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BIOASSAY OF SELENIUM SULFIDE (Gavage) FOR POSSIBLE CARCINOGENICITY

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

BIOASSAY OF

SELENIUM SULFIDE (GAVAGE)

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
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SELENIUM SULFIDE
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Carcinogenesis Testing Program
National Cancer Institute/National Toxicology Program

FOREWORD

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

CONTRIBUTORS

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

The NCI project officers who were responsible for selecting the protocols used in this bioassay were Drs. N. P. Page (1,2) and C. Cueto (1, 12). The principal investigators were Drs. M. B. Powers (3,4) and R. W. Voelker (3). Ms. K. J. Petrovics (3) was responsible for data management, and Mr. G. Najarian (3,5) for animal care. Histopathologic examinations were performed on rats by Dr. D. R. Patterson (3) and on mice by Dr. D.A. Banas (3) and were reviewed by Dr. R. W. Voelker (3); the diagnoses included in this report represent their interpretations. The pathology report and selected slides were evaluated by the NCI Pathology Working Group as described in Ward et al. (1978).

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (6). Statistical analyses were performed by Dr. J. R. Joiner (7), using methods selected for the bioassay program by Dr. J.J. Gart (8).

Chemicals used in this bioassay were analyzed at Midwest Research Institute (9), and dose mixtures containing the test chemical were analyzed at Hazleton Laboratories by Dr. C. L. Guyton (3) and Mr. E. Missaghi (3). The results of these analyses were reviewed by Dr. C. W. Jameson (7,10).

This report was prepared at Tracor Jitco (7) in collaboration with Hazleton Laboratories and NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens (7,11) toxicologist; Dr. R. L. Schueler, pathologist; Ms. L. A. Owen and Mr. W. D. Reichardt, bioscience writers; and Dr. W. D. Theriault and Ms. M.W. Glasser, technical editors.

The following scientists at NCI (1) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr. (12), Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Charles K. Grieshaber, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry Mahar, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel (13), Dr. Marcelina B. Powers, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of selenium sulfide for possible carcinogenicity was conducted by administering this substance by gavage to F344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were administered selenium sulfide suspended in 0.5% aqueous carboxymethylcellulose 7 days per week for 103 weeks at either 3 or 15 mg/kg/day for rats and 20 or 100 mg/kg/day for mice. As vehicle controls, groups of 50 rats and 50 mice of each sex were administered only the 0.5% aqueous carboxymethylcellulose. Similar groups of untreated controls also were used. All surviving rats and mice were killed and necropsied at week 104 or 105.

The significant effects that could be related to administration of selenium sulfide at the doses used were decreased body weight and increased tumor formation in female mice and in rats of each sex. Dosed rats and female mice had an increased incidence of hepatocellular carcinomas and adenomas. Dosed female mice also had an increased incidence of alveolar/bronchiolar carcinomas and adenomas.

Under the conditions of this bioassay, selenium sulfide was carcinogenic for F344 rats and female B6C3F1 mice, inducing hepatocellular carcinomas in male and female rats and female mice and alveolar/bronchiolar carcinomas and adenomas in female mice. Selenium sulfide was not carcinogenic for male mice; but they may have been able to tolerate higher doses.

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I. INTRODUCTION

SeS

SELENIUM SULFIDE

Selenium sulfide (CAS 7446-34-6; NCI C50033) is an ingredient in dandruff shampoos used in concentrations of 1% in products sold over-the-counter and 2.5% in products which are available by prescription only (Physician's Desk Reference, 1977). Prescription shampoos have been shown in clinical studies to be of therapeutic value against dandruff (Chesterman, 1972). An antimitotic mechanism of action is suggested by data showing that selenium sulfide decreases the rate of incorporation of radioactively labeled thymidine into the DNA of dermal epithelial cells (Plewig and Kligman, 1969). Approximately 200 kg of selenium sulfide is estimated to be used annually for this purpose (IARC, 1975).

Unpublished results discussed by Cummins and Kimura (1971) indicate that selenium is not absorbed percutaneously by man following repeated weekly applications on the scalp over a period of 1 year, but absorption may occur through an open lesion on the scalp. In an uncontrolled case study, Ransone et al. (1961) reported that a woman with an excoriated scalp eruption suffered tremors, lethargy, abdominal pain, and vomiting after having used selenium sulfide shampoos 2 or 3 times weekly for 8 months. The level of selenium in this patient's urine was as high as 32 μg/ml. As a result of this report, selenium sulfide shampoos are not recommended for use when the scalp is abraded or inflamed (AMA Dept. of Drugs, 1977).

Cummins and Kimura (1971) reported the oral LD_{50} of selenium sulfide in male Sprague-Dawley rats to be 138 mg/kg body weight. Henschler and Kirschner (1969) estimated the oral LD_{50} of this compound in female NMRI mice to be 3,700 mg/kg. It was suggested by Cummins and Kimura (1971) that the magnitude of this difference in toxicity might be due to the different particle sizes used in each test. Shampoo formulations in which selenium sulfide is incorporated with wetting agents, sequestrants, a fungicide, and other ingredients (Physician's Desk Reference, 1977) have oral LD_{50}'s in male Sprague-Dawley rats of 14.2 ml/kg (1% selenium sulfide) and 5.3 ml/kg (2.5% selenium sulfide) (Cummins and Kimura, 1971). In female Swiss Webster

mice, the oral LD_{50}'s of selenium sulfide shampoos are 7.8 ml/kg (1% selenium sulfide) and 4.9 ml/kg (2.5% selenium sulfide) (Cummins and Kimura, 1971).

Selenium toxicity in industry is usually due to exposure to selenium dioxide, which is an irritant and has caused pulmonary edema, skin burns, and conjunctivitis in man (Glover, 1970, 1972). A garlic odor on the breath resulting from the metabolite methylselenide is a common sign of selenium poisoning (Ransone et al., 1961). Selenium toxicity also has been encountered in livestock that have grazed on plants which accumulate selenium (Olson, 1969). Some forms of selenium such as selenide, selenite, and selenate, in which selenium exists in -2, +4, and +6 stages of oxidation, have been extensively studied because of their dual role as nutrients and toxic substances. The +2 form has not been extensively studied. Sodium selenite and sodium selenate have been used in animal feeds and as injectables to prevent selenium deficiency diseases in livestock and poultry (IARC, 1975). The threshold for the occurrence of selenium deficiency disease in rats has been estimated at 10 ng/g in feed (National Academy of Sciences, 1976). The signs of deficiency disease, e.g., hair loss, retarded growth, and reproductive failure, can be reversed by supplementing animal diets with 0.1 ppm sodium selenite (McCoy and Weswig, 1969). Liver necrosis, also a sign of deficiency disease, has been prevented by administering sodium selenite daily at a dose of 13 μg/100 g feed, equivalent to 4 μg/100 g feed of elemental selenium, or 0.25 μg selenium per animal per day (Schwarz and Foltz, 1957). Selenium may also be essential for humans. Although the evidence is not conclusive, selenium deficiency may play a role in Kwashiorkor, periodontal disease, sudden infant death syndrome, and cardiovascular disease (National Academy of Sciences, 1976).

The possible carcinogenicity of selenium compounds in animals and humans has been considered in numerous reviews (Frost, 1972; IARC, 1975; Schmidt, 1974; Committee on Medical and Biologic Effects of Environmental Pollutants, 1976). The authors of these reviews have concluded either that selenium has not been shown to be carcinogenic in tests performed with selenide, selenite or selenate or that the data are insufficient to allow an evaluation of the carcinogenicity of the selenium compounds.

Epidemiological evidence shows that workers exposed to selenium died from cancer or from other causes at rates that were not different from the rates expected (Glover, 1970). Evidence of lower death rates from cancer in geographical regions where the soil had an elevated selenium content or where human populations had elevated levels of selenium in the blood has been viewed as unconvincing (IARC, 1975); however, according to age-adjusted and age-specific data for cancer mortality, statistically significant evidence was reported for lower rates of human cancer deaths in geographical areas where forage food for animals was high in selenium (Shamberger et al., 1976).

Selenium sulfide was selected for testing by the NCI Carcinogenesis Testing Program because of the possibility of percutaneous absorption in man from its use in dandruff shampoos. Dermal application studies, separately reported, were conducted under the protocols of the NCI Carcinogenesis Testing Program with selenium sulfide and with a shampoo formulation containing 2.5% selenium sulfide (NCI TR 197, 1980; NCI TR 199, 1980). For the present study, the oral route of administration was selected to provide maximum systemic exposure to possible target organs.

II. MATERIALS AND METHODS

A. Chemical

Selenium sulfide was obtained as a single batch (Lot No. 47E204) from City Chemical Corporation (New York, N. Y.). Analyses performed at Midwest Research Institute included elemental analysis, melting point, and X-ray diffraction (Appendix E). The results of the elemental analysis, which were intermediate between theoretical values of selenium monosulfide and selenium disulfide, suggest that the test substance was a mixture of the two chemicals. However, the melting point of the test sample, 115° to 117°C, was nearer to the 118° to 119°C reported for the monosulfide (Weast, 1974-1975) than to the 100°C reported for the disulfide. The results of elemental analysis may be consistent with mixtures of selenium mono and disulfides or of selenium monosulfide, selenium, and sulfur, and they suggest that the selenium in the test material used in this bioassay was present primarily as the monosulfide. As further evidence of its identity, the X-ray diffraction pattern (Appendix E) of the test material was consistent with patterns reported for selenium monosulfide (Smith, 1960; Virodov, 1964). The test material is referred to in this report by the common name selenium sulfide.

The test material was stored in its original plastic bottle at room temperature (20° to 21°C) for the duration of the bioassay.

B. Dosage Preparation

Working suspensions of selenium sulfide (2, 3, 10, and 15 mg/ml) in aqueous 0.5% carboxymethylcellulose (Sigma Chemical Company, St. Louis, Mo.) were prepared weekly by mixing the test material with the carboxymethylcellulose solution in a tissue grinder prior to dilution to the desired concentration and final mixing with a stirrer. The working suspensions, which were stored at 3° to 5°C, were resuspended with a magnetic stirrer. The particle size distributions were not determined.

The stability of the test compound in the vehicle (0.5% aqueous carboxymethylcellulose) was confirmed by X-ray diffraction (Appendix F). This test was conducted to determine whether the type of vehicle used had any effect on the selenium sulfide in the mixture used. The chemical was prepared as described and then extracted and analyzed. The results of this assay were that the X-ray diffraction patterns for all the samples had similar d spacings and all had the same major line. The relative intensities of the lines differed from sample to sample. The major band in all samples corresponded to that of selenium sulfide (Se_4S_4; empirical formula SeS). The variable line intensities obtained indicate that the samples could contain varying amounts of selenium and sulfur molecular species in addition to selenium sulfide.

Amounts of selenium sulfide in the gavage mixture were determined by analysis of extracts (Appendix G). The mean concentrations for the analyzed samples (10 to 15 mg/kg) were within 6% of the theoretical concentrations, and the coefficient of variation did not exceed 11.0%.

C. Animals

F344 (Fischer) rats and B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center (Frederick, Maryland). The animals were acclimated for 7 to 14 days, determined to be free from observable disease or parasites, and assigned to various groups so that the mean animal weight per cage was approximately the same. At the beginning of the chronic studies, the rats were approximately 4 and the mice approximately 6 weeks old.

D. Animal Maintenance

The rats and mice were housed in solid-bottom polycarbonate cages (Maryland Plastic, Federalsburg, Md.) covered with stainless steel cage lids and nonwoven, spun-bonded Filtek fiber filter bonnets (Filtek, Appleton, Wis.). Initially, rats and mice were housed five per cage; however, at about week 60, the number of rats per cage was reduced from five to three.

All cages were furnished with heat-treated hardwood chip bedding (Sani-chips®, Shurfire Products Corporation, Beltsville, Md.) which was

changed twice per week. Diets of presterilized Wayne® Sterilizable Lab Meal (Allied Mills, Inc., Chicago, Ill.) and untreated well water were provided ad libitum.

Feed hoppers and water bottles were refilled twice per week. Cages, water bottles, and sipper tubes were washed at 81°C twice per week, feed hoppers once per week, and cage racks once per month. An industrial dishwasher was used for water bottles and sipper tubes; a cage and rack washer was used for the feed hoppers, cages, and racks. The detergent used in these washers was Acclaim® (Economics Laboratory, St. Paul, Minn.).

Animal rooms were maintained at 20° to 24°C, and the relative humidity was 45% to 55%. Incoming air was filtered in a single-pass system, through 2-inch-thick disposable fiberglass filters at a rate that allowed 12 changes of room air per hour. Fluorescent lighting was provided on a 12-hour per day cycle.

Rats and mice were housed in separate rooms, and control animals were housed in the same room as the respective dosed animals. The rats were housed in the same room as rats on studies of the following chemicals:

Feed Studies

(CAS 119-53-9) benzoin
(CAS 13463-67-7) titanium dioxide
(CAS 89-78-1) dl-menthol
(CAS 120-61-6) dimethyl terephthalate

Gavage Studies

(CAS 127-69-5) sulfisoxazole
(CAS 108-60-1) bis(2-chloro-1-methylethyl) ether

Mice were housed in the same room as mice on studies of the following chemicals:

Feed Studies

(CAS 119-53-9) benzoin
(CAS 13463-67-7) titanium dioxide
(CAS 89-78-1) dl-menthol
(CAS 120-61-6) dimethyl terephthalate

Gavage Studies

(CAS 127-69-5) sulfisoxazole
(CAS 108-60-1) bis(2-chloro-1-methylethyl) ether

E. Subchronic Studies

Subchronic gavage studies were conducted to determine the concentrations of selenium sulfide used in the chronic studies (referred to in this report as "low" and "high" doses).

Selection of doses fed to rats and mice in the subchronic study (Table 1) was based on LD_{50} values obtained in a study in which suspensions of selenium sulfide in 0.5% aqueous carboxymethylcellulose were administered daily for 17 days (rats: male 112 mg/kg, female 56 mg/kg; mice: male 805 mg/kg, female 316 mg/kg). In the subchronic study, suspensions were administered to groups of 10 rats and 10 mice of each sex (Table 1) once per day, 7 days per week, for 13 weeks, and the animals were then observed for 1 additional week. Control groups consisting of 10 males and 10 females of each species received the carboxymethylcellulose vehicle. All animals were weighed weekly and were killed and necropsied at week 14. Representative tissues were examined microscopically, as described in the section on chronic studies. The doses administered, the survival of animals in each dosed group at the end of the study, and the mean body weights of dosed groups at week 13, expressed as percentages of mean body weights of control groups, are shown in Table 1.

In rats, there was no evidence that selenium sulfide, at the doses tested, adversely affected survival or growth rate or produced gross pathologic lesions. Urine stains were observed during the last three weeks of the study in a few males and in most of the females at the highest dose (31.6 mg/kg/day); otherwise, physical appearance and behavior were comparable in dosed and control groups. Histomorphologic alterations, observed only in the livers of the rats receiving the highest dose, were limited to focal coagulation necrosis with infiltration by inflammatory cells. The low and high doses for the chronic studies of rats were set at 3 and 15 mg/kg/day, 5 days per week.

Table 1. Dosage, Survival, and Mean Body Weights of Rats and Mice Administered Selenium Sulfide by Gavage for 13 weeks

Males			Females		
Dose (a) (mg/kg/day)	Survival(b)	Mean Weight at Week 13 (% of Control)	Dose (a) (mg/kg/day)	Survival(b)	Mean Weight at Week 13 as % of Control
RATS					
0	10/10	100	0	10/10	100
3.2	10/10	102	3.2	10/10	98
5.6	10/10	105	5.6	10/10	101
10.0	10/10	103	10.0	10/10	101
17.8	10/10	100	17.8	10/10	100
31.6	10/10	99	31.6	10/10	95
MICE					
0	10/10	100	0	10/10	100
21.6	10/10	104	21.6	10/10	104
46.4	10/10	104	46.4	10/10	104
100.0	10/10	108	100.0	9/9(c)	104
216.0	10/10	104	216.0	8/9(c)	104
464.0	9/10	96	464.0	6/10	83

(a) Dosed animals were administered a suspension of the test chemical in 0.5% aqueous carboxymethylcellulose 7 days per week. Gavage mixtures were prepared in concentrations to achieve dose volumes of 1 ml/kg body weight for rats and 10 ml/kg body weight for mice. Volumes administered were adjusted at each weighing period.
(b) Number surviving/number in group.
(c) One animal missing from this group.

