, CHRONIC		1 (5%)		1 (2%)	1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (5%)				
GRANULOMA, NOS			1 (2%)	1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)	
HYPERPLASIA, ADENOMATOUS		1 (5%)			
HISTIOCYTOSIS			6 (13%)		
HYPERPLASIA, LYMPHOID				1 (2%)	
#LUNG/ALVEOLI	(20)	(19)	(45)	(50)	(48)
INFLAMMATION, FOCAL				1 (2%)	
HISTIOCYTOSIS					2 (4%)
HEMATOPOIETIC SYSTEM					
#BONE MARROW	(19)	(17)	(47)	(49)	(15)
HYPERPLASIA, HEMATOPOIETIC		1 (6%)			
#SPLEEN	(20)	(18)	(46)	(49)	(47)
HEMORRHAGE				1 (2%)	
FIBROSIS				1 (2%)	
INFARCT, NOS		1 (6%)			
HEMOSIDEROSIS	12 (60%)	1 (6%)	34 (74%)	12 (24%)	1 (2%)
HEMATOPOIESIS		1 (6%)	4 (9%)	11 (22%)	
#LYMPH NODE	(17)	(15)	(46)	(44)	(15)
INFLAMMATION, ACUTE					1 (7%)
HYPERPLASIA, RETICULUM CELL				1 (2%)	
#MANDIBULAR L. NODE	(17)	(15)	(46)	(44)	(15)
HYPERPLASIA, LYMPHOID					1 (7%)
#MESENTERIC L. NODE	(17)	(15)	(46)	(44)	(15)
INFLAMMATION, CHRONIC				2 (5%)	
#THYMUS	(1)		(6)	(2)	
THYROGLOSSAL DUCT CYST			2 (33%)		
CIRCULATORY SYSTEM					
#HEART	(20)	(18)	(45)	(48)	(47)
DEGENERATION, NOS					1 (2%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
#MYOCARDIUM	(20)	(18)	(45)	(48)	(47)
INFLAMMATION, FOCAL	1 (5%)			3 (6%)	
INFLAMMATION, CHRONIC FOCAL	2 (10%)		11 (24%)		
FIBROSIS	1 (5%)	1 (6%)	4 (9%)	1 (2%)	
FIBROSIS, FOCAL	4 (20%)		1 (2%)		
DEGENERATION, NOS				4 (8%)	6 (13%)
*PULMONARY ARTERY	(20)	(20)	(50)	(50)	(50)
CALCIFICATION, FOCAL			1 (2%)		
DIGESTIVE SYSTEM					
#LIVER	(20)	(19)	(49)	(49)	(48)
CYST, NOS			1 (2%)		
CONGESTION, PASSIVE					1 (2%)
INFLAMMATION, NECROTIZING	1 (5%)				
INFLAMMATION, ACUTE FOCAL				1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)		
HEPATITIS, TOXIC		1 (5%)			
DEGENERATION, NOS					2 (4%)
NECROSIS, NOS					3 (6%)
NECROSIS, COAGULATIVE					1 (2%)
METAMORPHOSIS FATTY					1 (2%)
BASOPHILIC CYTO CHANGE		1 (5%)	3 (6%)	3 (6%)	
FOCAL CELLULAR CHANGE		3 (16%)		2 (4%)	
HYPERPLASIA, NOS		3 (16%)		1 (2%)	
HYPERPLASIA, FOCAL		1 (5%)			
LEUKEMOID REACTION			1 (2%)		
#LIVER/CENTRILOBULAR	(20)	(19)	(49)	(49)	(48)
DEGENERATION, NOS					4 (8%)
NECROSIS, NOS					5 (10%)
NECROSIS, COAGULATIVE					1 (2%)
METAMORPHOSIS FATTY	1 (5%)				
#BILE DUCT	(20)	(19)	(49)	(49)	(48)
HYPERPLASIA, NOS	4 (20%)		5 (10%)		
HYPERPLASIA, FOCAL	2 (10%)		2 (4%)		
#PANCREAS	(18)	(18)	(46)	(48)	(46)
ATROPHY, NOS				1 (2%)	
ATROPHY, FOCAL					1 (2%)
#PANCREATIC ACINUS	(18)	(18)	(46)	(48)	(46)
ATROPHY, FOCAL	1 (6%)		4 (9%)		

