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
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SELENIUM SULFIDE (GAVAGE)

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

and

National Toxicology Program
Research Triangle Park
Box 12233
North Carolina 27709

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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August 1980
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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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(9) Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri.
(10) Now with the Carcinogenesis Testing Program.
(11) Now with Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland.
(12) Now with Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, Maryland.
(13) Now with Office of Director, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.
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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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$\mu$g/100 g feed, equivalent to 4 $\mu$g/100 g feed of elemental selenium, or 0.25 $\mu$g 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 \((\text{Se}_4\text{S}_4\); 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

<table>
<thead>
<tr>
<th></th>
<th>Males Mean Weight at Week 13</th>
<th>Females Mean Weight at Week 13 as % of Control</th>
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<tr>
<td>Dose (a)</td>
<td>Surviv-</td>
<td></td>
</tr>
<tr>
<td>(mg/kg/day)</td>
<td>val(b)</td>
<td>(% of Control)</td>
</tr>
<tr>
<td>RATS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10/10</td>
<td>100</td>
</tr>
<tr>
<td>3.2</td>
<td>10/10</td>
<td>102</td>
</tr>
<tr>
<td>5.6</td>
<td>10/10</td>
<td>105</td>
</tr>
<tr>
<td>10.0</td>
<td>10/10</td>
<td>103</td>
</tr>
<tr>
<td>17.8</td>
<td>10/10</td>
<td>100</td>
</tr>
<tr>
<td>31.6</td>
<td>10/10</td>
<td>99</td>
</tr>
<tr>
<td>MICE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10/10</td>
<td>100</td>
</tr>
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<td>21.6</td>
<td>10/10</td>
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<td>46.4</td>
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<td>100.0</td>
<td>10/10</td>
<td>108</td>
</tr>
<tr>
<td>216.0</td>
<td>10/10</td>
<td>104</td>
</tr>
<tr>
<td>464.0</td>
<td>9/10</td>
<td>96</td>
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</table>

(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 
<table>
<thead>
<tr>
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<th>Dosed (weeks)</th>
<th>Observed (weeks)</th>
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<td></td>
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<tr>
<td>Untreated-Control</td>
<td>50</td>
<td>0</td>
<td>104-105</td>
<td></td>
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<tr>
<td>Vehicle-Control (c)</td>
<td>50</td>
<td>0</td>
<td>103</td>
<td>1</td>
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<td>15</td>
<td>103</td>
<td>1-2</td>
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<tr>
<td>Untreated-Control</td>
<td>50</td>
<td>0</td>
<td>104-105</td>
<td></td>
</tr>
<tr>
<td>Vehicle-Control (c)</td>
<td>50</td>
<td>0</td>
<td>103</td>
<td>1</td>
</tr>
<tr>
<td>Low-Dose</td>
<td>50</td>
<td>3</td>
<td>103</td>
<td>1</td>
</tr>
<tr>
<td>High-Dose</td>
<td>50</td>
<td>15</td>
<td>103</td>
<td>1-2</td>
</tr>
</tbody>
</table>

(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

<table>
<thead>
<tr>
<th>Sex and Test Group</th>
<th>Initial No. of Animals (a)</th>
<th>Selenium Sulfide Dose (b) (mg/kg/day)</th>
<th>Time on Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dosed (weeks)</td>
</tr>
<tr>
<td><strong>MALES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated-Control</td>
<td>50</td>
<td>0</td>
<td>104</td>
</tr>
<tr>
<td>Vehicle-Control (c)</td>
<td>50</td>
<td>0</td>
<td>103</td>
</tr>
<tr>
<td>Low-Dose</td>
<td>50</td>
<td>20</td>
<td>103</td>
</tr>
<tr>
<td>High-Dose</td>
<td>50</td>
<td>100</td>
<td>103</td>
</tr>
<tr>
<td><strong>FEMALES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated-Control</td>
<td>50</td>
<td>0</td>
<td>104</td>
</tr>
<tr>
<td>Vehicle-Control (c)</td>
<td>50</td>
<td>0</td>
<td>103</td>
</tr>
<tr>
<td>Low-Dose</td>
<td>50</td>
<td>20</td>
<td>103</td>
</tr>
<tr>
<td>High-Dose</td>
<td>50</td>
<td>100</td>
<td>103</td>
</tr>
</tbody>
</table>

(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

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MALES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>1/48(2%)</td>
<td>0/50(0%)</td>
<td>0/50(0%)</td>
<td>14/49(29%)</td>
</tr>
<tr>
<td>Neoplastic Nodules</td>
<td>3/48(6%)</td>
<td>1/50(2%)</td>
<td>0/50(0%)</td>
<td>15/49(31%)</td>
</tr>
<tr>
<td><strong>FEMALES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>0/50(0%)</td>
<td>0/50(0%)</td>
<td>0/50(0%)</td>
<td>21/50(42%)</td>
</tr>
<tr>
<td>Neoplastic Nodules</td>
<td>0/50(0%)</td>
<td>1/50(2%)</td>
<td>0/50(0%)</td>
<td>25/50(50%)</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integumentary System:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoacanthoma of the Skin (b)</td>
<td>3/50 (6)</td>
<td>2/50 (4)</td>
<td>2/49 (4)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.058</td>
<td>0.059</td>
<td>0.667</td>
</tr>
<tr>
<td>Upper Limit</td>
<td>5.570</td>
<td>5.680</td>
<td>0.680</td>
</tr>
<tr>
<td>Weeks to First Observed Tumor (f)</td>
<td>104</td>
<td>104</td>
<td>105</td>
</tr>
<tr>
<td><strong>Integumentary System:</strong></td>
<td>Fibroma of the Subcutaneous Tissue (b)</td>
<td>2/50 (4)</td>
<td>4/50 (8)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.101</td>
<td>0.000</td>
<td>2.000</td>
</tr>
<tr>
<td>Upper Limit</td>
<td>21.316</td>
<td>3.448</td>
<td>0.000</td>
</tr>
<tr>
<td>Weeks to First Observed Tumor (f)</td>
<td>104</td>
<td>91</td>
<td>--</td>
</tr>
<tr>
<td><strong>Integumentary System:</strong></td>
<td>Fibrosarcoma of the Subcutaneous Tissue (b)</td>
<td>2/50 (4)</td>
<td>5/50 (10)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.432</td>
<td>0.183</td>
<td>2.500</td>
</tr>
<tr>
<td>Upper Limit</td>
<td>25.286</td>
<td>17.671</td>
<td>1.531</td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>100</td>
<td>75</td>
<td>105</td>
</tr>
<tr>
<td><strong>Hematopoietic System:</strong></td>
<td>Lymphoma or Leukemia (b)</td>
<td>7/50 (14)</td>
<td>15/50 (30)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>P=0.027</td>
<td>P=0.045</td>
<td>P=0.015</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.907</td>
<td>1.082</td>
<td>2.143</td>
</tr>
<tr>
<td>Upper Limit</td>
<td>5.663</td>
<td>6.400</td>
<td>2.478</td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>67</td>
<td>92</td>
<td>69</td>
</tr>
</tbody>
</table>
Table 5. Analyses of the Incidence of Primary Tumors in Male Rats
Administered Selenium Sulfide by Gavage (a)

(continued)

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver: Hepatocellular Carcinoma (b)</td>
<td>0/50 (0)</td>
<td>0/50 (0)</td>
<td>14/49 (29)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>--</td>
<td>--</td>
<td>P less than 0.001</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td>--</td>
<td>--</td>
<td>Infinite</td>
</tr>
<tr>
<td>Lower Limit</td>
<td>--</td>
<td>--</td>
<td>4.452</td>
</tr>
<tr>
<td>Upper Limit</td>
<td>--</td>
<td>--</td>
<td>Infinite</td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>--</td>
<td>--</td>
<td>105</td>
</tr>
</tbody>
</table>

| 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            | --       | 90         |

| 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)

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid: C-cell Carcinoma or Adenoma (b)</strong></td>
<td>1/50 (2)</td>
<td>5/49 (10)</td>
<td>2/47 (4)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>5.102</td>
<td>2.128</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>236.025</td>
<td>122.810</td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>104</td>
<td>103</td>
<td>105</td>
</tr>
<tr>
<td><strong>Preputial Gland: Carcinoma, NOS (b)</strong></td>
<td>7/50 (14)</td>
<td>10/50 (20)</td>
<td>12/49 (24)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>1.429</td>
<td>1.749</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>4.072</td>
<td>4.802</td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>104</td>
<td>79</td>
<td>105</td>
</tr>
<tr>
<td><strong>Testis: Interstitial-cell Tumor (b)</strong></td>
<td>41/50 (82)</td>
<td>45/50 (90)</td>
<td>47/49 (96)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>P=0.024</td>
<td>N.S.</td>
<td>P=0.028</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>1.098</td>
<td>1.170</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>1.259</td>
<td>1.257</td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>87</td>
<td>79</td>
<td>87</td>
</tr>
</tbody>
</table>