In mice, there was no evidence of any effect from the test chemical at the four lower doses tested (21.6 to 216 mg/kg/day), with the exception of one death in the females receiving 216 mg/kg/day. At the highest dose (464 mg/kg/day), body weight gain was moderately suppressed in the females relative to the corresponding controls; one death occurred in the males, and four in the females. From week 3 to week 14, almost all females and some of the males at the highest dose appeared thin, showed a hunched posture, or both. No compound-related lesions were observed at necropsy; however, there was an increase in the incidence and severity of microscopic interstitial nephritis in the mice receiving 464 mg/kg/day. The low and high doses for chronic studies on mice were set at 20 mg/kg/day and 100 mg/kg/day, 5 days per week.

F. Chronic Studies

The test groups, doses administered to rats and mice, and durations of the chronic gavage studies are shown in Tables 2 and 3.

G. Clinical Examinations and Pathology

Observations made of the test animals were recorded twice daily. Examinations of animals for clinical signs and the presence of palpable masses were performed and recorded weekly. Mean body weights were recorded every 2 weeks for the first 12 weeks and then monthly for the remaining 93 weeks with few exceptions.

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

Gross and microscopic examinations were performed on major tissues, major organs, and all gross lesions from killed animals and from animals found dead. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, pancreas, stomach, small intestine, large intestine, kidney,

Table 2. Experimental Design for Chronic Selenium Sulfide Gavage Studies in Rats

Sex and Test Group	Initial No. of Animals(a)	Selenium Sulfide Dose(b) (mg/kg/day)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
MALES				
Untreated-Control	50	0		104-105
Vehicle-Control(c)	50	0	103	1
Low-Dose	50	3	103	1
High-Dose	50	15	103	1-2
FEMALES				
Untreated-Control	50	0		104-105
Vehicle-Control(c)	50	0	103	1
Low-Dose	50	3	103	1
High-Dose	50	15	103	1-2

(a) Rats were approximately 4 weeks of age when placed on study. All rats were received in the same shipment.
(b) Dosed rats were administered a suspension of the test chemical in 0.5% aqueous carboxymethylcellulose 7 days per week. Gavage mixtures were prepared in concentrations to achieve dose volumes of 1 ml/kg body weight. Volumes administered were adjusted at each weighing period.
(c) Vehicle controls received volumes of 0.5% aqueous carboxymethylcellulose equal to those of the test solutions administered.

Table 3. Experimental Design for Chronic Selenium Sulfide Gavage Studies in Mice

Sex and Test Group	Initial No. of Animals(a)	Selenium Sulfide Dose(b) (mg/kg/day)	Time on Study	
			Dosed (weeks)	Observed (weeks)
MALES				
Untreated-Control	50	0		104
Vehicle-Control(c)	50	0	103	1
Low-Dose	50	20	103	1-2
High-Dose	50	100	103	1-2
FEMALES				
Untreated-Control	50	0		104
Vehicle-Control(c)	50	0	103	1
Low-Dose	50	20	103	1-2
High-Dose	50	100	103	1-2

(a) Mice were approximately 6 weeks of age when placed on study. All mice were received in the same shipment.
(b) Dosed mice were administered a suspension of the test chemical in 0.5% aqueous carboxymethylcellulose 7 days per week. Gavage mixtures were prepared in concentrations to achieve dose volumes of 10 ml/kg body weight. Volumes administered were adjusted at each weighing period.
(c) Vehicle controls received volumes of 0.5% aqueous carboxymethylcellulose equal to those of the test solutions administered.

urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Occasionally, additional tissues were also examined microscopically. Special staining techniques were utilized as necessary.

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

H. Data Recording and Statistical Analyses

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

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

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

have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for two dosed groups are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 is made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.025. When this correction was used, it is discussed in the narrative section. It is not presented in the tables, where the Fisher exact P values are shown.

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

The approximate 95 percent confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that, in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result has occurred (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero). When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of the high-dose groups of male and female rats were similar to those of the corresponding untreated- and vehicle-control groups for the first 16 weeks of the bioassay but were lower thereafter (Figure 1). Mean body weights of low-dose, untreated-control, and vehicle-control groups were comparable throughout the bioassay.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered selenium sulfide by gavage at the doses of this bioassay, together with those of the untreated and vehicle controls, are shown by the Kaplan and Meier curves in Figure 2. The untreated-control group is not included in the statistical analysis because the test condition of the vehicle-control group resembles more closely that of the dosed groups. The result of the Tarone test for a dose-related trend in mortality, using the high-dose, low-dose, and vehicle-control groups, is not significant in either sex.

In male rats, 40/50 (80%) of the high-dose group, 38/50 (76%) of the low-dose group, and 40/50 (80%) of the vehicle-control group lived to the end of the bioassay. In females, 38/50 (76%) of the high-dose group, 39/50 (78%) of the low-dose group, and 38/50 (76%) of the vehicle-control group lived to the end of the study.

C. Pathology (Rats)

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

An increased incidence of primary liver tumors that occurred in male and female high-dose F344 rats is shown in the Table 4.

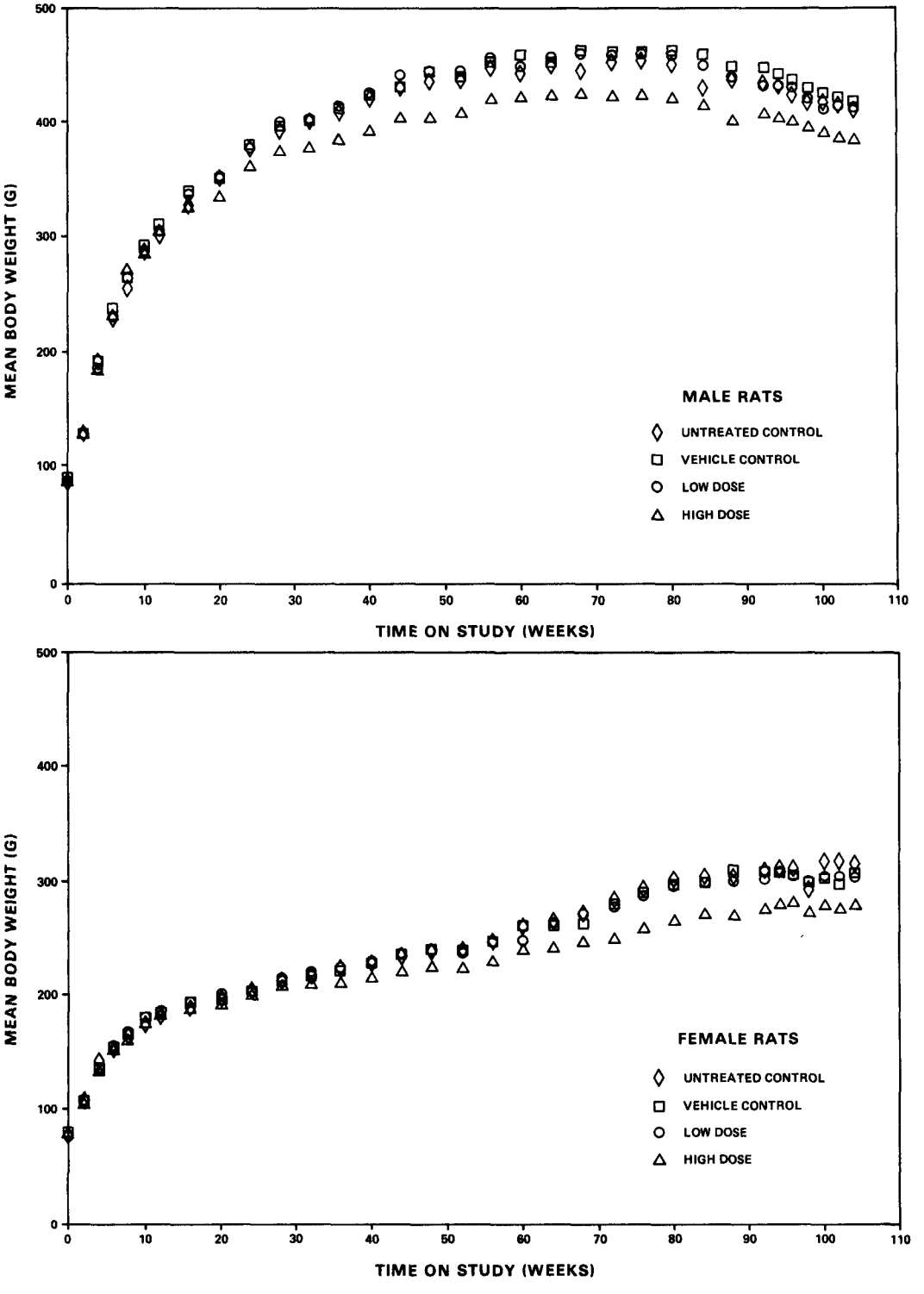

Figure 1. Growth Curves for Rats Administered Selenium Sulfide by Gavage

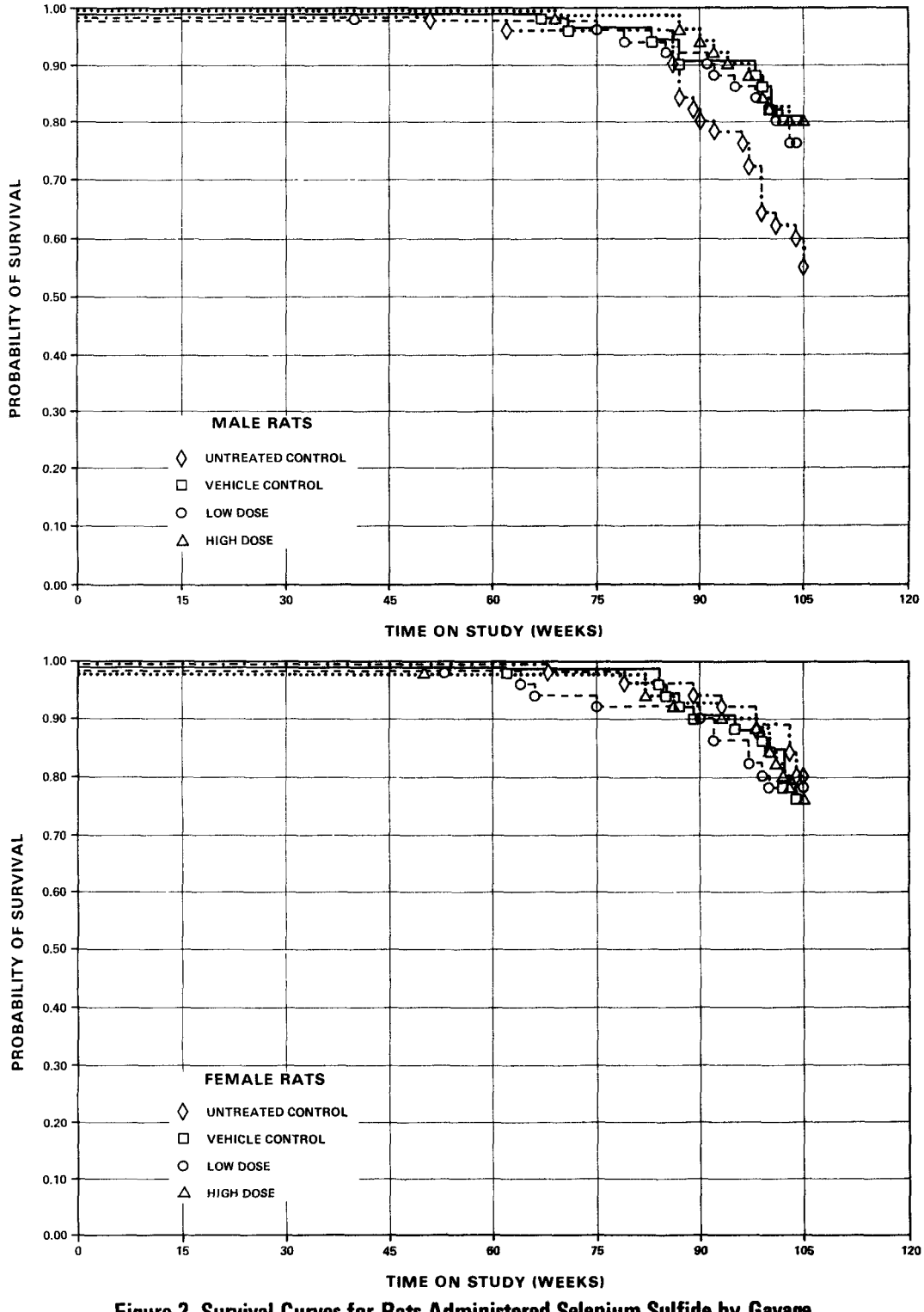

Figure 2. Survival Curves for Rats Administered Selenium Sulfide by Gavage

Table 4. Incidence of Primary Liver Tumors in Male and Female F344 Rats

Tumor	Untreated Control	Vehicle Control	Low Dose	High Dose
MALES				
Hepatocellular Carcinoma	1/48(2%)	0/50(0%)	0/50(0%)	14/49(29%)
Neoplastic Nodules	3/48(6%)	1/50(2%)	0/50(0%)	15/49(31%)
FEMALES				
Hepatocellular Carcinoma	0/50(0%)	0/50(0%)	0/50(0%)	21/50(42%)
Neoplastic Nodules	0/50(0%)	1/50(2%)	0/50(0%)	25/50(50%)

Neoplastic nodules were usually single, rather well-defined areas characterized by altered hepatocytes. In most instances, the hepatocytes were larger than normal, eosinophilic, and occasionally vacuolated. The normal architecture was altered, usually resulting in a solid mass of hepatocytes or a trabecular pattern rather than the normal hepatic cords. The mass compressed the adjacent parenchyma around the periphery. Anaplasia and mitoses were minimal.

Hepatocellular carcinomas were usually large multinodular masses, often encompassing entire liver lobes or even multiple lobes. The histologic appearance of these neoplasms varied from areas appearing similar to normal to much more anaplastic areas. The neoplastic hepatocytes varied from small basophilic cells to very large eosinophilic and occasionally vacuolated cells. Mitoses were variable. No distant metastases were observed in any of the rats bearing hepatocellular carcinomas.

An increased incidence of focal cellular changes in the liver was noted in high-dose male rats but not in the remaining dosed groups of each sex.

A compound-related increase in pigmentation in the lungs was observed and was characterized by accumulations of dark, slightly granular-appearing pigment in the interstitial areas and in some peribronchial areas. In most cases, the pigment appeared to be located within cells, principally in macrophages. No evidence of inflammation relative to the pigment deposits was noted. Lung pigmentation was found in 47/49 (96%) high-dose males, 1/50 (2%) low-dose males, 45/50 (90%) high-dose females, and 36/50 (72%) low-dose females but not in control males or females.

Other neoplasms and degenerative, proliferative, and inflammatory lesions that occurred were similar in numbers and kind to those that usually occur in aged F344 control rats.

The histopathologic examination indicates that under the conditions of this bioassay the occurrence of increased incidences of primary hepatic neoplasms in high-dose male and female rats and of focal cellular changes in the high-dose males is related to the long-term administration of selenium sulfide. Abnormal pigment deposition within lung parenchyma also occurred, apparently due to administration of the test chemical.

D. Statistical Analyses of Results (Rats)

Tables 5 and 6 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more groups. The untreated-control group is not included in the tables of statistical analysis because the test condition of the vehicle-control group resembles more closely that of the dosed groups. A significantly higher incidence of male rats with hematopoietic tumors was observed in the untreated-control group than in the vehicle-control group.

The result of the Cochran-Armitage test (P=0.027) indicates a positive dose-related trend in the incidence of either lymphoma or leukemia in male rats, and the result of the Fisher exact test shows that the incidence of these tumors in the high-dose group is significantly higher (P=0.015) than that in the vehicle-control group. However, the incidence in the untreated-control group is 21/49 (43%), compared with 7/50 (14%) in the vehicle-control group, 15/50 (30%) in the low-dose group, and 17/49 (35%) in the high-dose group. In females, the results of the statistical tests for lymphoma or leukemia are not significant.