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
#GASTRIC MUCOSA	(20)	(19)	(46)	(48)	(48)
DILATATION, NOS	10 (50%)		32 (70%)		
#SMALL INTESTINE	(17)	(19)	(46)	(48)	(48)
INFLAMMATION, FOCAL				1 (2%)	
INFLAMMATION, CHRONIC				4 (8%)	
HYPERPLASIA, LYMPHOID				1 (2%)	
#ILEUM	(17)	(19)	(46)	(48)	(48)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)	
HYPERPLASIA, LYMPHOID				1 (2%)	
#LARGE INTESTINE	(18)	(14)	(46)	(47)	(45)
INFLAMMATION, NOS				1 (2%)	
NEMATODIASIS		3 (21%)		4 (9%)	
#COLON	(18)	(14)	(46)	(47)	(45)
NEMATODIASIS		2 (14%)		7 (15%)	
PARASITISM	8 (44%)		11 (24%)		
URINARY SYSTEM					
#KIDNEY	(20)	(19)	(49)	(47)	(48)
HEMORRHAGE					1 (2%)
INFLAMMATION, CHRONIC	2 (10%)	1 (5%)	15 (31%)	10 (21%)	22 (46%)
NEPHROSIS, CHOLEMIC			1 (2%)		
NECROSIS, MEDULLARY			1 (2%)		
INFARCT, HEALED	1 (5%)				
HYPERPLASIA, TUBULAR CELL			1 (2%)		
#KIDNEY/CORTEX	(20)	(19)	(49)	(47)	(48)
CYST, NOS					1 (2%)
#KIDNEY/TUBULE	(20)	(19)	(49)	(47)	(48)
CAST, NOS					1 (2%)
#URINARY BLADDER	(17)	(17)	(33)	(44)	(34)
HYPERPLASIA, EPITHELIAL				1 (2%)	
ENDOCRINE SYSTEM					
#PITUITARY	(20)	(18)	(44)	(43)	(48)
CYST, NOS	3 (15%)		1 (2%)	5 (12%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
HEMORRHAGIC CYST			1 (2%)	1 (2%)	
ANGIECTASIS			2 (5%)		
#ADRENAL	(19)	(19)	(49)	(47)	(48)
CONGESTION, NOS					5 (10%)
HEMORRHAGE					2 (4%)
HEMORRHAGIC CYST					1 (2%)
NECROSIS, NOS					3 (6%)
NECROSIS, HEMORRHAGIC			1 (2%)		
CYTOPLASMIC VACUOLIZATION	2 (11%)		2 (4%)		
ANGIECTASIS	1 (5%)		6 (12%)		
#ADRENAL CORTEX	(19)	(19)	(49)	(47)	(48)
HEMORRHAGE					1 (2%)
HYPERPLASIA, NODULAR				1 (2%)	
#THYROID	(15)	(19)	(42)	(49)	(29)
HYPERPLASIA, ADENOMATOUS			1 (2%)		