(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)

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integumentary System: Fibroma of the Subcutaneous Tissue (b)</td>
<td>0/50 (0)</td>
<td>3/50 (6)</td>
<td>2/50 (4)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td>—</td>
<td>2.000</td>
<td>1.333</td>
</tr>
<tr>
<td>Lower Limit</td>
<td>—</td>
<td>0.759</td>
<td>0.438</td>
</tr>
<tr>
<td>Upper Limit</td>
<td>—</td>
<td>5.989</td>
<td>4.331</td>
</tr>
<tr>
<td>Weeks to First Observed Tumor (f)</td>
<td>—</td>
<td>97</td>
<td>105</td>
</tr>
</tbody>
</table>

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) | — | 37.000 |
| Lower Limit | — | 6.933 |
| Upper Limit | — | 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)

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary: Chromophobe Adenoma (b)</td>
<td>23/50 (46)</td>
<td>14/49 (29)</td>
<td>11/48 (23)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>P=0.021 (N)</td>
<td>N.S.</td>
<td>P=0.014 (N)</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.621</td>
<td>0.498</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>1.101</td>
<td>0.936</td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>84</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>Adrenal: Pheochromocytoma (b)</td>
<td>4/50 (8)</td>
<td>2/50 (4)</td>
<td>4/49 (8)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.500</td>
<td>1.020</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>3.183</td>
<td>5.183</td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>102</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>Mammary Gland: Fibroadenoma (b)</td>
<td>13/50 (26)</td>
<td>15/50 (30)</td>
<td>8/50 (16)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>1.154</td>
<td>0.615</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>2.349</td>
<td>1.454</td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>62</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Clitoral Gland: Carcinoma, NOS (b)</td>
<td>3/50 (6)</td>
<td>3/50 (6)</td>
<td>1/50 (2)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>1.000</td>
<td>0.333</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>7.133</td>
<td>3.983</td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>102</td>
<td>99</td>
<td>105</td>
</tr>
</tbody>
</table>
Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Selenium Sulfide by Gavage (a)

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

(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

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated Control</td>
<td>Vehicle Control Dose</td>
</tr>
<tr>
<td>Number of Tissues</td>
<td>49 50 50 50</td>
<td>50 49 50 49</td>
</tr>
<tr>
<td>Examined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>17(35%) 15(30%) 11(22%) 23(46%)</td>
<td>2(4%) 0(0%) 1(2%) 22(45%)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>3(6%) 0(0%) 3(6%) 0(0%)</td>
<td>1(2%) 0(0%) 1(2%) 6(12%)</td>
</tr>
<tr>
<td>Adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor-bearing</td>
<td>20(41%) 15(30%) 14(28%) 23(46%)</td>
<td>3(6%) 0(0%) 2(4%) 25(50%)</td>
</tr>
<tr>
<td>Animals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Incidence of Primary Lung Tumors in Mice

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

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integumentary System:</strong> Fibrosarcoma of the Subcutaneous Tissue (b)</td>
<td>4/50 (8)</td>
<td>4/50 (8)</td>
<td>1/50 (2)</td>
</tr>
<tr>
<td><strong>P Values (c,d)</strong></td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Relative Risk (e)</strong></td>
<td>1.000</td>
<td>0.250</td>
<td></td>
</tr>
<tr>
<td><strong>Lower Limit</strong></td>
<td>0.197</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td><strong>Upper Limit</strong></td>
<td>5.083</td>
<td>2.411</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks to First Observed Tumor (f)</strong></td>
<td>100</td>
<td>82</td>
<td>89</td>
</tr>
<tr>
<td><strong>Lung:</strong> Alveolar/Bronchiolar Carcinoma or Adenoma (b)</td>
<td>4/50 (8)</td>
<td>10/50 (20)</td>
<td>13/50 (26)</td>
</tr>
<tr>
<td><strong>P Values (c,d)</strong></td>
<td>P=0.022</td>
<td>N.S.</td>
<td>P=0.016</td>
</tr>
<tr>
<td><strong>Relative Risk (e)</strong></td>
<td>2.500</td>
<td>3.250</td>
<td></td>
</tr>
<tr>
<td><strong>Lower Limit</strong></td>
<td>0.779</td>
<td>1.091</td>
<td></td>
</tr>
<tr>
<td><strong>Upper Limit</strong></td>
<td>10.246</td>
<td>12.780</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks to First Observed Tumor</strong></td>
<td>73</td>
<td>82</td>
<td>96</td>
</tr>
<tr>
<td><strong>Hematopoietic System:</strong> Lymphoma or Leukemia (b)</td>
<td>4/50 (8)</td>
<td>12/50 (24)</td>
<td>8/50 (16)</td>
</tr>
<tr>
<td><strong>P Values (c,d)</strong></td>
<td>N.S.</td>
<td>P=0.027</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Departure from Linear Trend (g)</strong></td>
<td>P=0.032</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relative Risk (e)</strong></td>
<td>3.000</td>
<td>2.000</td>
<td></td>
</tr>
<tr>
<td><strong>Lower Limit</strong></td>
<td>0.986</td>
<td>0.576</td>
<td></td>
</tr>
<tr>
<td><strong>Upper Limit</strong></td>
<td>11.938</td>
<td>8.339</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks to First Observed Tumor</strong></td>
<td>89</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td><strong>All Sites:</strong> Hemangiosarcoma or Hemangioma (b)</td>
<td>5/50 (10)</td>
<td>1/50 (2)</td>
<td>3/50 (6)</td>
</tr>
<tr>
<td><strong>P Values (c,d)</strong></td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Relative Risk (e)</strong></td>
<td>0.200</td>
<td>0.600</td>
<td></td>
</tr>
<tr>
<td><strong>Lower Limit</strong></td>
<td>0.004</td>
<td>0.098</td>
<td></td>
</tr>
<tr>
<td><strong>Upper Limit</strong></td>
<td>1.699</td>
<td>2.910</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks to First Observed Tumor</strong></td>
<td>63</td>
<td>105</td>
<td>64</td>
</tr>
</tbody>
</table>
Table 9. Analyses of the Incidence of Primary Tumors in Male Mice Administered Selenium Sulfide by Gavage (a)

(continued)

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver: Hepatocellular Carcinoma (b)</td>
<td>15/50 (30)</td>
<td>11/50 (22)</td>
<td>23/50 (46)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>P=0.014</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td>0.733</td>
<td>1.533</td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.340</td>
<td>0.878</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>1.532</td>
<td>2.739</td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>100</td>
<td>82</td>
<td>89</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung: Alveolar/Bronchiolar Carcinoma (b)</strong></td>
<td>0/49 (0)</td>
<td>1/50 (2)</td>
<td>4/49 (8)</td>
</tr>
<tr>
<td><strong>P Values (c,d)</strong></td>
<td>P=0.013</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Relative Risk (e)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>Infinite</td>
<td>Infinite</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>0.053</td>
<td>0.928</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks to First Observed Tumor</strong></td>
<td>—</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td><strong>Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)</strong></td>
<td>0/49 (0)</td>
<td>3/50 (6)</td>
<td>12/49 (24)</td>
</tr>
<tr>
<td><strong>P Values (c,d)</strong></td>
<td>P less than 0.001</td>
<td>N.S.</td>
<td>P less than 0.001</td>
</tr>
<tr>
<td><strong>Relative Risk (e)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>Infinite</td>
<td>Infinite</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>0.590</td>
<td>3.670</td>
<td></td>
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<tr>
<td><strong>Weeks to First Observed Tumor</strong></td>
<td>—</td>
<td>78</td>
<td>98</td>
</tr>
<tr>
<td><strong>Hematopoietic System: Lymphoma or Leukemia (b)</strong></td>
<td>17/49 (35)</td>
<td>22/50 (44)</td>
<td>17/49 (35)</td>
</tr>
<tr>
<td><strong>P Values (c,d)</strong></td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Relative Risk (e)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>1.268</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>0.740</td>
<td>0.548</td>
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<tr>
<td><strong>Weeks to First Observed Tumor</strong></td>
<td>77</td>
<td>74</td>
<td>65</td>
</tr>
<tr>
<td><strong>All Sites: Hemangiosarcoma or Hemangioma (b)</strong></td>
<td>2/49 (4)</td>
<td>3/50 (6)</td>
<td>4/49 (8)</td>
</tr>
<tr>
<td><strong>P Values (c,d)</strong></td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Relative Risk (e)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>1.470</td>
<td>2.000</td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>0.176</td>
<td>0.302</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks to First Observed Tumor</strong></td>
<td>104</td>
<td>101</td>
<td>98</td>
</tr>
<tr>
<td>Topography: Morphology</td>
<td>Vehicle Control</td>
<td>Low Dose</td>
<td>High Dose</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Liver: Hepatocellular Carcinoma (b)</strong></td>
<td>0/49 (0)</td>
<td>1/50 (2)</td>
<td>22/49 (45)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>P less than 0.001</td>
<td>N.S.</td>
<td>P less than 0.001</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td>Infinite</td>
<td>7.171</td>
<td>Infinite</td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.053</td>
<td>Infinite</td>
<td>7.171</td>
</tr>
<tr>
<td>Upper Limit</td>
<td>Infinite</td>
<td>Infinite</td>
<td>Infinite</td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>--</td>
<td>105</td>
<td>74</td>
</tr>
</tbody>
</table>

| 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 | 8.233 | Infinite |
| Lower Limit | 0.290 | Infinite | 8.233 |
| Upper Limit | Infinite | 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 | 0.000 |
| Lower Limit | 0.000 | 0.000 | 0.000 |
| Upper Limit | 3.803 | 3.706 | 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 | 0.400 |
| Lower Limit | 0.004 | 0.040 | 0.040 |
| Upper Limit | 1.665 | 2.310 | 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 Cavage (a) (continued)