In both sexes of rats, the results of the Fisher exact tests for direct comparison of high-dose and control groups are significant (P less than 0.001) for the incidence of hepatocellular carcinomas and for the combined incidence of hepatocellular carcinomas and neoplastic nodules. The statistical conclusion is that the incidences of tumors of the liver in both sexes of rats are associated with administration of the test chemical.

In male rats, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of interstitial-cell tumors of the testis is significant (P=0.024), but the result of the Fisher exact test for direct comparison of incidences in the low-dose and control groups is not significant. The Fisher exact comparison of incidences in the high-dose and control groups shows a P value of 0.028, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. No historical records of this laboratory in which aqueous carboxymethylcellulose is used as a vehicle are available to date

for comparison. It has been our experience, however, that interstitial-cell tumors occur in 75% to 100% of control aged male F344 rats.

In female rats, significant results in the negative direction are observed in the incidence of chromophobe adenomas of the pituitary.

Table 5. Analyses of the Incidence of Primary Tumors in Male Rats Administered Selenium Sulfide by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Integumentary System: Keratocanthoma of the Skin (b)	3/50 (6)	2/50 (4)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.667	0.680
Lower Limit	0.058	0.059	
Upper Limit	5.570	5.680	
Weeks to First Observed Tumor (f)	104	104	105
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	2/50 (4)	4/50 (8)	0/49 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		2.000	0.000
Lower Limit	0.301	0.000	
Upper Limit	21.316	3.448	
Weeks to First Observed Tumor (f)	104	91	--
Integumentary System: Fibrosarcoma of the Subcutaneous Tissue (b)	2/50 (4)	5/50 (10)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		2.500	1.531
Lower Limit	0.432	0.183	
Upper Limit	25.286	17.671	
Weeks to First Observed Tumor	100	75	105
Hematopoietic System: Lymphoma or Leukemia (b)	7/50 (14)	15/50 (30)	17/49 (30)
P Values (c,d)	P=0.027	P=0.045	P=0.015
Relative Risk (e)		2.143	2.478
Lower Limit	0.907	1.082	
Upper Limit	5.663	6.400	
Weeks to First Observed Tumor	67	92	69

Table 5. Analyses of the Incidence of Primary Tumors in Male Rats Administered Selenium Sulfide by Gavage (a)
(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	0/50 (0)	0/50 (0)	14/49 (29)
P Values (c,d)	--	--	P less than 0.001
Relative Risk (e)		--	Infinite
Lower Limit		--	4.452
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	105
Liver: Hepatocellular Carcinoma or Neoplastic Nodule (b)	1/50 (2)	0/50 (0)	24/49 (49)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001
Relative Risk (e)		0.000	24.490
Lower Limit		0.000	4.317
Upper Limit		18.658	967.869
Weeks to First Observed Tumor	104	--	90
Pituitary: Chromophobe Adenoma (b)	6/47 (13)	3/47 (6)	2/45 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.500	0.348
Lower Limit		0.085	0.036
Upper Limit		2.191	1.826
Weeks to First Observed Tumor	104	103	103
Adrenal: Pheochromocytoma (b)	8/50 (16)	9/50 (18)	8/49 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.125	1.020
Lower Limit		0.420	0.363
Upper Limit		3.079	2.869
Weeks to First Observed Tumor	87	95	105

Table 5. Analyses of the Incidence of Primary Tumors in Male Rats Administered Selenium Sulfide by Gavage (a)
(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma or Adenoma (b)	1/50 (2)	5/49 (10)	2/47 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		5.102	2.128
Lower Limit		0.601	0.115
Upper Limit		236.025	122.810
Weeks to First Observed Tumor	104	103	105
Preputial Gland: Carcinoma, NOS (b)	7/50 (14)	10/50 (20)	12/49 (24)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.429	1.749
Lower Limit		0.535	0.696
Upper Limit		4.072	4.802
Weeks to First Observed Tumor	104	79	105
Testis: Interstitial-cell Tumor (b)	41/50 (82)	45/50 (90)	47/49 (96)
P Values (c,d)	P=0.024	N.S.	P=0.028
Relative Risk (e)		1.098	1.170
Lower Limit		0.918	0.997
Upper Limit		1.269	1.267
Weeks to First Observed Tumor	87	79	87

(a) Dosed groups received 3 or 15 mg/kg/day.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the vehicle-control group.
(f) Weeks to first observed tumor is based on time of death with tumor.

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Selenium Sulfide by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	0/50 (0)	3/50 (6)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		Infinite	Infinite
Lower Limit		0.601	0.296
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor (f)	—	97	105
Hematopoietic System: Leukemia (b)	6/50 (12)	12/50 (24)	8/50 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		2.000	1.333
Lower Limit		0.759	0.438
Upper Limit		5.989	4.331
Weeks to First Observed Tumor	85	90	82
Liver: Hepatocellular Carcinoma (b)	0/50 (0)	0/50 (0)	21/50 (42)
P Values (c,d)		—	P less than 0.001
Relative Risk (e)		—	Infinite
Lower Limit		—	6.811
Upper Limit		—	Infinite
Weeks to First Observed Tumor	—	—	86
Liver: Hepatocellular Carcinoma or Neoplastic Nodule (b)	1/50 (2)	0/50 (0)	37/50 (74)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001
Departure from Linear Trend (g)	P=0.028		
Relative Risk (e)		0.000	37.000
Lower Limit		0.000	6.933
Upper Limit		18.658	1358.679
Weeks to First Observed Tumor	67	—	86

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Selenium Sulfide by Gavage (a)
(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	23/50 (46)	14/49 (29)	11/48 (23)
P Values (c,d)	P=0.021 (N)	N.S.	P=0.014 (N)
Relative Risk (e)		0.621	0.498
Lower Limit		0.340	0.250
Upper Limit		1.101	0.936
Weeks to First Observed Tumor	84	92	93
Adrenal: Pheochromocytoma (b)	4/50 (8)	2/50 (4)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.500	1.020
Lower Limit		0.047	0.201
Upper Limit		3.318	5.183
Weeks to First Observed Tumor	102	105	105
Mammary Gland: Fibroadenoma (b)	13/50 (26)	15/50 (30)	8/50 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.154	0.615
Lower Limit		0.574	0.243
Upper Limit		2.349	1.454
Weeks to First Observed Tumor	62	75	100
Clitoral Gland: Carcinoma, NOS (b)	3/50 (6)	3/50 (6)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.000	0.333
Lower Limit		0.140	0.006
Upper Limit		7.133	3.983
Weeks to First Observed Tumor	102	99	105

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Selenium Sulfide by Gavage (a)
(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	5/47 (11)	7/48 (15)	8/50 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.371	1.504
Lower Limit		0.404	0.469
Upper Limit		5.109	5.452
Weeks to First Observed Tumor	95	105	86

(a) Dosed groups received 3 or 15 mg/kg/day.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the vehicle-control group.
(f) Weeks to first observed tumor is based on time of death with tumor.
(g) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of dosed male and female groups of mice were not altered by administration of the test chemical (Figure 3). Palpable nodules or tissue masses were observed at a slightly greater frequency in the dosed male groups than in the other groups.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered selenium sulfide by gavage at the doses of this bioassay, together with those of the untreated and vehicle controls, are shown by the Kaplan and Meier curves in Figure 4. In the statistical analysis, the untreated-control group is not included because the test condition of the vehicle-control group resembles more closely that of the dosed groups. The result of the Tarone test for dose-related trend in mortality, using the high-dose, low-dose, and vehicle-control groups, is not significant in either sex.

In male mice, 35/50 (70%) of the high-dose group, 33/50 (66%) of the low-dose group, and 30/50 (60%) of the vehicle-control group lived to the end of the bioassay. In females, 39/50 (78%) of each dosed group and 43/50 (86%) of the vehicle-control group lived to the end of the bioassay.

Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

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

There was an increase in the incidence of primary tumors of the liver in high-dose female mice as well as a marginal increase in the incidence of

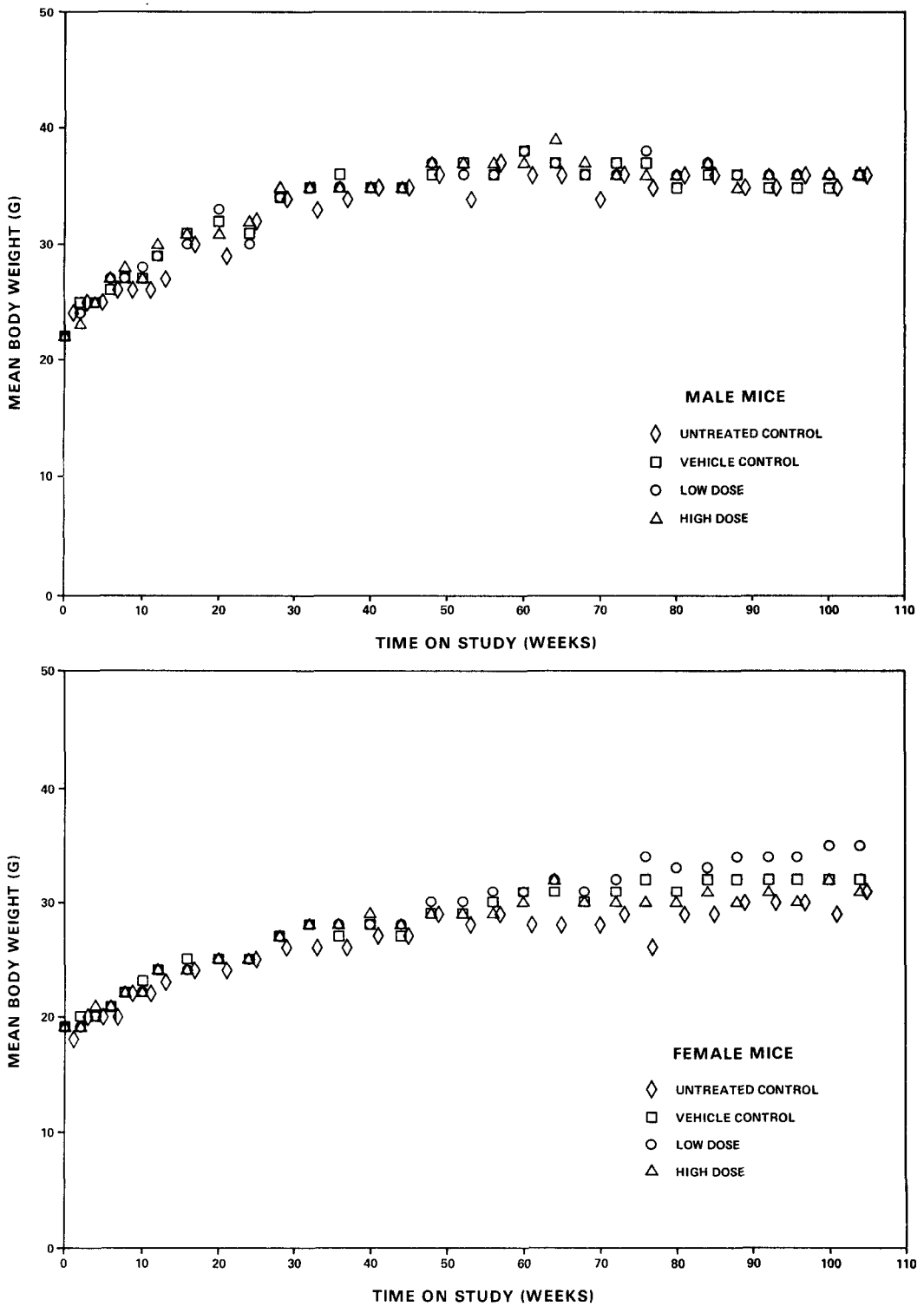

Figure 3. Growth Curves for Mice Administered Selenium Sulfide by Gavage

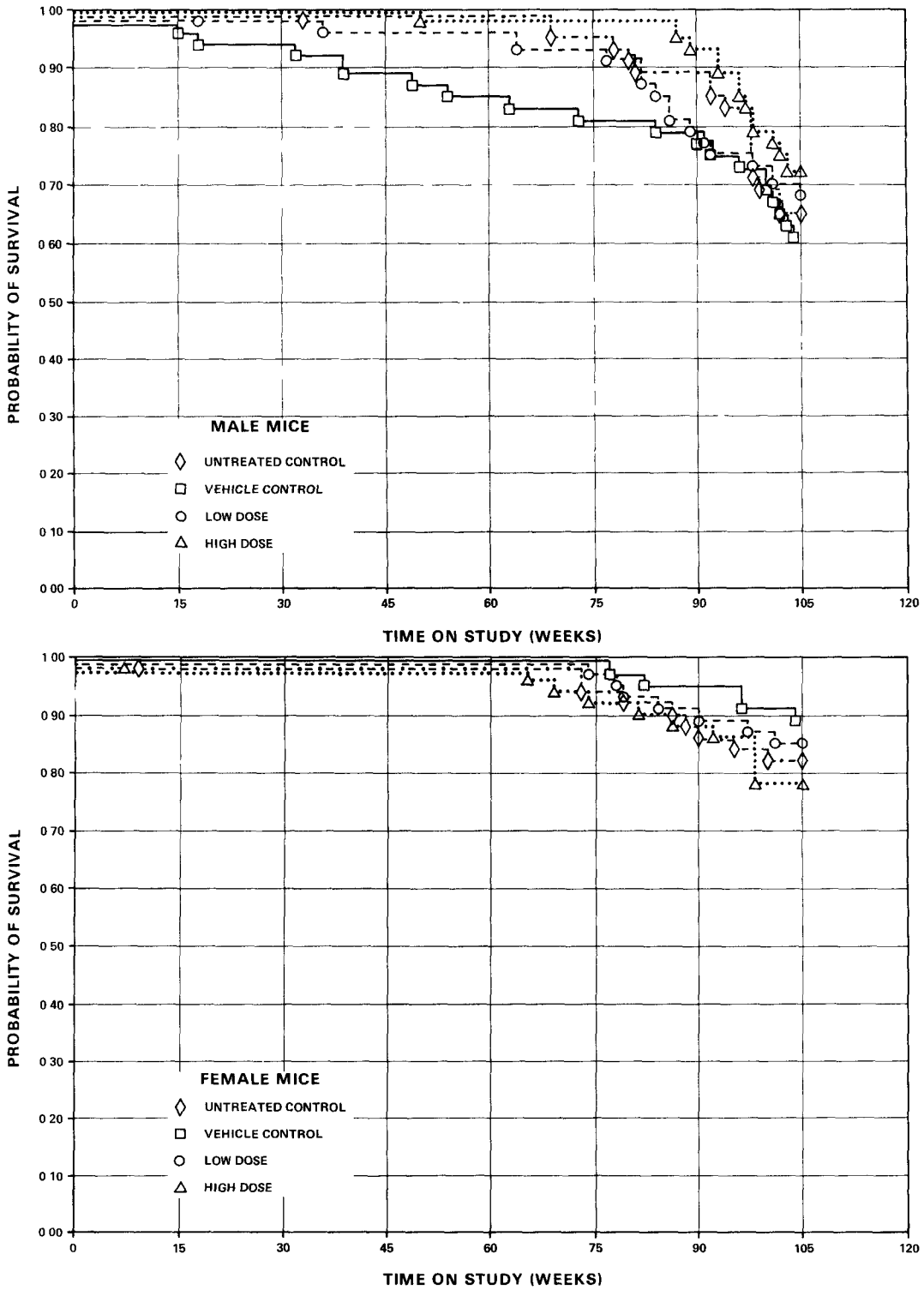

Figure 4. Survival Curves for Mice Administered Selenium Sulfide by Gavage

these tumors in high-dose males. The incidences of hepatocellular carcinomas and adenomas in the dosed and control groups are presented in Table 7.

Hepatocellular adenomas were usually single and consisted of enlarged hepatocytes forming a nodular mass with compression of adjacent parenchyma. Cellular atypia and mitoses were minimal.

Hepatocellular carcinomas varied from single nodules to multinodular masses often encompassing several liver lobes. Individual hepatocytes varied considerably in morphology from large eosinophilic cells to small, darkly staining hepatocytes. In many cases, there was marked variation in cellular type from one portion of the neoplasm to another. The number of mitoses varied. The number of hepatocellular carcinomas metastasizing to the lungs was comparable in vehicle-control and high-dose males. No metastases to the lungs were observed in female mice.

An increased incidence of primary tumors of the lung was observed in high-dose mice (Table 8).