HYPERPLASIA, C-CELL			3 (7%)	1 (2%)	
#THYROID FOLLICLE	(15)	(19)	(42)	(49)	(29)
COLLAPSE					1 (3%)
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(20)	(20)	(50)	(50)	(50)
DILATATION/DUCTS				1 (2%)	
CYST, NOS		1 (5%)			
CYSTIC DUCTS			1 (2%)		
HYPERPLASIA, CYSTIC		1 (5%)			
LACTATION		1 (5%)			
#UTERUS	(18)	(20)	(48)	(50)	(47)
HYDROMETRA			1 (2%)		
CYST, NOS				1 (2%)	
INFLAMMATION, NOS			1 (2%)		
INFLAMMATION, SUPPURATIVE			4 (8%)		1 (2%)
PYOMETRA		2 (10%)	1 (2%)	3 (6%)	
ABSCESS, NOS	1 (6%)				
#CERVIX UTERI	(18)	(20)	(48)	(50)	(47)
INFLAMMATION, NOS				1 (2%)	
ABSCESS, NOS				1 (2%)	
FIBROSIS				1 (2%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
#UTERUS/ENDOMETRIUM	(18)	(20)	(48)	(50)	(47)
CYST, NOS		1 (5%)			
INFLAMMATION, NOS				6 (12%)	4 (9%)
INFLAMMATION, SUPPURATIVE				5 (10%)	1 (2%)
INFLAMMATION, ACUTE		1 (5%)	1 (2%)	2 (4%)	2 (4%)
INFLAMMATION, CHRONIC SUPPURATIV				2 (4%)	
FIBROSIS				1 (2%)	
HYPERPLASIA, NOS			2 (4%)	1 (2%)	
HYPERPLASIA, CYSTIC			2 (4%)	1 (2%)	
#UTERUS/MYOMETRIUM	(18)	(20)	(48)	(50)	(47)
INFLAMMATION, CHRONIC	1 (6%)				
#OVARY	(17)	(20)	(46)	(50)	(46)
CYST, NOS	1 (6%)	3 (15%)	2 (4%)	2 (4%)	1 (2%)
FOLLICULAR CYST, NOS		1 (5%)			
PAROVARIAN CYST			1 (2%)		
INFLAMMATION, NECROTIZING					1 (2%)
INFLAMMATION, CHRONIC				1 (2%)	
GRANULOMA, NOS	1 (6%)				
NECROSIS, NOS					1 (2%)
CORPUS LUTEUM					1 (2%)
NERVOUS SYSTEM					
#BRAIN/MENINGES	(20)	(19)	(48)	(48)	(48)
INFLAMMATION, HEMORRHAGIC					1 (2%)
#BRAIN	(20)	(19)	(48)	(48)	(48)
INFLAMMATION, FOCAL			1 (2%)		
NECROSIS, FOCAL		1 (5%)			
#CEREBELLUM	(20)	(19)	(48)	(48)	(48)
MINERALIZATION					1 (2%)
SPECIAL SENSE ORGANS					
NONE					
MUSCULOSKELETAL SYSTEM					
NONE					