<table>
<thead>
<tr>
<th>Topography: Morphology</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus: Endometrial Stromal Polyp (b)</td>
<td>1/49 (2)</td>
<td>3/50 (6)</td>
<td>0/49 (0)</td>
</tr>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td>2.940</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>151.180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>104</td>
<td>105</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Harderin Gland: Adenoma (b)</th>
<th>2/49 (4)</th>
<th>0/50 (0)</th>
<th>4/49 (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P Values (c,d)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Relative Risk (e)</td>
<td>0.000</td>
<td>2.000</td>
<td></td>
</tr>
<tr>
<td>Lower Limit</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Limit</td>
<td>3.313</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks to First Observed Tumor</td>
<td>104</td>
<td>—</td>
<td>105</td>
</tr>
</tbody>
</table>

(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
nonmetastasizing 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 subse-
sequently 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 lymphomas/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 thio carbamate 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.
VII. BIBLIOGRAPHY


Federal Register, 8 Jan 1974, p. 1355.


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

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANIMALS INITIALLY IN STUDY</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>ANIMALS NECROPSIED</td>
<td>49</td>
<td>50</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>ANIMALS EXAMINED HISTOPATHOLOGICALLY</td>
<td>48</td>
<td>50</td>
<td>50</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTEGUMENTARY SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Squamous cell papilloma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Basal-cell carcinoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Trichoepithelioma</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>Subcut Tissue</em></td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Trichoepithelioma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fibroma</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>5 (10%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td><strong>RESPIRATORY SYSTEM</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>(48)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Alveolar/bronchiolar adenoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Alveolar/bronchiolar carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-cell carcinoma, metastatic</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
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<td><strong>HEMATOPOIETIC SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multiple organs</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Malig. lymphoma, lymphocytic type</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
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<td>Malig. lymphoma, histiocytic type</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Myelomonocytic leukemia</td>
<td>20 (41%)</td>
<td>6 (12%)</td>
<td>13 (26%)</td>
<td>16 (33%)</td>
</tr>
<tr>
<td>Granulocytic leukemia</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Monocytic leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Spleen</em></td>
<td>(48)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Mesothelioma, metastatic</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Myelomonocytic leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied

55
### TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

<table>
<thead>
<tr>
<th>System</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>#SUBMANDIBULAR L. NODE</strong></td>
<td>(48)</td>
<td>(50)</td>
<td>(49)</td>
<td>(49)</td>
</tr>
<tr>
<td>FIBROSARcoma, METASTATIC</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CIRCULATORY SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#ABDOMINAL CAVITY</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>HEMANGiosARcoma, METASTATIC</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#SPLEEN</td>
<td>(48)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>HEMANGiosARcoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIGESTIVE SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#SALIVARY GLAND</td>
<td>(48)</td>
<td>(50)</td>
<td>(48)</td>
<td>(49)</td>
</tr>
<tr>
<td>FIBROSARcoma, INVASIVE</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#LIVER</td>
<td>(48)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>NEOPLASTIC NODULE</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>15 (31%)</td>
<td></td>
</tr>
<tr>
<td>HEPATOCellular CARCINOMA</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSTEosARcoma, METASTATIC</td>
<td>1 (2%)</td>
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<tr>
<td><strong>URINARY SYSTEM</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>#URINARY BLADDER</td>
<td>(47)</td>
<td>(45)</td>
<td>(47)</td>
<td>(47)</td>
</tr>
<tr>
<td>PAPILLOMA, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIBROSARcoma, INVASIVE</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ENDOCRINE SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>#PITUITARY</td>
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<td>(47)</td>
<td>(47)</td>
<td>(45)</td>
</tr>
<tr>
<td>CHROMOPHobe ADenoma</td>
<td>6 (13%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>ACIDOPHIL ADenoma</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>#ADRENAL</td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
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<tr>
<td>CORTICAL ADenoma</td>
<td>1 (2%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PHEOCHROMOCytoma, MALIGNANT</td>
<td>11 (23%)</td>
<td>5 (10%)</td>
<td>9 (18%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>PHEOCHROMOCytoma, MALIGNANT</td>
<td>3 (6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#THYROID</td>
<td>(47)</td>
<td>(50)</td>
<td>(49)</td>
<td>(47)</td>
</tr>
<tr>
<td>FOLLICULAR-CELL ADenoma</td>
<td>1 (2%)</td>
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</table>

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
### TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

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

* Number of animals examined microscopically
* Number of animals necropsied
### TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

<table>
<thead>
<tr>
<th>MESOTHELIOMA, MALIGNANT</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
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<tbody>
<tr>
<td>ALL OTHER SYSTEMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*MULTIPLE ORGANS</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>MESOTHELIOMA, METASTATIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADIPOSE TISSUE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MESOTHELIOMA, METASTATIC</td>
<td></td>
<td></td>
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</table>

#### ANIMAL DISPOSITION SUMMARY

<table>
<thead>
<tr>
<th>Animals Initially in Study</th>
<th>Untreated</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Death</td>
<td>19</td>
<td>9</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Moribund Sacrifice</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Scheduled Sacrifice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidentally Killed</td>
<td>28</td>
<td>40</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Terminal Sacrifice</td>
<td></td>
<td></td>
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<tr>
<td>Animal Missing</td>
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</tbody>
</table>

\[\text{\footnotesize}\textsuperscript{a} Includes autolyzed animals\]

#### TUMOR SUMMARY

<table>
<thead>
<tr>
<th>Total Animals with Primary Tumors*</th>
<th>Untreated</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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</thead>
<tbody>
<tr>
<td>Total Primary Tumors</td>
<td>47</td>
<td>48</td>
<td>49</td>
<td>49</td>
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<tr>
<td>Total Secondary Tumors#</td>
<td>43</td>
<td>46</td>
<td>48</td>
<td>48</td>
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<tr>
<td>Total Benign Tumors</td>
<td>64</td>
<td>63</td>
<td>71</td>
<td>64</td>
</tr>
<tr>
<td>Total Malignant Tumors</td>
<td>27</td>
<td>22</td>
<td>27</td>
<td>36</td>
</tr>
<tr>
<td>Total Secondary Tumors#</td>
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<td>4</td>
</tr>
<tr>
<td>Total Uncertain Tumors#</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total Animals with Tumors Uncertain-Benign or Malignant</td>
<td>5</td>
<td>1</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Total Uncertain Tumors</td>
<td>5</td>
<td>1</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

\[\text{\footnotesize}\textsuperscript{a} Primary Tumors: All tumors except secondary tumors\]

\[\text{\footnotesize}\textsuperscript{b} Secondary Tumors: Metastatic tumors or tumors invasive into an adjacent organ\]
<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals Initially in Study</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Animals Necropsied</td>
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<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Animals Examined Histopathologically</td>
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<td><strong>INTEGUMENTARY SYSTEM</strong></td>
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</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>(50) (50)</td>
<td>(50) (50)</td>
<td>(50)</td>
<td>(50)</td>
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<tr>
<td>Basal-Cell Tumor</td>
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</tr>
<tr>
<td>Keratoacanthoma</td>
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</tr>
<tr>
<td>Subcut Tissue</td>
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<tr>
<td>Fibroma</td>
<td>(50) (50)</td>
<td>(50) (50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Fibrosarcoma, Invasive</td>
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<td></td>
</tr>
<tr>
<td><strong>RESPIRATORY SYSTEM</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma, Nos, Metastatic</td>
<td>(50) (50)</td>
<td>(50) (50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Alveolar/Bronchiolar Adenoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar/Bronchiolar Carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymoma, Metastatic</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEMATOPOIETIC SYSTEM</strong></td>
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</tr>
<tr>
<td>Multiple Organs</td>
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<tr>
<td>Myelomonocytic Leukemia</td>
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<td>(50) (50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Monocytic Leukemia</td>
<td>11 (22%)</td>
<td>6 (12%)</td>
<td>12 (24%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Thymus</td>
<td>(50) (21)</td>
<td>(27)</td>
<td></td>
<td>(11)</td>
</tr>
<tr>
<td>Adenocarcinoma, Nos</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Thymoma, Malignant</td>
<td>1 (4%)</td>
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<td></td>
</tr>
<tr>
<td><strong>CIRCULATORY SYSTEM</strong></td>
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</tr>
<tr>
<td>Spleen</td>
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<td></td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td>(50) (50)</td>
<td>(50) (50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
</tbody>
</table>