Alveolar/bronchiolar adenomas were usually small solitary lesions located in the subpleural area or immediately adjacent to a bronchiole. The cells involved varied from cuboidal to tall columnar and tended to be situated perpendicular to the basement membrane in a single layer. These cells were arranged in complex papillary projections forming discrete nodules and compressing adjacent alveolar walls. Mitoses were rare.

Alveolar/bronchiolar carcinomas were less discrete lesions and tended to be larger and occasionally multiple, consisting of a confluence of two or more nodules. The individual cells tended to be less rigidly arranged along basement membranes and were often piling up into multiple layers or arranged in solid sheets of cells without a papillary pattern. The cells often showed increased basophilia and a moderate mitotic index. Evidence of invasion into adjacent vessels or extension into bronchioles and adjacent lung parenchyma was frequently present.

Other neoplasms and degenerative, proliferative, and inflammatory lesions that occurred were similar in number and kind to those which usually occur in aged B6C3F1 control mice.

The histopathologic examination indicates that under the conditions of this bioassay the occurrence of increased incidences of primary neoplasms of

Table 7. Incidence of Hepatocellular Carcinomas and Adenomas in Dosed and Control Groups of Mice

	Male				Female			
	Untreated Control	Vehicle Control	Low Dose	High Dose	Untreated Control	Vehicle Control	Low Dose	High Dose
Number of Tissues Examined	49	50	50	50	50	49	50	49
Hepato-cellular Carcinoma	17(35%)	15(30%)	11(22%)	23(46%)	2(4%)	0(0%)	1(2%)	22(45%)
Hepato-cellular Adenoma	3(6%)	0(0%)	3(6%)	0(0%)	1(2%)	0(0%)	1(2%)	6(12%)
Tumor-bearing Animals	20(41%)	15(30%)	14(28%)	23(46%)	3(6%)	0(0%)	2(4%)	25(50%)

Table 8. Incidence of Primary Lung Tumors in Mice

	Male				Female			
	Untreated Control	Vehicle Control	Low Dose	High Dose	Untreated Control	Vehicle Control	Low Dose	High Dose
Number of Tissues Examined	49	50	50	50	50	49	50	49
Alveolar/ Bronchiolar Carcinoma	1(2%)	1(2%)	2(4%)	2(4%)	0(0%)	0(0%)	1(2%)	4(8%)
Alveolar/ Bronchiolar Adenoma	8(16%)	3(6%)	8(16%)	12(24%)	2(4%)	0(0%)	2(4%)	8(16%)
Tumor-bearing Animals	9(18%)	4(8%)	10(20%)	13(26%)	2(4%)	0(0%)	3(6%)	12(24%)

the liver and lung in high-dose B6C3F1 mice is related to the long-term administration of selenium sulfide.

D. Statistical Analyses of Results (Mice)

Tables 9 and 10 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more groups. The untreated-control group is not included in the statistical analysis because the test condition of the vehicle-control group resembles more closely that of the dosed groups. A higher incidence of alveolar/bronchiolar adenomas or carcinomas was observed in the untreated-control groups of male and female mice than in the respective vehicle controls.

In male mice, the Fisher exact comparison of the incidences of lymphoma and leukemia in the low-dose and control groups shows a P value of 0.027, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The incidence of these tumors in the high-dose males is not significant by the Fisher exact test nor is the result of the Cochran-Armitage test significant for dose-related trend in incidence.

The result of the Cochran-Armitage test for positive dose-related trend in the incidence of male mice with either alveolar/bronchiolar carcinomas or adenomas is significant (P=0.022). The Fisher exact test shows that the incidence in the high-dose group is significantly higher than that in the vehicle-control group (P=0.016). However, the incidence in the untreated-control group is 9/48 (18%), compared with 4/50 (8%) in the vehicle-control group, 10/50 (20%) in the low-dose group, and 13/50 (26%) in the high-dose group. Tests using the untreated-control group incidence indicate no significant results.

In females, the Cochran-Armitage test shows that the incidence of animals with either alveolar/bronchiolar carcinomas or adenomas is significant (P less than 0.001). The Fisher exact test shows that the incidence in the high-dose group is significantly higher than that in the vehicle-control group (P less than 0.001) and also significantly higher than that in the untreated-control group (P less than 0.003). The statistical

conclusion is that the incidence of these lung tumors in female mice is associated with the administration of selenium sulfide.

The untreated female mice of this study were observed to have an incidence of 2/50 (4%) of these tumors. When this incidence is tested using the incidence in the low-dose group of 3/50 (6%) and the incidence in the high-dose group of 12/49 (24%), the findings indicate a significant positive linear trend (P less than 0.001) and also a significantly higher incidence (P=0.003) in the high-dose group compared with the untreated-control group. Other control groups that were maintained in the same room as the mice of this study had incidences as follows: 1/49 (2%) in the vehicle-control group matched with dl-menthol; 6/49 (12%) in the vehicle-control group matched with benzoin; and 4/48 (8%) in the vehicle-control group matched dimethyl terephthalate. When each of these control group incidences is used in the Cochran-Armitage test together with the dosed group incidence seen in selenium sulfide, a significant positive trend is indicated (P less than or equal to 0.012). The Fisher exact tests between the high-dose group and the controls of either benzoin or dimethyl terephthalate result in a probability level greater than 0.025. Overall, the statistical conclusion is that the administration of the chemical appears to be associated with the lung tumors, but the development of 6/49 (12%) such tumors in vehicle controls used in the bioassay of benzoin indicates a high variability of such tumors in this room.

The result of the Cochran-Armitage test on the incidence of female mice with hepatocellular carcinomas or adenomas is significant (P less than 0.001). The Fisher exact test shows that the incidence in the high-dose group is significantly higher (P less than 0.001) than that in the control group. The statistical conclusion is that the incidence of these liver tumors in female mice is associated with the administration of this test chemical. In males, the result of the Cochran-Armitage test is significant (P=0.026), but the results of the Fisher exact test are not significant.

The statistical conclusion is that alveolar/bronchiolar adenomas or carcinomas of the lung appear to be associated with the administration of selenium sulfide to female mice, but the variability in control groups in the room used for this study should be considered.

Table 9. Analyses of the Incidence of Primary Tumors in Male Mice Administered Selenium Sulfide by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Integumentary System: Fibrosarcoma of the Subcutaneous Tissue (b)	4/50 (8)	4/50 (8)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.000	0.250
Lower Limit		0.197	0.005
Upper Limit		5.083	2.411
Weeks to First Observed Tumor (f)	100	82	89
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	4/50 (8)	10/50 (20)	13/50 (26)
P Values (c,d)	P=0.022	N.S.	P=0.016
Relative Risk (e)		2.500	3.250
Lower Limit		0.779	1.091
Upper Limit		10.246	12.780
Weeks to First Observed Tumor	73	82	96
Hematopoietic System: Lymphoma or Leukemia (b)	4/50 (8)	12/50 (24)	8/50 (16)
P Values (c,d)	N.S.	P=0.027	N.S.
Departure from Linear Trend (g)	P=0.032		
Relative Risk (e)		3.000	2.000
Lower Limit		0.986	0.576
Upper Limit		11.938	8.539
Weeks to First Observed Tumor	89	77	87
All Sites: Hemangiosarcoma or Hemangioma (b)	5/50 (10)	1/50 (2)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.200	0.600
Lower Limit		0.004	0.098
Upper Limit		1.699	2.910
Weeks to First Observed Tumor	63	105	64

Table 9. Analyses of the Incidence of Primary Tumors in Male Mice Administered Selenium Sulfide by Gavage (a)
(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	15/50 (30)	11/50 (22)	23/50 (46)
P Values (c,d)	P=0.014	N.S.	N.S.
Relative Risk (e)		0.733	1.533
Lower Limit		0.340	0.878
Upper Limit		1.532	2.739
Weeks to First Observed Tumor	100	82	89
Liver: Hepatocellular Carcinoma or Adenoma (b)	15/50 (30)	14/50 (28)	23/50 (46)
P Values (c,d)	P=0.026	N.S.	N.S.
Relative Risk (e)		0.933	1.533
Lower Limit		0.469	0.878
Upper Limit		1.845	2.739
Weeks to First Observed Tumor	100	82	89

(a) Dosed groups received 20 or 100 mg/kg/day.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the vehicle-control group.
(f) Weeks to first observed tumor is based on time of death with tumor.
(g) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 10. Analyses of the Incidence of Primary Tumors in Female Mice Administered Selenium Sulfide by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	0/49 (0)	1/50 (2)	4/49 (8)
P Values (c,d)	P=0.013	N.S.	N.S.
Relative Risk (e)		Infinite	Infinite
Lower Limit		0.053	0.928
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	—	105	105
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	0/49 (0)	3/50 (6)	12/49 (24)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001
Relative Risk (e)		Infinite	Infinite
Lower Limit		0.590	3.670
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	—	78	98
Hematopoietic System: Lymphoma or Leukemia (b)	17/49 (35)	22/50 (44)	17/49 (35)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.268	1.000
Lower Limit		0.740	0.548
Upper Limit		2.201	1.825
Weeks to First Observed Tumor	77	74	65
All Sites: Hemangiosarcoma or Hemangioma (b)	2/49 (4)	3/50 (6)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		1.470	2.000
Lower Limit		0.176	0.302
Upper Limit		16.980	21.298
Weeks to First Observed Tumor	104	101	98

Table 10. Analyses of the Incidence of Primary Tumors in Female Mice Administered Selenium Sulfide by Gavage (a)
(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	0/49 (0)	1/50 (2)	22/49 (45)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001
Relative Risk (e)		Infinite	Infinite
Lower Limit		0.053	7.171
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	74
Liver: Hepatocellular Carcinoma or Adenoma (b)	0/49 (0)	2/50 (4)	25/49 (51)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001
Relative Risk (e)		Infinite	Infinite
Lower Limit		0.290	8.233
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	74
Pituitary Chromophobe Adenoma (b)	2/42 (5)	0/37 (0)	0/38 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		3.803	3.706
Weeks to First Observed Tumor	104	—	--
Mammary Gland: Adenocarcinoma (b)	5/49 (10)	1/50 (2)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.196	0.400
Lower Limit		0.004	0.040
Upper Limit		1.665	2.310
Weeks to First Observed Tumor	104	105	105

Table 10. Analyses of the Incidence of Primary Tumors in Female Mice Administered Selenium Sulfide by Gavage (a)
(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	1/49 (2)	3/50 (6)	0/49 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		2.940	0.000
Lower Limit		0.246	0.000
Upper Limit		151.180	18.651
Weeks to First Observed Tumor	104	105	—
Harderin Gland: Adenoma (b)	2/49 (4)	0/50 (0)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (e)		0.000	2.000
Lower Limit		0.000	0.302
Upper Limit		3.313	21.298
Weeks to First Observed Tumor	104	—	105

(a) Dosed groups received 20 or 100 mg/kg/day.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the vehicle-control group.

V. DISCUSSION

Mean body weights of the high-dose groups of male and female rats were lower than those of corresponding untreated- or vehicle-control groups after week 16 of the bioassay, while those of the low-dose groups were essentially the same as those of the controls throughout the bioassay. Mean body weights of the high- and low-dose groups of male and female mice were not related to the administration of selenium sulfide. Mortality was not significantly affected by administration of the test chemical to the rats or the mice of either sex. Because of the low mortality and the lack of significant change in mean body weight, male mice may have been able to tolerate higher doses.

Hepatocellular carcinomas occurred in the high-dose groups of male and female rats and female mice at incidences that were significantly higher (P less than 0.001) than those of corresponding vehicle-control groups. It should be noted that the high dose was five times as large as the low dose. In male mice, the incidences of the tumors were significant (P=0.014) only for dose-related trend.

Lymphomas or leukemias occurred with a dose-related trend (P=0.027) in male rats and occurred at an incidence that was significantly higher (P=0.015) in high-dose male rats than that of the corresponding vehicle-control group. Since the incidence of these tumors was lower in the low-dose group (15/50) and in the high-dose group (17/49) than in the untreated controls (21/49), their occurrence in male rats cannot be clearly related to administration of the test chemical. In mice, these tumors occurred at incidences that were significant (P=0.027) only when low-dose males were directly compared with corresponding vehicle controls; however, this level of significance is below the level (P=0.025) required when the Bonferroni criterion is used for multiple comparison.

Pigmentation was observed in the lungs of the dosed rats and was associated with administration of the selenium sulfide.

Alveolar/bronchiolar carcinomas or adenomas occurred with a dose-related trend (P less than or equal to 0.022) in the high-dose groups of male and female mice at incidences that were significantly higher (P less than or

equal to 0.016) than those of corresponding male or female vehicle-control groups. Since these lung tumors were observed in 9/49 (18%) of the untreated-control and in 13/50 (26%) of the high-dose males, their occurrence in male mice cannot be clearly related to administration of the test chemical.

Several carcinogenicity studies have been performed with selenides (Se^{-2}), selenites (Se^{+4}), and selenates (Se^{+6}). The results of these studies have been negative, inconclusive, or flawed due to the lack of adequate experimental design or proper management of the study. As a result, no conclusive evidence is available which relates selenium to tumor induction, and the conclusions from these studies lack corroboration (IARC, 1975).

In a study conducted by Nelson et al. (1943), adenomas or low-grade nonmetastisizing carcinomas of the liver were observed in 11/53 female Osborne-Mendel rats that survived 18 to 24 months on seleniferous corn or wheat or on diets containing 5, 7, or 10 ppm selenium added as a mixture of ammonium potassium sulfide and ammonium potassium selenide. Adenomatoid hyperplasias were seen in four rats. Cirrhosis of the liver was observed in 43/53 test animals, and liver tumors occurred only in animals with cirrhosis. Cirrhosis was first observed during the fourth month. Although the incidence of tumors in control rats used in other studies performed by these workers was less than 1% (Fitzhugh et al., 1944), simultaneous control animals were not included in the Nelson study. Subsequently, an FDA review of this study concluded that "whether or not these tumors resulted from cirrhosis caused by the nutritionally inadequate test diets cannot be determined" (Federal Register, 1974).

In another study, male rats of unspecified strain fed 4.3 ppm selenium, as sodium selenate, developed liver tumors at an incidence of 15% in one test, 5% in a second test, and 0% in a third; the overall incidence was 4%, compared with an incidence of 0% in 10,000 untreated rats observed in the same laboratory (Volgarev and Tscherkes, 1967). Early deaths due to selenate toxicity may have limited the development of liver tumors in the dosed groups; and infestation by a parasite associated with tumors subsequently found in the experimental animals may have been related to the reported incidence of tumors (Federal Register, 1974).

Schroeder and Mitchener (1971) reported that male and female Long-Evans rats administered sodium selenite or sodium selenate in the drinking water at 2 ppm selenium for the first year and at 3 ppm selenium for the remaining periods of survival developed mammary adenocarcinomas and fibrosarcomas, sarcomas, and lymphoma/leukemias at an incidence (62.5%) that was significantly higher than that in the corresponding controls (30.8%). A critical evaluation could not be made, however, since all necropsied animals were not examined histologically, and the median survival was longer in the selenate-dosed animals (males 847 days, females 929 days) than in the controls (males 813 days, females 814 days) (Frost, 1972; IARC, 1975). The incidences of the tumors in the animals administered the selenite were not significant when compared with those of the controls; however, due to the toxicity of the selenite at the concentrations used, half of the males died by day 58 and half of the females by day 348.

Hyperplastic lesions were observed in the livers from approximately 50% of male and female Wistar rats which survived more than 282 days on diets containing 0.5 or 2 ppm selenium as selenite or selenate.
The incidences of tumors in the treated animals were not significantly different from those of the controls, but survival was markedly shortened at the higher concentrations (Harr et al., 1967).

Male and female Swiss mice administered selenite or selenate in the drinking water at 3 ppm selenium developed tumors at an incidence comparable with that in corresponding controls (Schroeder and Mitchener, 1972). Female C3H/St mice administered selenium oxide in drinking water at 2 ppm developed a lower incidence (10%) of mammary tumors than did the control animals (Schrauzer and Ishmael, 1974). Male and female B6C3F1 and B6AKF1 mice administered selenium diethyl-dithiocarbamate by gavage at 10 mg/kg body weight daily for 3 weeks and then in the diet at 26 ppm for about 18 months (Innes et al., 1969; NTIS, 1968) developed significantly higher incidences of liver tumors in the dosed B6C3F1 males (67%) than in the corresponding controls (0%). The incidences of these tumors were not significant in B6C3F1 females or in B6AKF1 mice of either sex. However, it was not clear from this bioassay or from bioassays of related compounds whether the increased incidence of the tumors was due to the selenium or to the thiocarbamate component (IARC, 1975).