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

TABLE C2 (CONCLUDED)

	LOW DOSE CONTROL (VEH) 11-1070	HIGH AND MEDIUM DOSE CONTROL (VEH) 11-1076	LOW DOSE 11-1078	MEDIUM DOSE 11-1074	HIGH DOSE 11-1072
BODY CAVITIES					
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)	(50)
STEATITIS				3 (6%)	
*PELVIS	(20)	(20)	(50)	(50)	(50)
NECROSIS, FAT				1 (2%)	
*PLEURA	(20)	(20)	(50)	(50)	(50)
FOAM-CELL					13 (26%)
*MESENTERY	(20)	(20)	(50)	(50)	(50)
NECROSIS, NOS		1 (5%)			
ALL OTHER SYSTEMS					
NONE					
SPECIAL MORPHOLOGY SUMMARY					
NO LESION REPORTED		1		2	1
AUTO/NECROPSY/HISTO PERF	1		1		
AUTO/NECROPSY/NO HISTO					2

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH STYRENE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH STYRENE

	CONTROL (VEH) 22-2075	LOW DOSE 22-2073	HIGH DOSE 22-2071
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(50)
CYST, NOS		1 (2%)	3 (6%)
*SUBCUT TISSUE	(20)	(49)	(50)
ABSCESS, NOS		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(45)	(49)
CONGESTION, NOS			2 (4%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, INTERSTITIAL			2 (4%)
PNEUMONIA, CHRONIC MURINE	3 (15%)		2 (4%)
INFLAMMATION, CHRONIC			1 (2%)
#LUNG/ALVEOLI	(20)	(45)	(49)
HEMORRHAGE			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(46)	(43)
MYELOSCLEROSIS		1 (2%)	
HYPERPLASIA, GRANULOCYTIC		4 (9%)	
#SPLEEN	(17)	(41)	(44)
HYPERPLASIA, LYMPHOID	1 (6%)	1 (2%)	
HEMATOPOIESIS		1 (2%)	3 (7%)
#MESENTERIC L. NODE	(14)	(35)	(27)
HYPERPLASIA, RETICULUM CELL		1 (3%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (VEH) 22-2075	LOW DOSE 22-2073	HIGH DOSE 22-2071
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(46)	(46)
INFLAMMATION, NOS	1 (5%)		
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(49)
MINERALIZATION			1 (2%)
CONGESTION, PASSIVE			1 (2%)
NECROSIS, NOS			3 (6%)
NECROSIS, FOCAL		1 (2%)	1 (2%)
INFARCT, NOS			1 (2%)
METAMORPHOSIS FATTY	1 (5%)		1 (2%)
CALCIFICATION, NOS			1 (2%)
BASOPHILIC CYTO CHANGE	1 (5%)		
EOSINOPHILIC CYTO CHANGE		1 (2%)	1 (2%)
GLYCOGENIC CELL			1 (2%)
HYPERPLASIA, NODULAR	1 (5%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
#LIVER/CENTRILOBULAR	(20)	(48)	(49)
NECROSIS, NOS			2 (4%)
NECROSIS, COAGULATIVE			1 (2%)
#LIVER/PERIPORTAL	(20)	(48)	(49)
HEMORRHAGE			1 (2%)
#PANCREAS	(17)	(45)	(46)
INFLAMMATION, ACUTE		1 (2%)	
#PEYERS PATCH	(19)	(48)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#LARGE INTESTINE	(20)	(23)	(44)
NEMATODIASIS			1 (2%)
#COLON	(20)	(23)	(44)
NEMATODIASIS	2 (10%)		
URINARY SYSTEM			
#KIDNEY	(20)	(48)	(48)
HYDRONEPHROSIS	1 (5%)		1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 22-2075	LOW DOSE 22-2073	HIGH DOSE 22-2071
INFLAMMATION, INTERSTITIAL	1 (5%)		
INFLAMMATION, CHRONIC		1 (2%)	
#KIDNEY/TUBULE	(20)	(48)	(48)
NECROSIS, NOS	1 (5%)		
HYPERPLASIA, FOCAL			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(14)	(29)	(35)
HYPERPLASIA, FOCAL			1 (3%)
#ADRENAL MEDULLA	(14)	(29)	(35)
PIGMENTATION, NOS		3 (10%)	4 (11%)
#THYROID	(19)	(44)	(39)
GOITER COLLOID	1 (5%)		
HYPERPLASIA, C-CELL			1 (3%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(19)	(36)	(46)
HYPERPLASIA, CYSTIC			2 (4%)
*SEMINAL VESICLE	(20)	(49)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
NERVOUS SYSTEM			
#CEREBRUM	(19)	(47)	(49)
CORPORA AMYLACEA		1 (2%)	
#BRAIN	(19)	(47)	(49)
CORPORA AMYLACEA	7 (37%)	12 (26%)	11 (22%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D1 (CONCLUDED)

	CONTROL (VEH) 22-2075	LOW DOSE 22-2073	HIGH DOSE 22-2071
BODY CAVITIES			
*MESENTERY	(20)	(49)	(50)
STEATITIS		1 (2%)	
NECROSIS, FAT	1 (5%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(50)
PIGMENTATION, NOS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	18	7
AUTO/NECROPSY/HISTO PERF		1	