* Number of Animals with Tissue Examined Microscopically
* Number of Animals Necropsied
### TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

<table>
<thead>
<tr>
<th>System</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIGESTIVE SYSTEM</strong></td>
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<td></td>
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</tr>
<tr>
<td># Salivary gland</td>
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<td>(50)</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
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<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Liver</td>
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<td>(50)</td>
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<tr>
<td>Neoplastic nodule</td>
<td>1 (2%)</td>
<td>25 (50%)</td>
<td>21 (42%)</td>
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</tr>
<tr>
<td>Hepatocellular carcinoma</td>
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</tr>
<tr>
<td><strong>URINARY SYSTEM</strong></td>
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</tr>
<tr>
<td></td>
<td>NONE</td>
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<td></td>
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</tr>
<tr>
<td><strong>ENDOCRINE SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Pituitary</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chromophobe adenoma</td>
<td>15 (33%)</td>
<td>23 (46%)</td>
<td>14 (29%)</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>Adrenal</td>
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<tr>
<td>Cortical adenoma</td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>1 (2%)</td>
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<td>2 (4%)</td>
<td>4 (8%)</td>
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<tr>
<td># Thyroid</td>
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<td>Follicular-cell adenoma</td>
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<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Follicular-cell carcinoma</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>C-cell adenoma</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
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<tr>
<td><strong>REPRODUCTIVE SYSTEM</strong></td>
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<tr>
<td># Mammary gland</td>
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<td></td>
</tr>
<tr>
<td>Adenoma, nos</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, nos</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary cystadenoma, nos</td>
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<td></td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>19 (38%)</td>
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<td>8 (16%)</td>
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<tr>
<td>Fibroadenoma</td>
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<tr>
<td># Preputial gland</td>
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</tr>
<tr>
<td>Carcinoma, nos</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied
<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cystadenoma, NOS</strong></td>
<td>UTERUS</td>
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<td><strong>Uterus</strong></td>
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<tr>
<td>Carcinoma-In-Situ, NOS</td>
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<td>(47)</td>
<td>(48)</td>
<td>(50)</td>
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<tr>
<td>Adenocarcinoma, NOS</td>
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</tr>
<tr>
<td>Endometrial Stromal Polyp</td>
<td>5 (10%)</td>
<td>5 (11%)</td>
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<td>8 (16%)</td>
</tr>
<tr>
<td>Endometrial Stromal Sarcoma</td>
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<td>1 (2%)</td>
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<td>UTERUS/ENDOMETRIUM</td>
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<td></td>
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</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
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<td>(47)</td>
<td>(48)</td>
<td>(50)</td>
</tr>
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<td><strong>Mesovarium</strong></td>
<td>MESOVARINIUM</td>
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<td>Adenocarcinoma, NOS. Metastatic</td>
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* Number of animals with tissue examined microscopically
* Number of animals necropsied

61
### TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

<table>
<thead>
<tr>
<th>ANIMAL DISPOSITION SUMMARY</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
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<tr>
<td>ANIMALS INITIALLY IN STUDY</td>
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<tr>
<td>NATURAL DEATH</td>
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<td>12</td>
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<td>MORIBUND SACRIFICE</td>
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<td>3</td>
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<td>SCHEDULED SACRIFICE</td>
<td>40</td>
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<td>38</td>
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<tr>
<td>ACCIDENTALLY KILLED</td>
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<td>TERMINAL SACRIFICE</td>
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<td>ANIMAL MISSING</td>
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 Includes autolyzed animals

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<tr>
<th>TUMOR SUMMARY</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
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<tbody>
<tr>
<td>TOTAL ANIMALS WITH PRIMARY TUMORS*</td>
<td>43</td>
<td>38</td>
<td>37</td>
<td>47</td>
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<td>TOTAL PRIMARY TUMORS</td>
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<td>63</td>
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<td>100</td>
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<tr>
<td>TOTAL ANIMALS WITH BENIGN TUMORS</td>
<td>34</td>
<td>33</td>
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<tr>
<td>TOTAL BENIGN TUMORS</td>
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<td>46</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH MALIGNANT TUMORS</td>
<td>17</td>
<td>14</td>
<td>17</td>
<td>29</td>
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<tr>
<td>TOTAL MALIGNANT TUMORS</td>
<td>17</td>
<td>15</td>
<td>17</td>
<td>37</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH SECONDARY TUMORS#</td>
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<td>3</td>
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<td>3</td>
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<tr>
<td>TOTAL SECONDARY TUMORS</td>
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<td></td>
<td>3</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT</td>
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<td>25</td>
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<tr>
<td>TOTAL UNCERTAIN TUMORS</td>
<td>2</td>
<td>25</td>
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</table>

EXCEPT SECONDARY TUMORS

EXCEPT 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

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals Initially in Study</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>Animals Missing</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals Necropsied</td>
<td>49</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>Animals Examined Histopathologically</td>
<td>49</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

#### Integumentary System

|                                | (49)               | (50)            | (50)     | (50)     |
|---                             | (49)               | (50)            | (50)     | (50)     |
| *Skin*                         |                    |                 |          |          |
| Squamous Cell Papilloma        | 1 (2%)             |                  |          |          |
| Basal-Cell Tumor               |                    |                  |          |          |
| *Subcut Tissue*                |                    |                 |          |          |
| 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

|                                | (49)               | (50)            | (50)     | (50)     |
|---                             | (49)               | (50)            | (50)     | (50)     |
| *Lung*                         |                    |                 |          |          |
| Adenocarcinoma, NOS, Metastatic| 2 (4%)             | 2 (4%)          | 3 (6%)   |          |
| Hepatocellular Carcinoma, Metast| 8 (16%)            | 3 (6%)          | 8 (16%)  | 12 (24%) |
| Alveolar/Bronchiolar Adenoma    | 1 (2%)             | 1 (2%)          | 2 (4%)   | 2 (4%)   |
| Cortical Carcinoma, Metastatic  |                    | 1 (2%)          |          |          |
| Sebaceous Adenocarcinoma, Metast| 1 (2%)             |                  |          |          |
| Fibrosarcoma, Metastatic       | 1 (2%)             | 1 (2%)          |          |          |
| Fibrous Histiocytoma, Metastatic| 1 (2%)             |                  |          |          |
| Osteosarcoma                   |                    |                  |          |          |