VI. CONCLUSIONS

Under the conditions of this bioassay, selenium sulfide was carcinogenic for F344 rats and female B6C3F1 mice, inducing hepatocellular carcinomas in rats and female mice and alveolar/bronchiolar carcinomas and adenomas in female mice. Selenium sulfide was not carcinogenic for male mice; however, because of the absence of effects on survival and mean body weight, male mice may have been able to tolerate higher doses.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED SELENIUM SULFIDE BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED SELENIUM SULFIDE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)	1 (2%)
BASAL-CELL CARCINOMA			1 (2%)	
TRICHOEPITHELIOMA				1 (2%)
KERATOACANTHOMA	2 (4%)	3 (6%)	2 (4%)	2 (4%)
*SUBCUT TISSUE	(49)	(50)	(50)	(49)
TRICHOEPITHELIOMA	1 (2%)	1 (2%)		
FIBROMA	2 (4%)	2 (4%)	4 (8%)	
FIBROSARCOMA	1 (2%)	2 (4%)	5 (10%)	3 (6%)
RESPIRATORY SYSTEM				
#LUNG	(48)	(50)	(50)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)			
ALVEOLAR/BRONCHIOLAR CARCINOMA				1 (2%)
C-CELL CARCINOMA, METASTATIC				1 (2%)
FIBROSARCOMA, METASTATIC	1 (2%)		1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
MYELOMONOCYTIC LEUKEMIA	20 (41%)	6 (12%)	13 (26%)	16 (33%)
GRANULOCYTIC LEUKEMIA		1 (2%)	1 (2%)	
MONOCYTIC LEUKEMIA				1 (2%)
#SPLEEN	(48)	(50)	(50)	(49)
MESOTHELIOMA, METASTATIC				1 (2%)
MYELOMONOCYTIC LEUKEMIA	1 (2%)		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#SUBMANDIBULAR L.NODE	(48)	(50)	(49)	(49)
FIBROSARCOMA, METASTATIC	1 (2%)			
CIRCULATORY SYSTEM				
*ABDOMINAL CAVITY	(49)	(50)	(50)	(49)
HEMANGIOSARCOMA, METASTATIC	1 (2%)			
#SPLEEN	(48)	(50)	(50)	(49)
HEMANGIOSARCOMA	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(50)	(48)	(49)
FIBROSARCOMA, INVASIVE			1 (2%)	
#LIVER	(48)	(50)	(50)	(49)
NEOPLASTIC NODULE	3 (6%)	1 (2%)		15 (31%)
HEPATOCELLULAR CARCINOMA	1 (2%)			14 (29%)
OSTEOSARCOMA, METASTATIC				1 (2%)
URINARY SYSTEM				
#URINARY BLADDER	(47)	(45)	(47)	(47)
PAPILLOMA, NOS		1 (2%)		
FIBROSARCOMA, INVASIVE			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(47)	(47)	(45)
CHROMOPHOBE ADENOMA		6 (13%)	3 (6%)	2 (4%)
ACIDOPHIL ADENOMA	1 (2%)			
#ADRENAL	(47)	(50)	(50)	(49)
CORTICAL ADENOMA				1 (2%)
PHEOCHROMOCYTOMA	11 (23%)	5 (10%)	9 (18%)	8 (16%)
PHEOCHROMOCYTOMA, MALIGNANT		3 (6%)		
#THYROID	(47)	(50)	(49)	(47)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)		1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
C-CELL ADENOMA		1 (2%)	4 (8%)	1 (2%)
C-CELL CARCINOMA			1 (2%)	1 (2%)
#PANCREATIC ISLETS	(48)	(50)	(49)	(49)
ISLET-CELL ADENOMA	3 (6%)		1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)		
FIBROADENOMA		1 (2%)	1 (2%)	
*PREPUTIAL GLAND	(49)	(50)	(50)	(49)
CARCINOMA,NOS	3 (6%)	7 (14%)	10 (20%)	12 (24%)
CYSTADENOMA, NOS			1 (2%)	
#TESTIS	(48)	(50)	(50)	(49)
INTERSTITIAL-CELL TUMOR	42 (88%)	41 (82%)	45 (90%)	47 (96%)
NERVOUS SYSTEM				
#BRAIN	(47)	(49)	(49)	(49)
ASTROCYTOMA		1 (2%)	1 (2%)	
#CEREBELLUM	(47)	(49)	(49)	(49)
MENINGIOMA		1 (2%)		
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(50)	(49)
FIBROSARCOMA	1 (2%)			
*EXTERNAL EAR	(49)	(50)	(50)	(49)
FIBROSARCOMA		1 (2%)		
MUSCULOSKELETAL SYSTEM				
*MUSCLE OF NECK	(49)	(50)	(50)	(49)
FIBROSARCOMA, INVASIVE			1 (2%)	
BODY CAVITIES				
*TUNICA VAGINALIS	(49)	(50)	(50)	(49)
MESOTHELIOMA, NOS	2 (4%)			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MESOTHELIOMA, MALIGNANT		1 (2%)		4 (8%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(49)
MESOTHELIOMA, METASTATIC				1 (2%)
ADIPOSE TISSUE				
MESOTHELIOMA, METASTATIC		1		
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	19	9	10	10
MORIBUND SACRIFICE	3	1	2	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	28	40	38	40
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	48	49	49
TOTAL PRIMARY TUMORS	98	88	104	132
TOTAL ANIMALS WITH BENIGN TUMORS	43	46	48	48
TOTAL BENIGN TUMORS	64	63	71	64
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	22	27	36
TOTAL MALIGNANT TUMORS	29	24	33	53
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	2	4
TOTAL SECONDARY TUMORS	3	1	4	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	5	1		15
TOTAL UNCERTAIN TUMORS	5	1		15
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 ADMINISTERED SELENIUM SULFIDE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)		
BASAL-CELL TUMOR	1 (2%)			
KERATOACANTHOMA				1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
FIBROMA			3 (6%)	2 (4%)
FIBROSARCOMA, INVASIVE				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA				1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)			
THYMOMA, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MYELOMONOCYTIC LEUKEMIA	11 (22%)	6 (12%)	12 (24%)	8 (16%)
MONOCYTIC LEUKEMIA	1 (2%)			
#THYMUS	(30)	(21)	(27)	(11)
ADENOCARCINOMA, NOS			1 (4%)	
THYMOMA, MALIGNANT				1 (9%)
CIRCULATORY SYSTEM				
#SPLEEN	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(50)	(50)	(50)
FIBROSARCOMA				1 (2%)
#LIVER	(50)	(50)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)		25 (50%)
HEPATOCELLULAR CARCINOMA				21 (42%)
#PANCREATIC DUCT	(50)	(50)	(50)	(50)
ADENOCARCINOMA, NOS				1 (2%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(45)	(50)	(49)	(48)
CHROMOPHOBE ADENOMA	15 (33%)	23 (46%)	14 (29%)	11 (23%)
#ADRENAL	(50)	(50)	(50)	(49)
CORTICAL ADENOMA				1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	4 (8%)	2 (4%)	4 (8%)
#THYROID	(49)	(49)	(50)	(49)
FOLLICULAR-CELL ADENOMA	1 (2%)			
FOLLICULAR-CELL CARCINOMA		1 (2%)		
C-CELL ADENOMA	4 (8%)		1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)		
ADENOCARCINOMA, NOS		2 (4%)		1 (2%)
PAPILLARY CYSTADENOMA, NOS			1 (2%)	
FIBROSARCOMA				1 (2%)
FIBROADENOMA	19 (38%)	13 (26%)	15 (30%)	8 (16%)
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA,NOS	3 (6%)	3 (6%)	3 (6%)	1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CYSTADENOMA, NOS				1 (2%)
#UTERUS	(48)	(47)	(48)	(50)
CARCINOMA-IN-SITU, NOS				1 (2%)
ADENOCARCINOMA, NOS		1 (2%)		
ENDOMETRIAL STROMAL POLYP	5 (10%)	5 (11%)	7 (15%)	8 (16%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)	1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(47)	(48)	(50)
ADENOCARCINOMA, NOS				1 (2%)
#MESOVARIUM	(48)	(47)	(48)	(49)
MESOTHELIOMA, NOS		1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SPHENOID AND ETHMOID	(50)	(50)	(50)	(50)
CHONDROMA				1 (2%)
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATHS	10	10	8	12
MORIBUND SACRIFICE		2	3	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	40	38	39	38
ANIMAL MISSING				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	43	38	37	47
TOTAL PRIMARY TUMORS	63	63	60	100
TOTAL ANIMALS WITH BENIGN TUMORS	34	33	30	29
TOTAL BENIGN TUMORS	46	46	43	38
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	14	17	29
TOTAL MALIGNANT TUMORS	17	15	17	37
TOTAL ANIMALS WITH SECONDARY TUMORS#		1		3
TOTAL SECONDARY TUMORS		1		3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2		25
TOTAL UNCERTAIN TUMORS		2		25
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

@ INCLUDES AUTOLYZED ANIMALS

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED SELENIUM SULFIDE BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED SELENIUM SULFIDE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
BASAL-CELL TUMOR	1 (2%)			
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
FIBROMA			1 (2%)	
FIBROSARCOMA	6 (12%)	4 (8%)	4 (8%)	1 (2%)
FIBROUS HISTIOCYTOMA		1 (2%)		
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)	
OSTEOSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	2 (4%)		3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA	8 (16%)	3 (6%)	8 (16%)	12 (24%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	2 (4%)	2 (4%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)		
SEBACEOUS ADENOCARCINOMA, METAST		1 (2%)		
FIBROSARCOMA, METASTATIC	1 (2%)	1 (2%)		1 (2%)
FIBROUS HISTIOCYTOMA, METASTATIC			1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	7 (14%)	5 (10%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	4 (8%)	2 (4%)	3 (6%)	3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
GRANULOCYTIC LEUKEMIA		1 (2%)	1 (2%)	
#DUODENUM	(49)	(49)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#THYMUS	(19)	(22)	(19)	(19)
ADENOCARCINOMA, NOS			1 (5%)	
LIPOSARCOMA		1 (5%)		
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)		
#SPLEEN	(49)	(50)	(50)	(50)
HEMANGIOMA				1 (2%)
HEMANGIOSARCOMA		2 (4%)	1 (2%)	
#MESENTERIC L. NODE	(49)	(50)	(49)	(50)
HEMANGIOMA				1 (2%)
#HEART	(49)	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC				1 (2%)
#LIVER	(49)	(50)	(50)	(50)
HEMANGIOSARCOMA		2 (4%)	1 (2%)	1 (2%)
#SMALL INTESTINE	(49)	(49)	(49)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)		
#PROSTATE	(49)	(50)	(48)	(49)
HEMANGIOSARCOMA, METASTATIC		1 (2%)		
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
HEPATOCELLULAR ADENOMA	3 (6%)		3 (6%)	
HEPATOCELLULAR CARCINOMA	17 (35%)	15 (30%)	11 (22%)	23 (46%)
FIBROSARCOMA, METASTATIC				1 (2%)
#BILE DUCT	(49)	(50)	(50)	(50)
CARCINOSARCOMA		1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(49)	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
CORTICAL CARCINOMA, METASTATIC		1 (2%)		
#STOMACH	(49)	(49)	(49)	(48)
CARCINOMA,NOS		1 (2%)		
SQUAMOUS CELL PAPILLOMA	1 (2%)			
#SMALL INTESTINE	(49)	(49)	(49)	(50)
ADENOCARCINOMA, NOS				1 (2%)
#JEJUNUM	(49)	(49)	(49)	(50)
CARCINOMA,NOS	1 (2%)			
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC				1 (2%)
#URINARY BLADDER	(49)	(50)	(49)	(49)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)		
ENDOCRINE SYSTEM				
#ADRENAL	(48)	(49)	(49)	(49)
CORTICAL ADENOMA		1 (2%)		
CORTICAL CARCINOMA		1 (2%)		
PHEOCHROMOCYTOMA		2 (4%)		
#THYROID	(47)	(47)	(49)	(48)
FOLLICULAR-CELL ADENOMA				1 (2%)
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
NONE				

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
*EYELID	(49)	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA		1 (2%)		
*HARDERIAN GLAND	(49)	(50)	(50)	(50)
CARCINOMA,NOS		1 (2%)		
ADENOMA, NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
CARCINOSARCOMA, METASTATIC		1 (2%)		
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	12	18	15	13
MORIBUND SACRIFICE		1		
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED	1	1	2	2
TERMINAL SACRIFICE	36	30	33	35
ANIMAL MISSING	1			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	29	35	36
TOTAL PRIMARY TUMORS	45	43	48	51
TOTAL ANIMALS WITH BENIGN TUMORS	12	8	13	15
TOTAL BENIGN TUMORS	13	8	14	15
TOTAL ANIMALS WITH MALIGNANT TUMORS	26	25	27	28
TOTAL MALIGNANT TUMORS	32	35	34	36
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	7	3	3
TOTAL SECONDARY TUMORS	3	9	5	7
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 ADMINISTERED SELENIUM SULFIDE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	50	49	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(49)	(50)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)			
*SUBCUT TISSUE	(50)	(49)	(50)	(49)
FIBROSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(49)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		2 (4%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	4 (8%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(49)	(50)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)	1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	3 (6%)	6 (12%)	8 (16%)	9 (18%)
MALIG LYMPHOMA, HISTIOCYTIC TYPE	10 (20%)	7 (14%)	3 (6%)	2 (4%)
MALIGNANT LYMPHOMA, MIXED TYPE	3 (6%)	3 (6%)	10 (20%)	4 (8%)
GRANULOCYTIC LEUKEMIA	1 (2%)	1 (2%)		1 (2%)
#MESENTERIC L. NODE	(48)	(48)	(50)	(48)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)			
CIRCULATORY SYSTEM				
*SUBCUT TISSUE	(50)	(49)	(50)	(49)
HEMANGIOMA		1 (2%)		
HEMANGIOSARCOMA				1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(50)	(49)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)	3 (6%)
#MESENTERIC L. NODE	(48)	(48)	(50)	(48)
HEMANGIOSARCOMA				1 (2%)
#LIVER	(50)	(49)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)	
#UTERUS	(50)	(49)	(50)	(49)
HEMANGIOMA	1 (2%)			
HEMANGIOSARCOMA		1 (2%)	1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(46)	(50)	(49)
ADENOCARCINOMA, NOS				1 (2%)
#LIVER	(50)	(49)	(50)	(49)
HEPATOCELLULAR ADENOMA	1 (2%)		1 (2%)	6 (12%)
HEPATOCELLULAR CARCINOMA	2 (4%)		1 (2%)	22 (45%)
#PANCREAS	(50)	(49)	(50)	(49)
CARCINOMA, NOS, METASTATIC	1 (2%)			
#STOMACH	(50)	(49)	(50)	(49)
CARCINOMA,NOS	1 (2%)			
SQUAMOUS CELL PAPILLOMA			1 (2%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(45)	(42)	(37)	(38)
CHROMOPHOBE ADENOMA	1 (2%)	2 (5%)		
#ADRENAL	(50)	(48)	(48)	(49)
PHEOCHROMOCYTOMA		1 (2%)		1 (2%)
#THYROID	(49)	(48)	(50)	(49)
FOLLICULAR-CELL ADENOMA	1 (2%)		1 (2%)	1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
C-CELL ADENOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(49)	(50)	(49)
ADENOCARCINOMA, NOS	1 (2%)	5 (10%)	1 (2%)	2 (4%)
#UTERUS	(50)	(49)	(50)	(49)
ENDOMETRIAL STROMAL POLYP	1 (2%)	1 (2%)	3 (6%)	
#OVARY	(50)	(49)	(50)	(49)
PAPILLARY CYSTADENOMA, NOS			1 (2%)	1 (2%)
GRANULOSA-CELL TUMOR				1 (2%)
SERTOLI-CELL TUMOR		1 (2%)		
TERATOMA, NOS				1 (2%)
#MESOVARIUM	(50)	(49)	(50)	(49)
CARCINOMA, NOS, METASTATIC	1 (2%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(49)	(50)	(49)
ADENOMA, NOS		2 (4%)		4 (8%)
MUSCULOSKELETAL SYSTEM				
*VERTEBRAL COLUMN	(50)	(49)	(50)	(49)
OSTEOSARCOMA			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	9	5	7	11
MORIBUND SACRIFICE				
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED		1	4	
TERMINAL SACRIFICE	41	43	39	39
ANIMAL MISSING		1		
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	24	31	42
TOTAL PRIMARY TUMORS	30	31	40	74
TOTAL ANIMALS WITH BENIGN TUMORS	7	7	10	15
TOTAL BENIGN TUMORS	8	8	10	21
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	20	26	38
TOTAL MALIGNANT TUMORS	22	23	30	51
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			1
TOTAL SECONDARY TUMORS	2			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				2
TOTAL UNCERTAIN TUMORS				2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