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH STYRENE

	CONTROL (VEH) 22-2076	LOW DOSE 22-2074	HIGH DOSE 22-2072
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		5	
ANIMALS NECROPSIED	20	45	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	45	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(20)	(44)	(48)
INFLAMMATION, FOCAL			1 (2%)
#LUNG	(20)	(44)	(48)
CONGESTION, NOS			3 (6%)
HEMORRHAGE			2 (4%)
INFLAMMATION, INTERSTITIAL	1 (5%)	1 (2%)	2 (4%)
PNEUMONIA, CHRONIC MURINE	1 (5%)	1 (2%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(42)	(41)
MYELOSCLEROSIS	6 (32%)	4 (10%)	2 (5%)
HYPERPLASIA, GRANULOCYTIC	1 (5%)	1 (2%)	2 (5%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#SPLEEN	(19)	(42)	(43)
INFLAMMATION, NOS	1 (5%)		
HEMOSIDEROSIS		2 (5%)	1 (2%)
HYPERPLASIA, NOS	2 (11%)	2 (5%)	
HYPERPLASIA, LYMPHOID	1 (5%)	4 (10%)	
HEMATOPOIESIS			1 (2%)
#CERVICAL LYMPH NODE	(17)	(29)	(39)
HYPERPLASIA, LYMPHOID	1 (6%)	1 (3%)	
#MEDIASTINAL L.NODE	(17)	(29)	(39)
HYPERPLASIA, LYMPHOID		1 (3%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL (VEH) 22-2076	LOW DOSE 22-2074	HIGH DOSE 22-2072
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(45)	(48)
HEMORRHAGE			1 (2%)
LIPOGRANULOMA	1 (5%)		
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL		1 (2%)	1 (2%)
CALCIFICATION, NOS		1 (2%)	
BASOPHILIC CYTO CHANGE		2 (4%)	
HYPERPLASIA, NODULAR			1 (2%)
HEMATOPOIESIS			1 (2%)
#LIVER/CENTRILOBULAR	(20)	(45)	(48)
NECROSIS, NOS		1 (2%)	1 (2%)
METAMORPHOSIS FATTY		1 (2%)	
*GALLBLADDER	(20)	(45)	(50)
NECROSIS, NOS			1 (2%)
CALCIFICATION, NOS			1 (2%)
#PANCREAS	(16)	(42)	(46)
CYSTIC DUCTS			1 (2%)
INFLAMMATION, NOS			1 (2%)
#PANCREATIC ACINUS	(16)	(42)	(46)
ATROPHY, NOS			1 (2%)
#STOMACH	(20)	(44)	(47)
PIGMENTATION, NOS			1 (2%)
#SMALL INTESTINE	(20)	(43)	(46)
HYPERPLASIA, LYMPHOID		1 (2%)	
#PEYERS PATCH	(20)	(43)	(46)
HYPERPLASIA, LYMPHOID		2 (5%)	
#COLON	(20)	(44)	(47)
NEMATODIASIS			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (VEH) 22-2076	LOW DOSE 22-2074	HIGH DOSE 22-2072
URINARY SYSTEM			
#KIDNEY	(20)	(45)	(48)
HYDRONEPHROSIS	1 (5%)	1 (2%)	
AMYLOIDOSIS			1 (2%)
CALCINOSIS, NOS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (2%)	
#KIDNEY/GLOMERULUS	(20)	(45)	(48)
FIBROSIS		1 (2%)	
AMYLOIDOSIS			1 (2%)
#URINARY BLADDER	(17)	(38)	(45)
INFLAMMATION, NOS		1 (3%)	
PERIARTERITIS	1 (6%)		
ENDOCRINE SYSTEM			
#ADRENAL MEDULLA	(13)	(40)	(40)
PIGMENTATION, NOS		2 (5%)	1 (3%)
#THYROID	(19)	(38)	(40)
HYPERPLASIA, C-CELL			1 (3%)
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(45)	(48)
DILATATION, NOS			1 (2%)
HEMORRHAGIC CYST		1 (2%)	
PYOMETRA	1 (5%)	2 (4%)	2 (4%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#CERVIX UTERI	(20)	(45)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(45)	(48)
CYST, NOS	3 (15%)	4 (9%)	4 (8%)
INFLAMMATION, NOS		1 (2%)	3 (6%)
INFLAMMATION, SUPPURATIVE	1 (5%)		
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, NOS		3 (7%)	1 (2%)
HYPERPLASIA, CYSTIC	5 (25%)	8 (18%)	3 (6%)