#### Hematopoietic System

|                                | (49)               | (50)            | (50)     | (50)     |
|---                             | (49)               | (50)            | (50)     | (50)     |
| *Multiple Organs*              |                    |                 |          |          |
| Malignant Lymphoma, Undifferent-Type| 1 (2%)        | 1 (2%)          | 7 (14%)  | 5 (10%)  |
| Malignant Lymphoma, Lymphocytic 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>
<thead>
<tr>
<th>Tissue</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAVITY &amp; LEUKEMIA</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
<td>(50)</td>
</tr>
<tr>
<td>DUODENUM</td>
<td>1 (2%)</td>
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<td>(49)</td>
<td>(49)</td>
</tr>
<tr>
<td>MALIG. LYMPHOMA, HISTIOCYTIC TYPE</td>
<td>(49)</td>
<td>(49)</td>
<td>(49)</td>
<td>(50)</td>
</tr>
<tr>
<td>THYUS</td>
<td>(19)</td>
<td>(22)</td>
<td>(19)</td>
<td>(19)</td>
</tr>
<tr>
<td>ADENOCARCINOMA, NOS</td>
<td>(50)</td>
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<td>(49)</td>
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<tr>
<td>LIPOSARCOMA</td>
<td>1 (5%)</td>
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<td>CIRCULATORY SYSTEM</td>
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<td>MULTIPLE ORGANS</td>
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<td>(50)</td>
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<td>(49)</td>
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<td>Spleen</td>
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<td>(50)</td>
</tr>
<tr>
<td>HEMANGIOSARCOMA</td>
<td>1 (2%)</td>
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<td>(50)</td>
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<td>Mesenteric L. Node</td>
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<td>(49)</td>
<td>(50)</td>
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<td>Hemangioma</td>
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<td>(49)</td>
<td>(49)</td>
<td>(50)</td>
</tr>
<tr>
<td>Heart</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
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<tr>
<td>FIBROSARCOMA, METASTATIC</td>
<td>(49)</td>
<td>(49)</td>
<td>(49)</td>
<td>(50)</td>
</tr>
<tr>
<td>Liver</td>
<td>(49)</td>
<td>(49)</td>
<td>(49)</td>
<td>(50)</td>
</tr>
<tr>
<td>HEMANGIOSARCOMA</td>
<td>2 (4%)</td>
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<td>(50)</td>
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<td>Small Intestine</td>
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<td>HEMANGIOSARCOMA, METASTATIC</td>
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<tr>
<td>Liver</td>
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<td>(49)</td>
<td>(49)</td>
<td>(50)</td>
</tr>
<tr>
<td>ADENOCARCINOMA, NOS, METASTATIC</td>
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<td>Hepatocellular Adenoma</td>
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<td>(49)</td>
</tr>
<tr>
<td>HEPATOCARCINOMA</td>
<td>17 (35%)</td>
<td>15 (30%)</td>
<td>11 (22%)</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Fibrosarcoma, Metastatic</td>
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<td>(49)</td>
<td>(49)</td>
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<tr>
<td>Liver</td>
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<td>(49)</td>
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<td>Bile duct</td>
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<td>(49)</td>
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<td>(50)</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>1 (2%)</td>
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<td>(49)</td>
<td>(49)</td>
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</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied
## TABLE 81. MALE MICE: NEOPLASMS (CONTINUED)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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<tr>
<td><strong>Pancreas</strong></td>
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<td>Adenocarcinoma, NOS, Metastatic</td>
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<td>(50)</td>
<td>1 (2%)</td>
<td>(50)</td>
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<tr>
<td>Cortical Carcinoma, Metastatic</td>
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<td></td>
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<tr>
<td><strong>Stomach</strong></td>
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<td>Carcinoma, NOS</td>
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<td>(49)</td>
<td>(48)</td>
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<td>Squamous cell papilloma</td>
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<td></td>
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</tr>
<tr>
<td><strong>Small intestine</strong></td>
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<td>Jejunum Carcinoma, NOS</td>
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<td>(49)</td>
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<tr>
<td>Kidney Fibrosarcoma, Metastatic</td>
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<td>(50)</td>
<td>(50)</td>
<td>(50) (2%)</td>
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<td><strong>Urinary bladder</strong></td>
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<td>Transitional-cell papilloma</td>
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<td>Adrenal</td>
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<td>(49)</td>
<td>(49)</td>
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<tr>
<td>Cortical adenoma</td>
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<tr>
<td>Cortical carcinoma</td>
<td>1 (2%)</td>
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<tr>
<td>Pheochromocytoma</td>
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<td>(47)</td>
<td>(49)</td>
<td>(48)</td>
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</table>

### Notes:
- # Number of animals with tissue examined microscopically
- * Number of animals necropsied
TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

<table>
<thead>
<tr>
<th>SPECIAL SENSE ORGANS</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EYELID</strong></td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Sebaceous Adenocarcinoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>HARDERIAN GLAND</strong></td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
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<tr>
<td>Carcinoma, NOS</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma, NOS</td>
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<td><strong>MUSCULOSKELETAL SYSTEM</strong></td>
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<td>None</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>BODY CAVITIES</strong></td>
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<td>None</td>
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</tr>
<tr>
<td><strong>ALL OTHER SYSTEMS</strong></td>
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</tr>
<tr>
<td><em>MULTIPLE ORGANS</em>*</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Carcinosarcoma, Metastatic</td>
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</tr>
</tbody>
</table>

**ANIMAL DISPOSITION SUMMARY**

<table>
<thead>
<tr>
<th>ANIMALS INITIALLY IN STUDY</th>
<th>50</th>
<th>50</th>
<th>50</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Death</td>
<td>12</td>
<td>18</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Moribund Sacrifice</td>
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</tr>
<tr>
<td>Scheduled Sacrifice</td>
<td>1</td>
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<td></td>
<td></td>
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<tr>
<td>Accidentally Killed</td>
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<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Terminal Sacrifice</td>
<td>36</td>
<td>30</td>
<td>33</td>
<td>35</td>
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<tr>
<td>Animal Missing</td>
<td>1</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes autolyzed animals

* Number of animals with tissue examined microscopically

* Number of animals necropsied
<table>
<thead>
<tr>
<th>Tumor Summary</th>
<th>Untreated Control</th>
<th>Vehichle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total animals with primary tumors*</td>
<td>32</td>
<td>29</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Total primary tumors</td>
<td>45</td>
<td>43</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>Total animals with benign tumors</td>
<td>12</td>
<td>8</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Total benign tumors</td>
<td>13</td>
<td>8</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Total animals with malignant tumors</td>
<td>26</td>
<td>25</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Total malignant tumors</td>
<td>32</td>
<td>35</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>Total animals with secondary tumors**</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Total secondary tumors</td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANIMALS INITIALLY IN STUDY</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>ANIMALS MISSING</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANIMALS NECROPSIED</td>
<td>50</td>
<td>49</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>ANIMALS EXAMINED HISTOPATHOLOGICALLY</td>
<td>50</td>
<td>49</td>
<td>50</td>
<td>49</td>
</tr>
</tbody>
</table>

**INTEGUMENTARY SYSTEM**

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>*SKIN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous Cell Papilloma</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
</tbody>
</table>

**RESPIRATORY SYSTEM**

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, NOS, Metastatic</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
</tbody>
</table>
| Alveolar-Bronchiol
tic Adenoma | 2 (4%)           | 2 (4%)         | 8 (16%)  |           |
| Alveolar-Bronchiolar Carcinoma | (50)              | (49)           | (50)     | (49)      |

**HEMATOPOIETIC SYSTEM**

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Multiple Organs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malig. Lymphoma, Undiffer-type</td>
<td>3 (6%)</td>
<td>6 (12%)</td>
<td>8 (16%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Malig. Lymphoma, Lymphocytic Type</td>
<td>10 (20%)</td>
<td>7 (14%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Malig. Lymphoma, Histocytic Type</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>10 (20%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Malignant Lymphoma, Mixed Type</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Granulocytic Leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesenteric L. Node</td>
<td>(48)</td>
<td>(48)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td>Malignant Lymphoma, Mixed Type</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CIRCULATORY SYSTEM**

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Subcut Tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangioma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied
<table>
<thead>
<tr>
<th>System</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIGESTIVE SYSTEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary Gland</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Liver</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Hepatocellular Adenoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Carcinoma, NOS, Metastatic</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Stomach</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Squamous Cell Papilloma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>URINARY SYSTEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENDOCRINE SYSTEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td>(45)</td>
<td>(42)</td>
<td>(37)</td>
<td>(38)</td>
</tr>
<tr>
<td>Chromophobe Adenoma</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>(50)</td>
<td>(48)</td>
<td>(48)</td>
<td>(49)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>(49)</td>
<td>(48)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Follicular-Cell Adenoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied
### TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-CELL ADENOMA</td>
<td></td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>REPRODUCTIVE SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammary Gland</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>1 (2%)</td>
<td>5 (10%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Uterus</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Endometrial Stromal Polyp</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Ovary</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Papillary Cystadenoma, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Granulosa-Cell Tumor</td>
<td></td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Sertoli-Cell Tumor</td>
<td></td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Teratoma, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesovarium</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Carcinoma, NOS, Metastatic</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NERVOUS SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SPECIAL SENSE ORGANS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harderian Gland</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Adenoma, NOS</td>
<td>2 (4%)</td>
<td></td>
<td></td>
<td>4 (8%)</td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebbral Column</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BODY CAVITIES</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALL OTHER SYSTEMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied

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TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANIMAL DISPOSITION SUMMARY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals Initially in Study</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Natural Deaths</td>
<td>9</td>
<td>5</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Moribund Sacrifice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scheduled Sacrifice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidentally Killed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal Sacrifice</td>
<td>41</td>
<td>43</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Animal Missing</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Includes autolyzed animals

**TUMOR SUMMARY**

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Animals with Primary Tumors</td>
<td>26</td>
<td>24</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Total Primary Tumors</td>
<td>30</td>
<td>31</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>Total Animals with Benign Tumors</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Total Benign Tumors</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Total Animals with Malignant Tumors</td>
<td>22</td>
<td>20</td>
<td>26</td>
<td>38</td>
</tr>
<tr>
<td>Total Malignant Tumors</td>
<td>22</td>
<td>23</td>
<td>30</td>
<td>51</td>
</tr>
<tr>
<td>Total Animals with Secondary Tumors</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total Secondary Tumors</td>
<td>2</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total Animals with Tumors Uncertain—Benign or Malignant</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Total Uncertain Tumors</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