@ INCLUDES AUTOLYZED ANIMALS

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED SELENIUM SULFIDE BY GAVAGE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED SELENIUM SULFIDE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(49)
INFLAMMATION, NOS	1 (2%)			
ULCER, NOS	1 (2%)			
EROSION	1 (2%)			
ACARIASIS		1 (2%)		
HYPERPLASIA, NOS	1 (2%)			
RESPIRATORY SYSTEM				
#TRACHEA	(48)	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)			
#LUNG/BRONCHIOLE	(48)	(50)	(50)	(49)
INFLAMMATION, ACUTE	1 (2%)			
#LUNG	(48)	(50)	(50)	(49)
CONGESTION, NOS	4 (8%)	3 (6%)	1 (2%)	
CONGESTION, PASSIVE		1 (2%)		
EDEMA, NOS	1 (2%)			
HEMORRHAGE		1 (2%)		
INFLAMMATION, SUPPURATIVE			1 (2%)	
BRONCHOPNEUMONIA SUPPURATIVE	1 (2%)			
BRONCHOPNEUMONIA, ACUTE	1 (2%)			
INFLAMMATION, ACUTE FOCAL				1 (2%)
BRONCHOPNEUMONIA ACUTE SUPPURATI		1 (2%)		
PNEUMONIA, CHRONIC MURINE	10 (21%)	40 (80%)	38 (76%)	36 (73%)
GRANULOMA, FOREIGN BODY		1 (2%)		
NECROSIS, FOCAL				1 (2%)
INFARCT HEMORRHAGIC		1 (2%)		
PIGMENTATION, NOS			1 (2%)	47 (96%)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
METAPLASIA, OSSEOUS		1 (2%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(48)	(50)	(49)	(48)
HYPOPLASIA, NOS			1 (2%)	
HYPERPLASIA, ERYTHROID	1 (2%)			
#SPLEEN	(48)	(50)	(50)	(49)
CONGESTION, NOS	2 (4%)			
HEMORRHAGIC CYST	1 (2%)			
HEMOSIDEROSIS			2 (4%)	2 (4%)
HEMATOPOIESIS			3 (6%)	6 (12%)
#LYMPH NODE	(48)	(50)	(49)	(49)
HEMORRHAGE		1 (2%)		
INFLAMMATION, CHRONIC			2 (4%)	
#SUBMANDIBULAR L.NODE	(48)	(50)	(49)	(49)
INFLAMMATION, ACUTE	2 (4%)			
#MANDIBULAR L. NODE	(48)	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)		
#CERVICAL LYMPH NODE	(48)	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)			
#BRONCHIAL LYMPH NODE	(48)	(50)	(49)	(49)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, ACUTE	1 (2%)			
PIGMENTATION, NOS				6 (12%)
#LUNG	(48)	(50)	(50)	(49)
LEUKEMOID REACTION		1 (2%)		
#THYMUS	(20)	(17)	(20)	(14)
ATROPHY, NOS		2 (12%)		
CIRCULATORY SYSTEM				
*MEDIASTINUM	(49)	(50)	(50)	(49)
PERIARTERITIS		1 (2%)		
#MESENTERIC L. NODE	(48)	(50)	(49)	(49)
LYMPHANGIECTASIS		1 (2%)	2 (4%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#LUNG	(48)	(50)	(50)	(49)
THROMBOSIS, NOS				1 (2%)
PERIARTERITIS		1 (2%)		
#HEART	(47)	(50)	(50)	(49)
THROMBOSIS, NOS			1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)		
PERIARTERITIS	2 (4%)		2 (4%)	1 (2%)
#AURICULAR APPENDAGE	(47)	(50)	(50)	(49)
MINERALIZATION				1 (2%)
THROMBOSIS, NOS	1 (2%)			4 (8%)
#MYOCARDIUM	(47)	(50)	(50)	(49)
MINERALIZATION	1 (2%)			
INFLAMMATION, CHRONIC	2 (4%)		1 (2%)	
FIBROSIS	23 (49%)	15 (30%)	14 (28%)	12 (24%)
FIBROSIS, DIFFUSE		4 (8%)		
*AORTA	(49)	(50)	(50)	(49)
MEDIAL CALCIFICATION	1 (2%)			
#LIVER	(48)	(50)	(50)	(49)
THROMBOSIS, NOS				1 (2%)
PERIVASCULITIS				1 (2%)
#PANCREAS	(48)	(50)	(49)	(49)
PERIARTERITIS	1 (2%)		1 (2%)	
*MESENTERY	(49)	(50)	(50)	(49)
PERIARTERITIS		1 (2%)		
#TESTIS	(48)	(50)	(50)	(49)
PERIARTERITIS		1 (2%)		
#ADRENAL	(47)	(50)	(50)	(49)
THROMBOSIS, NOS		1 (2%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(50)	(48)	(49)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC	1 (2%)			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#SUBMAXILLARY GLAND	(48)	(50)	(48)	(49)
ATROPHY, DIFFUSE		1 (2%)		
#LIVER	(48)	(50)	(50)	(49)
CONGESTION, NOS	2 (4%)	1 (2%)		
HEMORRHAGE	1 (2%)		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			
FIBROSIS, FOCAL				1 (2%)
CHOLANGIOFIBROSIS	5 (10%)			
PELIOSIS HEPATIS	6 (13%)		1 (2%)	27 (55%)
NECROSIS, NOS	1 (2%)			
NECROSIS, FOCAL			1 (2%)	3 (6%)
NECROSIS, HEMORRHAGIC				1 (2%)
NECROSIS, PERIPHERAL		1 (2%)		
INFARCT HEMORRHAGIC			1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	2 (4%)		1 (2%)
FOCAL CELLULAR CHANGE	18 (38%)	15 (30%)	16 (32%)	26 (53%)
ANGIECTASIS		5 (10%)	1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(48)	(50)	(50)	(49)
DEGENERATION, NOS	1 (2%)	2 (4%)	1 (2%)	
NECROSIS, NOS		4 (8%)	1 (2%)	1 (2%)
NECROSIS, DIFFUSE				1 (2%)
METAMORPHOSIS FATTY			1 (2%)	
#BILE DUCT	(48)	(50)	(50)	(49)
DILATATION, NOS				1 (2%)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, CHRONIC	11 (23%)			
HYPERPLASIA, NOS	15 (31%)		2 (4%)	2 (4%)
HYPERPLASIA, DIFFUSE		1 (2%)		
#PANCREAS	(48)	(50)	(49)	(49)
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)		
ATROPHY, NOS	1 (2%)	1 (2%)	5 (10%)	3 (6%)
ATROPHY, FOCAL	5 (10%)	11 (22%)	1 (2%)	3 (6%)
ATROPHY, DIFFUSE	1 (2%)	1 (2%)	2 (4%)	
#ESOPHAGUS	(48)	(50)	(50)	(49)
RUPTURE			1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
#STOMACH	(48)	(49)	(50)	(49)
MINERALIZATION	1 (2%)			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ULCER, FOCAL	4 (8%)	2 (4%)	4 (8%)	3 (6%)
INFLAMMATION, SUPPURATIVE	1 (2%)			
INFLAMMATION, CHRONIC		1 (2%)		
INFARCT, FOCAL				1 (2%)
#GASTRIC SUBMUCOSA	(48)	(49)	(50)	(49)
HEMORRHAGE				1 (2%)
#FORESTOMACH	(48)	(49)	(50)	(49)
INFLAMMATION, NOS	1 (2%)			
ULCER, NOS		1 (2%)		
#SMALL INTESTINE	(48)	(50)	(50)	(49)
NECROSIS, FAT		1 (2%)	1 (2%)	
#LARGE INTESTINE	(48)	(50)	(49)	(45)
PARASITISM	1 (2%)	1 (2%)	3 (6%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(48)	(50)	(50)	(49)
MINERALIZATION	1 (2%)			
CONGESTION, NOS		1 (2%)	1 (2%)	
PYELONEPHRITIS SUPPURATIVE	1 (2%)			
PYELONEPHRITIS, ACUTE			1 (2%)	
INFLAMMATION, CHRONIC	34 (71%)	41 (82%)	40 (80%)	41 (84%)
PIGMENTATION, NOS	5 (10%)			
#KIDNEY/TUBULE	(48)	(50)	(50)	(49)
PIGMENTATION, NOS	1 (2%)	2 (4%)		1 (2%)
#URINARY BLADDER	(47)	(45)	(47)	(47)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, ACUTE		1 (2%)		
ULCER, CHRONIC	1 (2%)			
HYPERPLASIA, EPITHELIAL				1 (2%)
#U.BLADDER/SUBMUCOSA	(47)	(45)	(47)	(47)
EDEMA, NOS			1 (2%)	
#SUBSEROSA OF URINARY	(47)	(45)	(47)	(47)
INFLAMMATION, NOS			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(47)	(47)	(45)
CYST, NOS	1 (2%)			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MULTIPLE CYSTS			1 (2%)	
HEMORRHAGE	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL				1 (2%)
#ADRENAL	(47)	(50)	(50)	(49)
CONGESTION, NOS		2 (4%)		
INFARCT, NOS		1 (2%)		
CYTOLOGIC DEGENERATION			1 (2%)	
#ADRENAL CORTEX	(47)	(50)	(50)	(49)
DEGENERATION, NOS	4 (9%)	2 (4%)	4 (8%)	5 (10%)
HYPERPLASIA, NODULAR	1 (2%)			
HYPERPLASIA, FOCAL		1 (2%)		1 (2%)
ANGIECTASIS		1 (2%)	1 (2%)	1 (2%)
#ADRENAL MEDULLA	(47)	(50)	(50)	(49)
HYPERPLASIA, NOS	3 (6%)			4 (8%)
HYPERPLASIA, FOCAL	3 (6%)	8 (16%)	2 (4%)	5 (10%)
#THYROID	(47)	(50)	(49)	(47)
FOLLICULAR CYST, NOS				3 (6%)
HYPERPLASIA, C-CELL	2 (4%)	5 (10%)	1 (2%)	4 (9%)
#PARATHYROID	(41)	(42)	(42)	(43)
HYPERPLASIA, NOS		1 (2%)		
#PANCREATIC ISLETS	(48)	(50)	(49)	(49)
HYPERPLASIA, NOS	1 (2%)	3 (6%)	1 (2%)	3 (6%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(49)
GALACTOCELE		1 (2%)	1 (2%)	1 (2%)
*PREPUTIAL GLAND	(49)	(50)	(50)	(49)
EPIDERMAL INCLUSION CYST	1 (2%)			
INFLAMMATION, ACUTE			1 (2%)	
DEGENERATION, CYSTIC	1 (2%)	1 (2%)		3 (6%)
HYPERPLASIA, NOS		1 (2%)		1 (2%)
#PROSTATE	(47)	(45)	(48)	(46)
INFLAMMATION, ACUTE	1 (2%)	4 (9%)	3 (6%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE/CHRONIC		10 (22%)	4 (8%)	
INFLAMMATION, CHRONIC	3 (6%)	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV	18 (38%)		7 (15%)	8 (17%)
HYPERPLASIA, FOCAL			1 (2%)	
#TESTIS	(48)	(50)	(50)	(49)
DEGENERATION, NOS			1 (2%)	
ATROPHY, NOS	5 (10%)	1 (2%)	2 (4%)	3 (6%)
ASPERMATOGENESIS		1 (2%)		
HYPOSPERMATOGENESIS		2 (4%)	4 (8%)	2 (4%)
HYPERPLASIA, INTERSTITIAL CELL	5 (10%)	8 (16%)		
*EPIDIDYMIS	(49)	(50)	(50)	(49)
STEATITIS			1 (2%)	
GRANULOMA, SPERMATIC	8 (16%)	1 (2%)		5 (10%)
NECROSIS, FAT		1 (2%)		
NERVOUS SYSTEM				
#LEPTOMENINGES	(47)	(49)	(49)	(49)
HEMORRHAGE	2 (4%)	3 (6%)	3 (6%)	4 (8%)
INFLAMMATION, CHRONIC		1 (2%)		
#BRAIN	(47)	(49)	(49)	(49)
INFARCT HEMORRHAGIC				1 (2%)
ATROPHY, PRESSURE				1 (2%)
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(50)	(49)
MICROPHTHALMIA			1 (2%)	
HEMORRHAGE	1 (2%)			
INFLAMMATION, CHRONIC				1 (2%)
SYNECHIA, ANTERIOR				1 (2%)
SYNECHIA, POSTERIOR	1 (2%)	2 (4%)		1 (2%)
CATARACT		2 (4%)		1 (2%)
*EYE ANTERIOR CHAMBER	(49)	(50)	(50)	(49)
HEMORRHAGE				1 (2%)
*EYEBALL TUNICA VASCU	(49)	(50)	(50)	(49)
INFLAMMATION, NOS			1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	3 (6%)		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*EYE/RETINA	(49)	(50)	(50)	(49)
DEGENERATION, NOS	1 (2%)			2 (4%)
ATROPHY, NOS	4 (8%)	6 (12%)	2 (4%)	1 (2%)
*EYE/CRYSTALLINE LENS	(49)	(50)	(50)	(49)
DEGENERATION, NOS	1 (2%)		1 (2%)	
*LENS CAPSULE	(49)	(50)	(50)	(49)
MINERALIZATION		1 (2%)		
DEGENERATION, NOS	2 (4%)			1 (2%)
*LENS CORTEX	(49)	(50)	(50)	(49)
DEGENERATION, NOS	1 (2%)			1 (2%)
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(49)	(50)	(50)	(49)
MINERALIZATION			1 (2%)	1 (2%)
BODY CAVITIES				
*ABDOMINAL CAVITY	(49)	(50)	(50)	(49)
NECROSIS, FAT	1 (2%)			1 (2%)
*PERITONEUM	(49)	(50)	(50)	(49)
INFLAMMATION, CHRONIC DIFFUSE				1 (2%)
*PLEURA	(49)	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, CHRONIC				1 (2%)
*PERICARDIUM	(49)	(50)	(50)	(49)
INFLAMMATION, CHRONIC			1 (2%)	
*MESENTERY	(49)	(50)	(50)	(49)
STEATITIS	2 (4%)		1 (2%)	
NECROSIS, FAT	1 (2%)	2 (4%)		1 (2%)
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
STEATITIS	4		1	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC FOCAL	1			
NECROSIS, FAT	1	1	1	
CONNECTIVE TISSUE				
INFLAMMATION, CHRONIC	1			
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/NO HISTO	1			
AUTOLYSIS/NO NECROPSY	1			1