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

TABLE D2 (CONTINUED)

	CONTROL (VEH) 22-2076	LOW DOSE 22-2074	HIGH DOSE 22-2072
#UTERUS/MYOMETRIUM	(20)	(45)	(48)
INFLAMMATION, NOS			1 (2%)
#OVARY	(15)	(26)	(23)
MINERALIZATION			1 (4%)
CYST, NOS	1 (7%)		1 (4%)
PAROVARIAN CYST	1 (7%)	1 (4%)	1 (4%)
HEMORRHAGIC CYST	2 (13%)		
SCLEROSIS			1 (4%)
NERVOUS SYSTEM			
#CEREBRUM	(20)	(44)	(48)
CORPORA AMYLACEA		1 (2%)	1 (2%)
#BRAIN	(20)	(44)	(48)
CORPORA AMYLACEA	5 (25%)	6 (14%)	8 (17%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(45)	(50)
INFLAMMATION, NOS			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(45)	(50)
NECROSIS, FAT			1 (2%)
*ABDOMINAL VISCERA	(20)	(45)	(50)
CONGESTION, NOS			1 (2%)
*MESENTERY	(20)	(45)	(50)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(45)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	

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

TABLE D2 (CONCLUDED)

	CONTROL (VEH) 22-2076	LOW DOSE 22-2074	HIGH DOSE 22-2072
AMYLOIDOSIS		1 (2%)	
PIGMENTATION, NOS			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	4	7
ANIMAL MISSING/NO NECROPSY		5	
AUTO/NECROPSY/NO HISTO			2

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

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

October 25, 1978

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, and State health officials. 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 Styrene for carcinogenicity.

The primary reviewer for the report on the bioassay of Styrene said that the conclusion in the report was that, under the conditions of test, there was an increased incidence of lung tumors in treated male mice. The finding provided suggestive evidence for the carcinogenicity of the compound. Although the lung tumors were statistically significant, they were not given more weight because the incidence in the matched vehicle controls was lower than expected based on historical data.

The secondary reviewer of the bioassay of Styrene said that the evidence was inadequate to suggest that the compound was carcinogenic in mice or rats, under the conditions of test. He opined that the increased incidence of lung tumors in male mice was an experimental vagary and that Styrene should be retested in a more susceptible strain. He continued that he knew of no compound that produced lung tumors in only one sex, as found in this study. He indicated that the statistical aspects of the study were overemphasized and insufficient attention was given to the tumor biology. In conclusion, the secondary reviewer said that the study was negative in both mice and rats, under the conditions of test, and recommended that Styrene be retested in a strain more susceptible to lung tumor induction.

A Program staff member pointed out that in a previous NCI study on a mixture of β-Nitrostyrene and Styrene, an increased incidence of lung tumors was observed among low dose treated male mice. He summarized the findings from several other studies in which rats and mice were exposed to Styrene. In three of them, there was a suggestion of an increased incidence of lung tumors among treated mice.

It was moved that the report on the bioassay of Styrene be accepted as written. It was further moved that the compound be considered for retest. The motion was seconded and approved unanimously.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Kenneth Wilcox, Michigan State Health Department

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* 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.

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