* Primary Tumors: All Tumors except Secondary Tumors

# Secondary Tumors: Metastatic Tumors or Tumors Invasive into an Adjacent Organ

---

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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

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals Initially in Study</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Animals Necropsied</td>
<td>49</td>
<td>50</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Animals Examined Histopathologically</td>
<td>48</td>
<td>50</td>
<td>49</td>
<td>49</td>
</tr>
</tbody>
</table>

### Integumentary System
<table>
<thead>
<tr>
<th>Lesion</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcer, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosion</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acariasis</td>
<td></td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Hyperplasia, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Respiratory System
<table>
<thead>
<tr>
<th>Lesion</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation, Suppurative</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung/Bronchiole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation, Acute</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestion, NOS</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Congestion, Passive</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation, Suppurative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchopneumonia Suppurative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchopneumonia, Acute</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation, Acute Focal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, Chronic MURINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granuloma, Foreign Body</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis, Focal</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct Hemorrhagic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmentation, NOS</td>
<td></td>
<td></td>
<td>1 (2%)</td>
<td>47 (96%)</td>
</tr>
<tr>
<td>Hyperplasia, Adenomatous</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperplasia, Alveolar Epithelium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied
<table>
<thead>
<tr>
<th>TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METAPLASIA, OSSEOUS</strong></td>
</tr>
<tr>
<td><em>BOHE MARROW</em></td>
</tr>
<tr>
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# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
# TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

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<tr>
<th>Tissue</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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<td>(49)</td>
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* Number of animals with tissue examined microscopically
* Number of animals necropsied
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* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
<table>
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<th>Lesion Type</th>
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<th>High Dose</th>
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* Number of animals with tissue examined microscopically
* Number of animals necropsied
<table>
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<tr>
<th>Lesion Description</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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<td>1 (49)</td>
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<td>Pancreatic Islets</td>
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<td>3 (50) (6%)</td>
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<td>3 (49)</td>
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<td>Hyperplasia, NOS</td>
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<td>1 (50) (2%)</td>
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<td>Mammary Gland</td>
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<td>1 (50) (2%)</td>
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<td>Galactocele</td>
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<td>Preputial Gland</td>
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<td>1 (50) (2%)</td>
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<td>1 (2%)</td>
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<td>Epidermal Inclusion Cyst</td>
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<tr>
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<td>1 (45) (2%)</td>
<td>1 (48)</td>
<td>1 (2%)</td>
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<tr>
<td>Degeneration, Cystic</td>
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<td>1 (45) (2%)</td>
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<td>Prostate</td>
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</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied
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<tr>
<th>Lesion Type</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
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<th>High Dose</th>
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<td><strong>Testis</strong></td>
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<td>10 (22%)</td>
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<td>Chronic Inflammation</td>
<td>3 (4%)</td>
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<td>2 (4%)</td>
<td>1 (2%)</td>
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<tr>
<td>Chronic Suppurative Inflammation</td>
<td>18 (38%)</td>
<td>7 (15%)</td>
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<td><strong>Epididymis</strong></td>
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<td>50 (100%)</td>
<td>49 (100%)</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
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<td>50 (100%)</td>
<td>50 (100%)</td>
<td>50 (100%)</td>
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<td>Steatitis</td>
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<td>1 (2%)</td>
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<td>Granuloma, Spermatic</td>
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<td>Necrosis, Fat</td>
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<td>1 (2%)</td>
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<td><strong>Nervous System</strong></td>
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<td>49 (40%)</td>
<td>49 (40%)</td>
<td>49 (40%)</td>
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<td>Hemorrhage</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
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<tr>
<td>Chronic Inflammation</td>
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<td>Infarct Hemorrhagic</td>
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<td>49 (40%)</td>
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<td>50 (100%)</td>
<td>50 (100%)</td>
<td>49 (100%)</td>
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<tr>
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<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Inflammation</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Synchia, Anterior</td>
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<td>50 (100%)</td>
<td>50 (100%)</td>
<td>49 (100%)</td>
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<tr>
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<td>50 (100%)</td>
<td>50 (100%)</td>
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<td>3 (6%)</td>
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<td>1 (2%)</td>
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</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied

83
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<tr>
<th>System</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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<td><strong>Eye/Retina</strong></td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
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<td>6 (12%)</td>
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<td>1 (2%)</td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
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<td>1 (2%)</td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
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<td>1 (2%)</td>
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<td></td>
</tr>
<tr>
<td><strong>Lens Cortex</strong></td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Degeneration, NOS</td>
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<td>(49)</td>
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<tr>
<td>Mineralization</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
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<td><strong>Peritoneum</strong></td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
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<td>Inflammation, Chronic Diffuse</td>
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<td>1 (2%)</td>
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</tr>
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<td><strong>Pleura</strong></td>
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<td>(50)</td>
<td>(49)</td>
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<tr>
<td>Inflammation, Suppurative</td>
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<td></td>
<td>1 (2%)</td>
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</tr>
<tr>
<td>Inflammation, Chronic</td>
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</tr>
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<td><strong>Pericardium</strong></td>
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<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Inflammation, Chronic</td>
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<td></td>
<td>1 (2%)</td>
<td></td>
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<td><strong>Mesentery</strong></td>
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<td>(50)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Steatitis</td>
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<td>1 (2%)</td>
<td></td>
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</tr>
<tr>
<td>Necrosis, Fat</td>
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<td><strong>Adipose Tissue</strong></td>
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# Number of animals with tissue examined microscopically
* Number of animals necropsied
**TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)**

<table>
<thead>
<tr>
<th>NONNEOPLASTIC LESIONS</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFLAMMATION, CHRONIC FOCAL NECROSIS, FAT</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>CONNECTIVE TISSUE INFLAMMATION, CHRONIC</strong></td>
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<td>1</td>
</tr>
</tbody>
</table>

**SPECIAL MORPHOLOGY SUMMARY**

| **AUTO/NECROPSY/NO HISTO** | 1 | | | |
| **AUTOLYSIS/NO NECROPSY** | 1 | | | 1 |

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED
### Summary of the Incidence of Nonneoplastic Lesions in Female Rats Administered Selenium Sulfide by Gavage

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANIMALS INITIALLY IN STUDY</td>
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<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>ANIMALS NECROPSIED</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>ANIMALS EXAMINED HISTOPATHOLOGICALLY</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

#### Integumentary System

- **Skin**
  - Inflammation, NOS (50) (50) (50) (50)
  - Ulcer, NOS (1/2%)
  - Hyperplasia, NOS (1/2%)

- **Subcut Tissue**
  - Granuloma, Foreign Body (50) (50) (50) (50)

#### Respiratory System

- **Larynx**
  - Inflammation, Suppurative (50) (50) (50) (50)

- **Trachea**
  - Inflammation, Chronic Suppurative (50) (50) (50) (50)

- **Lung**
  - Atelectasis (50) (50) (50) (50)
    - Congestion, NOS 5 (10%) 2 (4%) 1 (2%)
    - Edema, NOS 2 (4%) 1 (2%)
  - Inflammation, Suppurative (50) (50) (50) (50)
    - Pneumonia, Chronic Murine 14 (28%) 40 (80%) 43 (86%) 39 (78%)
    - Inflammation, Focal Granulomatous 1 (2%)
    - Granuloma, Foreign Body 1 (2%)
    - Fibrosis, Diffuse 1 (2%) 36 (72%) 45 (90%)

- **Lung/Alveoli**
  - Hemorrhage (50) (50) (50) (50)

#### Hematopoietic System

- **Bone Marrow**
  - Myelofibrosis (50) (50) (50) (50)

---

* Number of animals with tissue examined microscopically

* Number of animals necropsied
### Table C2. Female Rats: Nonneoplastic Lesions (Continued)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia, hematopoietic</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hemorrhage</td>
<td>16 (32%)</td>
<td>16 (32%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Lipoidosis</td>
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<tr>
<td>Hemoglobin</td>
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<tr>
<td>Lymphoid depletion</td>
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<tr>
<td>Leukemia reaction</td>
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<tr>
<td>Hyperplasia, lymphoid</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Submandibular l. node</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Inflammation, acute</td>
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* Number of animals with tissue examined microscopically
* Number of animals necropsied
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# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

88
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* Number of animals with tissue examined microscopically

* Number of animals necropsied

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# Number of animals with tissue examined microscopically
* Number of animals necropsied
**TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)**

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNTREATED VEHICLE CONTROL</td>
<td></td>
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<tr>
<td><strong>INFLAMMATION, CHRONIC SUPPURATIVE</strong></td>
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<tr>
<td>UTERUS</td>
<td>(48)</td>
<td>(47)</td>
<td>(48)</td>
<td>(50)</td>
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<tr>
<td>MUCOCOELE</td>
<td></td>
<td>1 (2%)</td>
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</tr>
<tr>
<td>HYDRODEMA</td>
<td></td>
<td>2 (4%)</td>
<td>5 (10%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>HEMORRHAGE</td>
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<td>HEMATOMA</td>
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<td>(48)</td>
<td>(50)</td>
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<tr>
<td>CYST, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
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<tr>
<td>MULTIPLE CYSTS</td>
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<td>1 (2%)</td>
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<tr>
<td>INFLAMMATION, ACUTE</td>
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<td>2 (4%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
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<td>HYPERPLASIA, CYSTIC</td>
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<td>1 (2%)</td>
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<td>(49)</td>
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<td>1 (2%)</td>
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<td>2 (4%)</td>
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<td>PUS</td>
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<tr>
<td>SYNECHIA, ANTERIOR</td>
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<tr>
<td>SYNECHIA, POSTERIOR</td>
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<td>INFLAMMATION, NOS</td>
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<td></td>
</tr>
<tr>
<td>ULCER, NOS</td>
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<td></td>
</tr>
<tr>
<td>INFLAMMATION, ACUTE</td>
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* Number of animals necropsied.