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED SELENIUM SULFIDE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		
ULCER, NOS		1 (2%)		
HYPERPLASIA, NOS			1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
GRANULOMA, FOREIGN BODY				1 (2%)
RESPIRATORY SYSTEM				
*LARYNX	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)			
#TRACHEA	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)			
#LUNG	(50)	(50)	(50)	(50)
ATELECTASIS			1 (2%)	
CONGESTION, NOS	4 (8%)	5 (10%)	2 (4%)	2 (4%)
EDEMA, NOS	2 (4%)			
INFLAMMATION, SUPPURATIVE	1 (2%)			1 (2%)
PNEUMONIA, CHRONIC MURINE	14 (28%)	40 (80%)	43 (86%)	39 (78%)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
GRANULOMA, FOREIGN BODY		1 (2%)		
FIBROSIS, DIFFUSE			1 (2%)	
PIGMENTATION, NOS			36 (72%)	45 (90%)
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(50)	(50)	(50)	(50)
MYELOFIBROSIS		1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	1 (2%)	1 (2%)	1 (2%)
#SPLEEN	(50)	(50)	(50)	(50)
HEMORRHAGE				2 (4%)
LIPOIDOSIS			1 (2%)	
HEMOSIDEROSIS	16 (32%)	16 (32%)	16 (32%)	14 (28%)
LYMPHOID DEPLETION			1 (2%)	
LEUKEMOID REACTION				1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)	
HEMATOPOIESIS	4 (8%)	4 (8%)	3 (6%)	2 (4%)
#SUBMANDIBULAR L.NODE	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)			
INFLAMMATION, CHRONIC	4 (8%)			
#MEDIASTINAL L.NODE	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)		
#MESENTERIC L. NODE	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)			
ANGIECTASIS		1 (2%)		
#LIVER	(50)	(50)	(50)	(50)
HEMATOPOIESIS				1 (2%)
#FORESTOMACH	(50)	(50)	(50)	(50)
PARAKERATOSIS	1 (2%)			
#THYMUS	(30)	(21)	(27)	(11)
CYST, NOS	1 (3%)			
CIRCULATORY SYSTEM				
#HEART	(50)	(50)	(50)	(49)
FIBROSIS	1 (2%)			
PERIARTERITIS	1 (2%)		2 (4%)	
#MYOCARDIUM	(50)	(50)	(50)	(49)
INFLAMMATION, CHRONIC	2 (4%)			
FIBROSIS	5 (10%)	6 (12%)		2 (4%)
CALCIFICATION, FOCAL				1 (2%)
*AORTA	(50)	(50)	(50)	(50)
MEDIAL CALCIFICATION				1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(50)	(50)	(50)
THROMBOSIS, NOS				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(50)	(50)	(50)
ATROPHY, NOS			1 (2%)	
#LIVER	(50)	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)		
CHOLANGIOFIBROSIS	1 (2%)			
DEGENERATION, NOS	1 (2%)	1 (2%)		1 (2%)
PELIOSIS HEPATIS				9 (18%)
NECROSIS, FOCAL	1 (2%)			1 (2%)
METAMORPHOSIS FATTY	1 (2%)	1 (2%)		2 (4%)
FOCAL CELLULAR CHANGE	37 (74%)	28 (56%)	29 (58%)	29 (58%)
ANGIECTASIS		1 (2%)		1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)	(50)
DEGENERATION, NOS	2 (4%)	3 (6%)		
NECROSIS, NOS	1 (2%)	4 (8%)	1 (2%)	
NECROSIS, DIFFUSE			1 (2%)	
#LIVER/PERIPORTAL	(50)	(50)	(50)	(50)
METAMORPHOSIS FATTY	1 (2%)			
#BILE DUCT	(50)	(50)	(50)	(50)
RETENTION OF CONTENT			1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	2 (4%)		1 (2%)	3 (6%)
HYPERPLASIA, NOS	2 (4%)			5 (10%)
HYPERPLASIA, FOCAL	1 (2%)			
#PANCREAS	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)		
ATROPHY, NOS			1 (2%)	1 (2%)
ATROPHY, FOCAL	1 (2%)	3 (6%)	1 (2%)	2 (4%)
ATROPHY, DIFFUSE				1 (2%)
#ESOPHAGUS	(50)	(50)	(50)	(50)
RUPTURE				1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)
HYPERKERATOSIS			1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(50)	(50)	(50)	(50)
ULCER, FOCAL	1 (2%)	2 (4%)		2 (4%)
INFLAMMATION, ACUTE		1 (2%)		
INFARCT, FOCAL			1 (2%)	
#GASTRIC SUBMUCOSA	(50)	(50)	(50)	(50)
EDEMA, NOS		1 (2%)		
#FORESTOMACH	(50)	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)			
ULCER, NOS	1 (2%)		1 (2%)	
ULCER, ACUTE		1 (2%)		
FIBROSIS	1 (2%)			
HYPERKERATOSIS	1 (2%)			
#LARGE INTESTINE	(50)	(50)	(50)	(50)
NEMATODIASIS				1 (2%)
PARASITISM		1 (2%)		1 (2%)
#COLON	(50)	(50)	(50)	(50)
ULCER, ACUTE		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
CALCULUS, NOS		2 (4%)		3 (6%)
CONGESTION, NOS		1 (2%)		
PYELONEPHRITIS SUPPURATIVE		1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	4 (8%)	3 (6%)	3 (6%)	7 (14%)
NEPHROPATHY, TOXIC		1 (2%)		
PIGMENTATION, NOS	2 (4%)	1 (2%)	2 (4%)	1 (2%)
#KIDNEY/CORTEX	(50)	(50)	(50)	(50)
CYST, NOS	1 (2%)			
#KIDNEY/TUBULE	(50)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
PIGMENTATION, NOS				1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)	
#URINARY BLADDER	(44)	(46)	(48)	(49)
HYPERPLASIA, EPITHELIAL			1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(45)	(50)	(49)	(48)
CYST, NOS	10 (22%)	1 (2%)	5 (10%)	1 (2%)
MULTIPLE CYSTS	5 (11%)		1 (2%)	1 (2%)
CONGESTION, NOS		1 (2%)		
HEMORRHAGE	4 (9%)	1 (2%)		
HEMORRHAGIC CYST			1 (2%)	
GRANULOMA, NOS			1 (2%)	
HEMOSIDEROSIS		1 (2%)	1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	3 (7%)	1 (2%)	2 (4%)	2 (4%)
ANGIECTASIS		1 (2%)		3 (6%)
#ADRENAL	(50)	(50)	(50)	(49)
HEMORRHAGIC CYST	1 (2%)			
INFLAMMATION, CHRONIC		1 (2%)		
ANGIECTASIS		1 (2%)		
#ADRENAL CORTEX	(50)	(50)	(50)	(49)
DEGENERATION, NOS	9 (18%)	8 (16%)	8 (16%)	8 (16%)
HYPERTROPHY, FOCAL			1 (2%)	
HYPERPLASIA, NODULAR				1 (2%)
HYPERPLASIA, FOCAL		1 (2%)		
ANGIECTASIS	3 (6%)	1 (2%)	5 (10%)	
#ADRENAL MEDULLA	(50)	(50)	(50)	(49)
HYPERPLASIA, NOS	3 (6%)		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	2 (4%)	
#THYROID	(49)	(49)	(50)	(49)
HYPERPLASIA, C-CELL	1 (2%)	1 (2%)	7 (14%)	4 (8%)
#PANCREATIC ISLETS	(50)	(50)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
GALACTOCELE	9 (18%)	8 (16%)	7 (14%)	
LACTATION		1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)	1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC SUPPURATIV				1 (2%)
DEGENERATION, CYSTIC				1 (2%)
#UTERUS	(48)	(47)	(48)	(50)
MUCOCELE		1 (2%)		
HYDROMETRA	2 (4%)		5 (10%)	1 (2%)
HEMORRHAGE		1 (2%)		
HEMATOMETRA	1 (2%)			1 (2%)
#UTERUS/ENDOMETRIUM	(48)	(47)	(48)	(50)
CYST, NOS		1 (2%)	1 (2%)	2 (4%)
MULTIPLE CYSTS	1 (2%)			
INFLAMMATION, ACUTE		2 (4%)		
HYPERPLASIA, CYSTIC			1 (2%)	2 (4%)
#OVARY/OVIDUCT	(48)	(47)	(48)	(50)
CYST, NOS				1 (2%)
#OVARY	(48)	(47)	(48)	(49)
FOLLICULAR CYST, NOS	1 (2%)	1 (2%)		
CONGESTION, NOS		4 (9%)	2 (4%)	
NERVOUS SYSTEM				
#LEPTOMENINGES	(50)	(50)	(50)	(49)
HEMORRHAGE			2 (4%)	
#BRAIN	(50)	(50)	(50)	(49)
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)	
ATROPHY, PRESSURE		4 (8%)	2 (4%)	
SPECIAL SENSE ORGANS				
*EYE	(50)	(50)	(50)	(50)
MICROPHTHALMIA		2 (4%)		
PUS			1 (2%)	
SYNECHIA, ANTERIOR			1 (2%)	
SYNECHIA, POSTERIOR		1 (2%)		1 (2%)
*EYE/CORNEA	(50)	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		
ULCER, NOS		1 (2%)		
INFLAMMATION, ACUTE				1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*EYEBALL TUNICA VASCU	(50)	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
*EYE/IRIS	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)	
*EYE/RETINA	(50)	(50)	(50)	(50)
DEGENERATION, NOS				1 (2%)
ATROPHY, NOS		5 (10%)	4 (8%)	1 (2%)
*LENS CAPSULE	(50)	(50)	(50)	(50)
MINERALIZATION	1 (2%)	1 (2%)		
DEGENERATION, NOS				1 (2%)
*LENS CORTEX	(50)	(50)	(50)	(50)
MINERALIZATION		1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM				
*SKULL	(50)	(50)	(50)	(50)
HEALED FRACTURE			1 (2%)	
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
STEATITIS	1 (2%)			
NECROSIS, FAT	1 (2%)		1 (2%)	
*PLEURA	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)	
*MESENTERY	(50)	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)	1 (2%)		1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)		
ADIPOSE TISSUE				
STEATITIS		1		1

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FOCAL			1	
NECROSIS, FAT	2	2		4

SPECIAL MORPHOLOGY SUMMARY

NONE

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED SELENIUM SULFIDE BY GAVAGE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED SELENIUM SULFIDE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	2 (4%)			
INFLAMMATION, GRANULOMATOUS	1 (2%)			
FIBROSIS	1 (2%)			
METAPLASIA, OSSEOUS	1 (2%)			
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
EDEMA, NOS			1 (2%)	
ABSCESS, NOS		1 (2%)		1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
GRANULOMA, NOS				1 (2%)
NECROSIS, FAT		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(50)	(50)
CONGESTION, NOS	2 (4%)	5 (10%)	5 (10%)	4 (8%)
EDEMA, NOS	1 (2%)			
HEMORRHAGE	1 (2%)	2 (4%)	5 (10%)	4 (8%)
INFLAMMATION, FOCAL		1 (2%)		
PNEUMONIA, CHRONIC MURINE	2 (4%)	2 (4%)	7 (14%)	3 (6%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
LEUKEMOID REACTION	1 (2%)			
#BONE MARROW	(49)	(50)	(49)	(50)
HYPERPLASIA, MEGAKARYOCYTIC	1 (2%)			
MYELOID METAPLASIA		2 (4%)		
#SPLEEN	(49)	(50)	(50)	(50)
ATROPHY, NOS		1 (2%)	1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
LEUKEMOID REACTION		1 (2%)	1 (2%)	
HYPERPLASIA, LYMPHOID	8 (16%)	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIESIS	3 (6%)	2 (4%)	2 (4%)	3 (6%)
#CERVICAL LYMPH NODE	(49)	(50)	(49)	(50)
INFLAMMATION, NOS		1 (2%)		
#MESENTERIC L. NODE	(49)	(50)	(49)	(50)
CONGESTION, NOS	3 (6%)	11 (22%)	4 (8%)	4 (8%)
INFLAMMATION, NOS	3 (6%)			2 (4%)
INFLAMMATION, ACUTE	1 (2%)			
HYPERPLASIA, RETICULUM CELL	1 (2%)		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	14 (29%)	5 (10%)	9 (18%)	5 (10%)
HEMATOPOIESIS	1 (2%)			1 (2%)
#LUNG	(49)	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (2%)			
#PEYERS PATCH	(49)	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)		
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
EMBOLUS, SEPTIC	1 (2%)			
#MESENTERIC L. NODE	(49)	(50)	(49)	(50)
LYMPHANGIECTASIS	1 (2%)			
#LUNG	(49)	(50)	(50)	(50)
EMBOLUS, SEPTIC		1 (2%)		
#HEART	(49)	(50)	(50)	(50)
DILATATION, NOS	1 (2%)	1 (2%)		
PERIARTERITIS		1 (2%)	1 (2%)	
METAPLASIA, OSSEOUS		1 (2%)		
#AURICULAR APPENDAGE	(49)	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)			
#MYOCARDIUM	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
DEGENERATION, NOS	1 (2%)			
*AORTA	(49)	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC				1 (2%)
#LIVER	(49)	(50)	(50)	(50)
THROMBOSIS, NOS				1 (2%)
#KIDNEY	(49)	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)		
DIGESTIVE SYSTEM				
*INTESTINAL TRACT	(49)	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)	
#SALIVARY GLAND	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC				1 (2%)
FIBROSIS				1 (2%)
#LIVER	(49)	(50)	(50)	(50)
CYST, NOS			1 (2%)	
CONGESTION, NOS			2 (4%)	
INFLAMMATION, FOCAL				1 (2%)
ABSCESS, NOS		1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)	
FIBROSIS			1 (2%)	
NECROSIS, NOS	3 (6%)	1 (2%)	2 (4%)	2 (4%)
INFARCT, NOS	3 (6%)		3 (6%)	2 (4%)
AMYLOIDOSIS		1 (2%)		
METAMORPHOSIS FATTY				1 (2%)
CALCIFICATION, NOS				1 (2%)
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(49)	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)		2 (4%)
#LIVER/HEPATOCYTES	(49)	(50)	(50)	(50)
INFLAMMATION, DIFFUSE			3 (6%)	
NECROSIS, NOS				1 (2%)
#PANCREAS	(49)	(50)	(50)	(50)
CYSTIC DUCTS				3 (6%)
#ESOPHAGUS	(49)	(50)	(50)	(50)
RUPTURE		1 (2%)		
INFLAMMATION, CHRONIC				1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(49)	(49)	(49)	(48)
ULCER, FOCAL	3 (6%)	2 (4%)	1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
HYPERKERATOSIS			1 (2%)	1 (2%)
ACANTHOSIS			1 (2%)	
#LARGE INTESTINE	(49)	(50)	(50)	(50)
NEMATODIASIS	1 (2%)	2 (4%)		1 (2%)
PARASITISM			4 (8%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		1 (2%)	1 (2%)
PYELONEPHRITIS SUPPURATIVE			1 (2%)	
INFLAMMATION, CHRONIC	6 (12%)	9 (18%)	15 (30%)	12 (24%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)		
NEPHROPATHY, TOXIC				1 (2%)
#URINARY BLADDER	(49)	(50)	(49)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, CHRONIC	2 (4%)			
HYPERPLASIA, EPITHELIAL			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(40)	(33)	(45)	(38)
CYST, NOS	2 (5%)			
#ADRENAL CORTEX	(48)	(49)	(49)	(49)
CYST, NOS			2 (4%)	
HYPERTROPHY, FOCAL			2 (4%)	
HYPERPLASIA, NOS			1 (2%)	
#ADRENAL MEDULLA	(48)	(49)	(49)	(49)
HYPERPLASIA, NOS	1 (2%)	2 (4%)	1 (2%)	
#THYROID	(47)	(47)	(49)	(48)
INFLAMMATION, FOCAL			1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
CYSTIC DUCTS			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
*PENIS	(49)	(50)	(50)	(50)
HEMORRHAGE			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
*PREPUTIAL GLAND	(49)	(50)	(50)	(50)
CYST, NOS				1 (2%)
HEMORRHAGE			1 (2%)	
ABSCESS, NOS			1 (2%)	
INFLAMMATION, CHRONIC			2 (4%)	
#PROSTATE	(49)	(50)	(48)	(49)
OBSTRUCTION, NOS			1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	1 (2%)	
*SEMINAL VESICLE	(49)	(50)	(50)	(50)
DISTENTION			1 (2%)	2 (4%)
CONGESTION, NOS			1 (2%)	
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC			1 (2%)	
ATROPHY, NOS		1 (2%)		
#TESTIS	(49)	(50)	(48)	(49)
HEMORRHAGE				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
CALCIFICATION, NOS			1 (2%)	
CALCIFICATION, FOCAL			1 (2%)	
ATROPHY, NOS		2 (4%)	2 (4%)	
HYPERPLASIA, INTERSTITIAL CELL			1 (2%)	
*EPIDIDYMIS	(49)	(50)	(50)	(50)
INFLAMMATION, NOS				2 (4%)
GRANULOMA, SPERMATIC	1 (2%)		2 (4%)	1 (2%)
NECROSIS, FAT			1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(49)	(49)	(49)	(50)
HEMORRHAGE				1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE				1 (2%)
ABSCESS, NOS				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(50)	(50)
ABSCESS, CHRONIC		1 (2%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(49)	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
*INGUINAL REGION	(49)	(50)	(50)	(50)
NECROSIS, FAT				1 (2%)
*PLEURA	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)		
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	5	7	3	3
ANIMAL MISSING/NO NECROPSY	1			