91
# TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

<table>
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<tr>
<th></th>
<th>UNTREATED</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
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<tr>
<td><strong>EYEBALL TUNICA VASCULITIS, NOS</strong></td>
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<td><strong>EYE/IRIS INFLAMMATION, CHRONIC</strong></td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
<td><strong>EYE/RETINA DEGENERATION, NOS</strong></td>
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<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
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<td><strong>LENS CAPSULE MINERALIZATION DEGENERATION, NOS</strong></td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
<td><strong>LENS CORTEX MINERALIZATION</strong></td>
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<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
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<td><strong>MUSCULOSKELETAL SYSTEM</strong></td>
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<td><strong>SKULL HEALED FRACTURE</strong></td>
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<td>(50)</td>
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<td><strong>BODY CAVITIES</strong></td>
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</tr>
<tr>
<td><strong>ABDOMINAL CAVITY STEATITIS NECROSIS, FAT</strong></td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>PLEURA INFLAMMATION, ACUTE FOCAL INFLAMMATION, PYOGRANULOMATOUS NECROSIS, FAT</strong></td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>MESENTERY NECROSIS, FAT</strong></td>
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<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
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<tr>
<td><strong>ALL OTHER SYSTEMS</strong></td>
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<tr>
<td><strong>MULTIPLE ORGANS CONGESTION, NOS STEATITIS</strong></td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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</tbody>
</table>

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
<table>
<thead>
<tr>
<th>Special Morphology Summary</th>
<th>NONE</th>
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* Number of animals with tissue examined microscopically

** TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED) **

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrosis, Focal Necrosis, Fat</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animals Initially in Study</strong></td>
<td>50</td>
<td>50</td>
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<tr>
<td><strong>Animals Missing</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Animals Necropsied</strong></td>
<td>49</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Animals Examined Histopathologically</strong></td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
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**In tegumentary System**

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<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
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<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
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<td>Inflammation, Chronic</td>
<td>2 (4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation, Granulomatous</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metaplasia, Osseous</td>
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**Subcut Tissue**

<table>
<thead>
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<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema, NOS</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Abscess, NOS</td>
<td>1 (2%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation, Granulomatous</td>
<td>1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granuloma, NOS</td>
<td>1 (2%)</td>
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<td></td>
</tr>
<tr>
<td>Necrosis, Fat</td>
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**Respiratory System**

<table>
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<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Congestion, NOS</td>
<td>2 (4%)</td>
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<td>4 (8%)</td>
</tr>
<tr>
<td>Edema, NOS</td>
<td>1 (2%)</td>
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<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>5 (10%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Inflammation, Focal</td>
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<td></td>
</tr>
<tr>
<td>Pneumonia, Chronic Murine</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>7 (14%)</td>
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**Hematopoietic System**

<table>
<thead>
<tr>
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<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Organs</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Leukemoid Reaction</td>
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</table>

**Bone Marrow**

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<th>Low Dose</th>
<th>High Dose</th>
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</thead>
<tbody>
<tr>
<td>Hyperplasia, Megakaryocytic</td>
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<td>Myeloid Metaplasia</td>
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**Spleen**

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</thead>
<tbody>
<tr>
<td>Atrophy, NOS</td>
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</tbody>
</table>

* Number of animals with tissue examined microscopically

* Number of animals necropsied
<table>
<thead>
<tr>
<th>Lesion Description</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
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<td>Leukemic Reaction</td>
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<td>1 (2%)</td>
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<td>Hematopoiesis</td>
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<td>2 (4%)</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
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<tr>
<td>Cervical Lymph Node</td>
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<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
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<td>Mesenteric L. Node</td>
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<td>Congestion, NOS</td>
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<td>(49)</td>
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<td>Inflammation, NOS</td>
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<td>Inflammation, Acute</td>
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<td>1 (2%)</td>
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<td>Hyperplasia, Reticulum Cell</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<td>Lungs</td>
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<td>Leukocytosis, NOS</td>
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<td>Peyer's Patch</td>
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<td>Hyperplasia, Lymphoid</td>
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<td>(49)</td>
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<td>(50)</td>
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<tr>
<td>Cervical Lymph Node</td>
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</tr>
<tr>
<td>Inflammation, NOS</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
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<tr>
<td>Mesenteric L. Node</td>
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<tr>
<td>Congestion, NOS</td>
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<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
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<tr>
<td>Lymphangiectasis</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
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<tr>
<td>Lymphangiectasis</td>
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<td>Metaplasia, Osseous</td>
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<td>1 (2%)</td>
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<td>Aorta</td>
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<td>Inflammation, NOS</td>
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</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied
TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

<table>
<thead>
<tr>
<th>Lesion Description</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
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</thead>
<tbody>
<tr>
<td><strong>INFLAMMATION, CHRONIC</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Liver</strong></td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
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<tr>
<td>Thrombosis, NOS</td>
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<td>Kidney</td>
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<td>Thrombosis, NOS</td>
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<td>Intestinal Tract</td>
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<td>(50)</td>
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<td>Salivary Gland</td>
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<td>Fibrosis</td>
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<td>Liver</td>
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<td>Fibrosis</td>
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<td>Amyloidosis</td>
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<td>Metaplasia Fatty</td>
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<tr>
<td><strong>Liver/Hepatocytes</strong></td>
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<td>Inflammation, Diffuse</td>
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<td>Necrosis, NOS</td>
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<td><strong>Pancreas</strong></td>
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<td>Cystic Ducts</td>
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* Number of animals with tissue examined microscopically
* Number of animals necropsied

99
### TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

<table>
<thead>
<tr>
<th>System</th>
<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
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<tr>
<td>Diffuse</td>
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<td>(49) 1 (2%)</td>
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<td>Chronic</td>
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<td>Pituitary</td>
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<tr>
<td>Hypertrophy, Focal</td>
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<tr>
<td>Hyperplasia, NOS</td>
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<td>Adrenal Medulla</td>
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<td>(49) 1 (2%)</td>
<td>(49) 1 (2%)</td>
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<td>Inflammation, Chronic</td>
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<tr>
<td>Focal</td>
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<td>Hyperplasia, Follicular-Cell</td>
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* Number of animals with tissue examined microscopically

* Number of animals necropsied
### TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

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<thead>
<tr>
<th></th>
<th>Untreated Control</th>
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<th>Low Dose</th>
<th>High Dose</th>
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<tr>
<td>Cystic ducts</td>
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<td>(50)</td>
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<tr>
<td>Inflammation, chronic</td>
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<td>1 (2%)</td>
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<td>Penis</td>
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<td>(50)</td>
<td>(50)</td>
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<td>Hemorrhage, chronic</td>
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<td>1 (2%)</td>
<td></td>
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</tr>
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<td>Preputial gland</td>
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<td>(50)</td>
<td>(50)</td>
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<tr>
<td>Cyst, nos</td>
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<td>(50)</td>
<td>(50)</td>
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<tr>
<td>Hemorrhage, chronic</td>
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<td>1 (2%)</td>
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</tr>
<tr>
<td>Preputial gland</td>
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<tr>
<td>Abscess, nos</td>
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<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation, chronic</td>
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<td>2 (4%)</td>
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<td>1 (2%)</td>
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<tr>
<td>Inflammation, suppurative</td>
<td></td>
<td></td>
<td>(50)</td>
<td>(50)</td>
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<tr>
<td>Inflammation, chronic</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy, nos</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
<td>Testis</td>
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<td>(49)</td>
<td>(49)</td>
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<tr>
<td>Hemorrhage, suppurative</td>
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<td>(48)</td>
<td>(48)</td>
</tr>
<tr>
<td>Inflammation, nos</td>
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<td>1 (2%)</td>
<td></td>
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<td>Calcification, focal</td>
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<td>1 (2%)</td>
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<tr>
<td>Calcification, focal</td>
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<td>1 (2%)</td>
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</tr>
<tr>
<td>Atrophy, nos</td>
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<td>2 (4%)</td>
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<td>(49)</td>
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</table>

* Number of animals with tissue examined microscopically

* Number of animals necropsied
<table>
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<tr>
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<th>UNTREATED CONTROL</th>
<th>VEHICLE CONTROL</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
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<tbody>
<tr>
<td><strong>INFLAMMATION, SUPPURATIVE</strong></td>
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<td><strong>INFLAMMATION, FOCAL GRANULOMATOUS</strong></td>
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</table>

SPECIAL SENSE ORGANS

*Eye*  
Abscess, Chronic  
(49) (50) (50) (50)

MUSCULOSKELETAL SYSTEM

None

BODY CAVITIES

*Peritoneum, NOS*  
Inflammation, Granulomatous  
(49) (50) (50) (50)

*Inguinal Region*  
Necrosis, Fat  
(49) (50) (50) (50)

*Pleura*  
Inflammation, Suppurative  
(49) (50) (50) (50)

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

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TABLE D2.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED SELENIUM SULFIDE BY GAVAGE

<table>
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<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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<td>Animals Examined Histopathologically</td>
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Integumentary System

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<td>Skin Inflammation, Necrotizing</td>
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<td>(50)</td>
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Respiratory System

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<th>High Dose</th>
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</thead>
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<td>1 (2%)</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
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<td>Hemorrhage</td>
<td>4 (8%)</td>
<td>8 (16%)</td>
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<tr>
<td>Inflammation, Suppurative</td>
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<td>1 (2%)</td>
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<tr>
<td>Pneumonia, Chronic Murine</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
<td>5 (10%)</td>
<td>5 (10%)</td>
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<td>Pigmentation, NOS</td>
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<td>Alveolar Macrophages</td>
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<td>Hyperplasia, Alveolar Epithelium</td>
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Hematopoietic System

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<td>Myeloid Metaplasia</td>
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<td>1 (2%)</td>
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</table>

* Number of animals with tissue examined microscopically

* Number of animals necropsied
<table>
<thead>
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<th>High Dose</th>
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<td><strong>LYMPH NODE</strong></td>
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<td>(48)</td>
<td>(50)</td>
<td>(48)</td>
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<td>1 (2%)</td>
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<td><strong>CERVICAL LYMPH NODE</strong></td>
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<td>(48)</td>
<td>(50)</td>
<td>(48)</td>
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<td>(48)</td>
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<tr>
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<td>HYPERPLASIA, LYMPHOID</td>
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<td>1 (3%)</td>
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**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>
<thead>
<tr>
<th>Tissue</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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<tr>
<td><strong>KAORTA</strong></td>
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<td></td>
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<td>(50)</td>
<td>(49)</td>
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<td><strong>CORONARY ARTERY</strong></td>
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<td>Inflammation Proliferative</td>
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<td>(4%)</td>
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<td>(50)</td>
<td>(49)</td>
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<tr>
<td>Embolus, Septic</td>
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<td>Periarteritis</td>
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<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
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<td>(50)</td>
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<td>Thrombosis, NOS</td>
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<td>(49)</td>
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<td><strong>LEFT OVARY</strong></td>
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<td>Thrombus, Organized</td>
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**DIGESTIVE SYSTEM**

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<td>Hemorrhage</td>
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<td>(46)</td>
<td>(50)</td>
<td>(49)</td>
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<td><strong>LIVER</strong></td>
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<td>Congestion, NOS</td>
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<td>(50)</td>
<td>(49)</td>
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<td>Hemorrhage</td>
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<td>(2%)</td>
<td>1 (2%)</td>
<td>(2%)</td>
</tr>
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<td>(2%)</td>
<td>1 (2%)</td>
<td>(2%)</td>
</tr>
<tr>
<td>Necrosis, NOS</td>
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<td>(2%)</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
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<td>(2%)</td>
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<td>Infarct, NOS</td>
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<td><strong>BILE DUCT</strong></td>
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<td>Cyst, NOS</td>
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<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Hyperplasia, NOS</td>
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<td>(2%)</td>
<td>1 (2%)</td>
<td>(2%)</td>
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<td><strong>SPANCREAS</strong></td>
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<td>Cystic ducts</td>
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<td>(49)</td>
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<td>3 (6%)</td>
<td>(6%)</td>
<td>1 (2%)</td>
<td>(2%)</td>
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* Number of animals with tissue examined microscopically
* Number of animals necropsied

105
<table>
<thead>
<tr>
<th>Lesion Description</th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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<tr>
<td>Necrosis, Focal</td>
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<td>(50)</td>
<td>(49)</td>
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<td>Esophagus Inflammation, Suppurative Inflammation, Chronic</td>
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<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
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<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
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<td>(48)</td>
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<td>Urinary Bladder Amyloidosis</td>
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<td>(49)</td>
<td>(48)</td>
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<td>(38)</td>
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<td>Adrenal Medulla Hyperplasia, NOS</td>
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<td>Thyroid Cystic Follicles</td>
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<td>(50)</td>
<td>(49)</td>
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* Number of animals with tissue examined microscopically
* Number of animals necropsied
### TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

<table>
<thead>
<tr>
<th>Tissue</th>
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<th>High Dose</th>
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<tr>
<td>REPRODUCTIVE SYSTEM</td>
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<td>Mammary gland</td>
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<tr>
<td>Uterus</td>
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<td>(50)</td>
<td>(49)</td>
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<tr>
<td>Hydrometra</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<td>Angiectasis</td>
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<td>Uterus/Endometrium</td>
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<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
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<tr>
<td>Inflammation, supplicative</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hyperplasia, cystic</td>
<td>41 (82%)</td>
<td>45 (92%)</td>
<td>40 (80%)</td>
<td>36 (73%)</td>
</tr>
<tr>
<td>Ovary/Oviduct</td>
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<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
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<td>Inflammation, chronic</td>
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<tr>
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<td>Special Sense Organs</td>
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<td>Eye</td>
<td>(50)</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>Inflammation, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Abscess, NOS</td>
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<tr>
<td>Phtisis Bulbi</td>
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<td>(49)</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Inflammation, focal</td>
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</tbody>
</table>

* Number of animals with tissue examined microscopically
* Number of animals necropsied

---

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### TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

<table>
<thead>
<tr>
<th></th>
<th>Untreated Control</th>
<th>Vehicle Control</th>
<th>Low Dose</th>
<th>High Dose</th>
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<td>Skeletal Muscle Parasitism</td>
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<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td></td>
<td>1 (2%)</td>
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<tr>
<td><strong>BODY CAVITIES</strong></td>
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<td>Peritoneum Inflammation, NOS</td>
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<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td></td>
<td>2 (4%)</td>
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</tr>
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<td><strong>ALL OTHER SYSTEMS</strong></td>
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<td><strong>SPECIAL MORPHOLOGY SUMMARY</strong></td>
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<td>Autolysis/No Necropsy</td>
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* Number of animals with tissue examined microscopically
* Number of animals necropsied
APPENDIX E

ANALYSIS OF SELENIUM SULFIDE
A. Elemental Analysis

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<tr>
<td>SeS</td>
<td>71.12</td>
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<td>SeS₂</td>
<td>55.18</td>
<td>44.82</td>
</tr>
<tr>
<td>Observed 11/15/74</td>
<td>61.0±0.6</td>
<td>40.93</td>
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<tr>
<td>Observed 7/19/79</td>
<td>59.97</td>
<td>40.7±0.2</td>
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B. Melting Point

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<th></th>
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<tr>
<td>SeS</td>
<td>118°-119°C (Weast, 1974-1975)</td>
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<tr>
<td>SeS₂</td>
<td>less than 100°C (Weast, 1974-1975)</td>
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<tr>
<td>Observed</td>
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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

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<th>Literature Values (a)</th>
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<td>d</td>
<td>intensity</td>
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<td>6.67</td>
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</tr>
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<td>6.28</td>
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<td>5.13</td>
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<td>4.42</td>
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<td>3.77</td>
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</table>

(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.

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APPENDIX F

ANALYSIS OF SELENIUM SULFIDE IN AQUEOUS CARBOXYMETHYLCHELULOSE 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.

<table>
<thead>
<tr>
<th>Theoretical Concentration in Suspensions (mg/ml)</th>
<th>Number of Samples</th>
<th>Sample Mean (mg/ml)</th>
<th>Coefficient of Variation (%)</th>
<th>Range (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>5</td>
<td>9.6</td>
<td>11.0</td>
<td>8.7-11.3</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>14.1</td>
<td>7.0</td>
<td>12.9-15.4</td>
</tr>
</tbody>
</table>
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, Frederick Cancer Research Center
Henry C. Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Louise Strong, University of Texas Health Sciences Center

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