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED SELENIUM SULFIDE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	50	49	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(49)	(50)	(49)
INFLAMMATION, NECROTIZING				1 (2%)
*SUBCUT TISSUE	(50)	(49)	(50)	(49)
ABSCESS, NOS				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(49)
CONGESTION, NOS	1 (2%)	1 (2%)	3 (6%)	3 (6%)
HEMORRHAGE		4 (8%)	8 (16%)	
INFLAMMATION, SUPPURATIVE				1 (2%)
PNEUMONIA, CHRONIC MURINE	3 (6%)	4 (8%)	5 (10%)	5 (10%)
PIGMENTATION, NOS		1 (2%)		
ALVEOLAR MACROPHAGES		1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM				3 (6%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(50)	(49)	(50)	(49)
FIBROUS OSTEODYSTROPHY			1 (2%)	1 (2%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)			
MYELOID METAPLASIA			1 (2%)	
#SPLEEN	(50)	(49)	(50)	(49)
FIBROSIS			1 (2%)	
NECROSIS, NOS			1 (2%)	
ATROPHY, NOS				1 (2%)
LEUKEMOID REACTION			1 (2%)	
HYPERPLASIA, LYMPHOID	3 (6%)	7 (14%)		2 (4%)
HEMATOPOIESIS	1 (2%)		3 (6%)	2 (4%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE	(48)	(48)	(50)	(48)
INFLAMMATION, NOS				1 (2%)
#CERVICAL LYMPH NODE	(48)	(48)	(50)	(48)
INFLAMMATION, NOS				1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)		2 (4%)
#BRONCHIAL LYMPH NODE	(48)	(48)	(50)	(48)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
#MESENTERIC L. NODE	(48)	(48)	(50)	(48)
CONGESTION, NOS				1 (2%)
INFLAMMATION, NOS		1 (2%)		3 (6%)
HYPERPLASIA, LYMPHOID	4 (8%)	5 (10%)	3 (6%)	6 (13%)
#LUNG	(50)	(49)	(50)	(49)
LEUKOCYTOSIS, NOS	1 (2%)			
#LIVER	(50)	(49)	(50)	(49)
HEMATOPOIESIS				2 (4%)
#PEYERS PATCH	(50)	(49)	(50)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)	
#ADRENAL CORTEX	(50)	(48)	(48)	(49)
HEMATOPOIESIS				1 (2%)
#THYMUS	(29)	(29)	(18)	(26)
HYPERPLASIA, LYMPHOID		1 (3%)		
CIRCULATORY SYSTEM				
#HEART	(50)	(49)	(50)	(49)
PERIARTERITIS	1 (2%)			
#HEART/ATRIUM	(50)	(49)	(50)	(49)
EMBOLUS, SEPTIC			1 (2%)	
#MYOCARDIUM	(50)	(49)	(50)	(49)
INFLAMMATION, NOS			2 (4%)	
INFLAMMATION, SUPPURATIVE			1 (2%)	
#MITRAL VALVE	(50)	(49)	(50)	(49)
PIGMENTATION, NOS			1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*AORTA	(50)	(49)	(50)	(49)
INFLAMMATION, NOS				1 (2%)
*CORONARY ARTERY	(50)	(49)	(50)	(49)
INFLAMMATION, SUPPURATIVE			2 (4%)	
INFLAMMATION PROLIFERATIVE			1 (2%)	
#LIVER	(50)	(49)	(50)	(49)
THROMBOSIS, NOS				1 (2%)
EMBOLUS, SEPTIC			1 (2%)	
#PANCREAS	(50)	(49)	(50)	(49)
PERIARTERITIS				1 (2%)
#KIDNEY	(50)	(49)	(50)	(48)
EMBOLUS, SEPTIC			1 (2%)	
PERIARTERITIS	1 (2%)			
#RIGHT OVARY	(50)	(49)	(50)	(49)
THROMBOSIS, NOS	1 (2%)			
#LEFT OVARY	(50)	(49)	(50)	(49)
THROMBUS, ORGANIZED	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(46)	(50)	(49)
HEMORRHAGE			2 (4%)	
#LIVER	(50)	(49)	(50)	(49)
CONGESTION, NOS	1 (2%)			
HEMORRHAGE	1 (2%)			
INFLAMMATION, FOCAL			1 (2%)	
NECROSIS, NOS	1 (2%)			2 (4%)
NECROSIS, FOCAL			2 (4%)	
INFARCT, NOS				1 (2%)
FOCAL CELLULAR CHANGE			1 (2%)	3 (6%)
#BILE DUCT	(50)	(49)	(50)	(49)
CYST, NOS			1 (2%)	1 (2%)
HYPERPLASIA, NOS				1 (2%)
#PANCREAS	(50)	(49)	(50)	(49)
CYSTIC DUCTS	3 (6%)	3 (6%)		1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FOCAL				1 (2%)
#PANCREATIC ACINUS	(50)	(49)	(50)	(49)
ATROPHY, NOS	1 (2%)	1 (2%)		
#ESOPHAGUS	(50)	(49)	(49)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
#STOMACH	(50)	(49)	(50)	(49)
ULCER, FOCAL		2 (4%)		1 (2%)
INFLAMMATION, CHRONIC		1 (2%)		1 (2%)
HYPERKERATOSIS				3 (6%)
ACANTHOSIS				2 (4%)
#LARGE INTESTINE	(49)	(49)	(50)	(49)
NEMATODIASIS	1 (2%)			
PARASITISM				1 (2%)
URINARY SYSTEM				
#KIDNEY	(50)	(49)	(50)	(48)
CYST, NOS	1 (2%)			
INFLAMMATION, CHRONIC	5 (10%)		5 (10%)	6 (13%)
GLOMERULOSCLEROSIS, NOS	1 (2%)			
AMYLOIDOSIS	1 (2%)		1 (2%)	
#KIDNEY/GLOMERULUS	(50)	(49)	(50)	(48)
NEPHROPATHY			1 (2%)	
#URINARY BLADDER	(49)	(48)	(49)	(48)
AMYLOIDOSIS	1 (2%)			
ENDOCRINE SYSTEM				
#PITUITARY	(45)	(42)	(37)	(38)
CYST, NOS			1 (3%)	
ANGIECTASIS			1 (3%)	
#ADRENAL MEDULLA	(50)	(48)	(48)	(49)
HYPERPLASIA, NOS				1 (2%)
#THYROID	(49)	(48)	(50)	(49)
CYSTIC FOLLICLES	1 (2%)			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	1 (2%)			
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			2 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(49)	(50)	(49)
METAPLASIA, SQUAMOUS		1 (2%)		
#UTERUS	(50)	(49)	(50)	(49)
HYDROMETRA	1 (2%)		1 (2%)	1 (2%)
ANGIECTASIS	1 (2%)			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)	
HYPERPLASIA, CYSTIC	41 (82%)	45 (92%)	40 (80%)	36 (73%)
#OVARY/OVIDUCT	(50)	(49)	(50)	(49)
INFLAMMATION, CHRONIC			1 (2%)	
#OVARY	(50)	(49)	(50)	(49)
CYSTIC FOLLICLES		2 (4%)	5 (10%)	5 (10%)
FOLLICULAR CYST, NOS	4 (8%)	1 (2%)		
PAROVARIAN CYST	7 (14%)	9 (18%)	13 (26%)	6 (12%)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, CHRONIC			1 (2%)	
AMYLOIDOSIS			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(50)	(49)	(50)	(49)
INFLAMMATION, NOS		1 (2%)		1 (2%)
ABSCESS, NOS				1 (2%)
PHTHISIS BULBI		1 (2%)		
*EYE/CORNEA	(50)	(49)	(50)	(49)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, FOCAL				1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(50)	(49)	(50)	(49)
PARASITISM	1 (2%)			
BODY CAVITIES				
*PERITONEUM	(50)	(49)	(50)	(49)
INFLAMMATION, NOS	2 (4%)			
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1		1	
ANIMAL MISSING/NO NECROPSY		1		
AUTOLYSIS/NO NECROPSY				1

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

APPENDIX E

ANALYSIS OF SELENIUM SULFIDE

Analysis of Selenium Sulfide
Midwest Research Institute

A. Elemental Analysis

Element	Se	S
Theory		
SeS	71.12	28.88
SeS_2	55.18	44.82
Observed 11/15/74	61.0±0.6	40.93
Observed 7/19/79	59.97	
	59.88	40.7±0.2

B. Melting Point

Literature	
SeS	118°-119°C (Weast, 1974-1975)
SeS_2	less than 100°C (Weast, 1974-1975)
Observed	115°-117°C

C. X-Ray Diffraction

Instrument: Debye-Scherrer camera with filtered Cu radiation, 50 kv, and 30 mamp.

Procedure: The X-ray diffraction pattern of the selenium sulfide powder used in this study was determined. Since a suitable standard was not available, intensities were recorded as approximations expressed in terms varying from "very weak" to "very strong."

Table E1. X-Ray Diffraction Values

Literature Values (a)		Found (b)	
d	intensity	d	intensity
6.67	10	6.78-6.18	band
6.28	20		
5.13	10	5.11	very weak
4.42	50	4.37	medium
		4.16	very weak
3.77	100	3.75	very strong
3.70	50		
3.54	50	3.51	medium
3.34	10	3.35	weak +
3.22	60	3.21	medium
3.14	40	3.11	medium -
3.06	30	3.04	weak +
2.97	10	2.95	weak
2.78	10	2.76	weak
2.63	20	2.63	weak +
2.58	10	2.56	weak
2.52	40	2.51	medium
2.44	10	2.43	very weak
2.24	20	2.24	weak +
		2.14-2.09	band
2.01	20	2.01	weak +
1.97	10	1.97	weak
1.92	10		
1.89	20	1.89	weak
1.83	10	1.83	weak -
1.78	30	1.79	weak +
1.74	10	1.74	very weak
1.71	20	1.71	weak
1.66	20	1.66	weak
1.63	20	1.63	weak
1.57	20	1.57	weak
1.53	10	1.53	weak
1.48	10	1.48	very weak
1.46	10	1.46	very weak

(a) Smith (1960), Virodov (1964)
(b) The approximation of intensities at different d values, as observed for the test material used in the bioassay, were consistent with the numerical values of intensities given in the literature for selenium monosulfide.

APPENDIX F

ANALYSIS OF SELENIUM SULFIDE IN AQUEOUS CARBOXYMETHYLCELLULOSE FOR STABILITY

Analysis of Selenium Sulfide in Aqueous
Carboxymethylcellulose for Stability

SPECIAL STABILITY STUDY

I. PURPOSE

To determine if the aqueous carboxymethylcellulose mixture used in the bioassay in any way decomposed or altered the selenium sulfide used in the bioassay.

II. ANALYSIS

A. SAMPLE PREPARATION

1. Sample 1: A 100-ml solution of 0.5% carboxymethylcellulose in deionized water was prepared. A 750-mg sample of selenium sulfide was weighed into a 50-ml volumetric flask and brought to volume with the above aqueous carboxymethyl cellulose (CMS) solution and mixed for 30 minutes on a vortex mixer. It was then left open to the atmosphere in the light for the next 30 minutes, with occasional shaking. The mixture was then shaken in a 125-ml separatory funnel for 2 minutes with 50 ml of carbon disulfide, allowed to separate and the bottom layer (CS_2 layer), and drained into a 100-ml beaker.

2. Sample 2: A control sample of the same approximate weight was dissolved in 50 ml of carbon disulfide in a 100-ml beaker. Both the sample and control beakers (Samples 1 and 2) were placed in a glove box on a marble slab covered by watchglasses and allowed to evaporate slowly overnight.

3. Sample 3: A selenium sulfide sample untreated, which had been stored refrigerated.

4. Sample 4: A selenium sulfide sample which was exposed overnight at room temperature in a beaker.

B. DESCRIPTION OF SAMPLES

Samples 1 and 2 crystallized with multiple crystal forms.

Sample 1 contained reddish orange crystals of 1-3 mm in length while Sample 2 contained crystals of the same color of about 1 mm in length. Both Samples 1 and 2 had the yellow crystals.

Sample 4 was unchanged in appearance from Sample 3.

C. X-RAY DIFFRACTION

X-ray diffraction analyses were performed on:

1. Samples 1 and 2: Total mix of 11 crystal types from each sample.

2. Samples 3 and 4: Representative sample of homogeneous material from each.

III. RESULTS

X-RAY DIFFRACTION

The x-ray diffraction patterns for all the samples had similar d spacings and all had the same major line. However, the relative intensities of the lines differed from sample to sample. The d spacing of the sample mix (1) and the control (2) corresponded well to each other and to a previously obtained pattern of the untreated selenium sulfide (report dated 11/15/74). Samples 3 and 4 also corresponded well to each other and to the previous untreated selenium sulfide sample.

APPENDIX G

ANALYSIS OF GAVAGE SUSPENSIONS FOR CONCENTRATION OF SELENIUM SULFIDE

APPENDIX G

Analysis of Gavage Suspensions For Concentration of Selenium Sulfide

The entire sample of selenium sulfide suspension in 0.5% aqueous carboxymethylcellulose was extracted three times with 25-ml portions of carbon disulfide. Duplicate assays were not performed. The extracts were combined, and a 30-ml aliquot was reduced to dryness using a flash evaporator. Five milliliters of concentrated nitric acid solution was added to the residue, and the acid was heated until brown gases no longer evolved and the solution became clear. The digest was transferred with distilled water to a volumetric flask, and the volume was adjusted to the mark. An analytical standard was prepared by adding a known amount of selenium sulfide to 0.5% aqueous carboxymethylcellulose. These known weights of selenium sulfide were extracted in carbon disulfide and were taken through the above procedure. The different samples were analyzed using atomic absorption.

Theoretical Concentration in Suspensions (mg/ml)	Number of Samples	Sample Analytical Mean (mg/ml)	Coefficient of Variation (%)	Range (mg/ml)
10	5	9.6	11.0	8.7-11.3
15	5	14.1	7.0	12.9-15.4

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

February 15, 1980

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

The primary reviewer for the report on the bioassay of selenium sulfide agreed with the conclusion that the compound was not carcinogenic, under the conditions of test. After a brief description of the experimental design and toxicity findings, the reviewer opined that selenium sulfide would not pose any significant human risk, based on results of the bioassay study.

The secondary reviewer noted that no attempt was made to determine how much of the selenium sulfide was absorbed. He said that the results of the subchronic study indicated that higher chronic dosages could have been administered and added that he was disturbed by the high early mortality of the animals. Based on these deficiencies, the reviewer questioned the validity of the study for assessing the potential risk of selenium sulfide for human beings.

The primary reviewer indicated that the study was not intended to determine if selenium sulfide had systemic effects, since a previous study done by gavage was meant for that purpose. The reviewer added that dermal toxicity had been demonstrated in this bioassay and that the administration of higher dosages could have resulted in excessive toxicity. In regard to the excessive mortality, the reviewer pointed out that the mouse strain used was selected because it was supposed to be particularly sensitive, although its lifespan was relatively shorter than other strains. The reviewer added that the validity of the study would depend upon how much of their natural lifespan the animals had lived. A Program staff member indicated that the survival of the animals was consistent with the longevity displayed by this strain in other studies. Another

staff member commented that, despite the study's limitations, it was sufficiently adequate that the results should be reported.

One Clearinghouse member said that selenium was a conundrum in that it is carcinogenic when given at high levels by gavage but it is an essential element at low levels. He added that there is some evidence that it may even act as an anti-carcinogen. Another member pointed out that sodium selenite or selanate is the form of selenium that is essential. He said it is a conundrum similar to cobalt, in which one form is an essential element and another a carcinogen. It was suggested that a paragraph be added to the bioassay report indicating the differences in the various forms of selenium. The primary reviewer moved that the report on the bioassay of selenium sulfide by dermal exposure be accepted as written. The motion was seconded and approved unanimously.

Members present were:

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

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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.

*U.S. GOVERNMENT PRINTING OFFICE : 1980 O-311-201/3141

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