National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 115
1978

BIOASSAY OF SULFALLATE FOR POSSIBLE CARCINOGENICITY

CAS No. 95-06-7

NCI-CG-TR-115

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

BIOASSAY OF

SULFALLATE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

DHEW Publication No. (NIH) 78-1370

REPORT ON THE BIOASSAY OF SULFALLATE
FOR POSSIBLE CARCINOGENICITY

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

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

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

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3, 5) and the analytical results were reviewed by Dr. N. Zimmerman (6); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathologic examinations were performed at the Hazleton Laboratories America, Inc. Histopathologic examinations of the rats were done by Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3). The histopathologic examinations of the mice were done by Dr. R. W. Voelker (3). The diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (7).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (6,9), using

methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (10).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (6), task leader Dr. M. R. Kornreich (6,11), senior biologist Ms. P. Walker (6), biochemist Mr. S. C. Drill (6), and technical editor Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1,11), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,12), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

---

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

2. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

3. Hazleton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia.

4. Now with the Center for Regulatory Services, 2347 Paddock Lane, Reston, Virginia.

5. Now with Rhodia, Inc., 23 Belmont Drive, Somerset, New Jersey.

6. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

7. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

8. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

9. Now with the Solar Energy Research Institute, Cole Boulevard, Golden, Colorado.

10. Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

11. Now with Clement Associates, Inc., 1010 Wisconsin Avenue, N.W., Washington, D.C.

12. Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay for possible carcinogenicity of sulfallate was conducted using Osborne-Mendel rats and B6C3F1 mice. Sulfallate was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty mice and 50 rats of each sex were placed on test as controls for the bioassay. The time-weighted average high and low dietary concentrations of sulfallate were, respectively, 410 and 250 ppm for male rats, 404 and 250 ppm for female rats, 1897 and 949 ppm for male mice, and 1815 and 908 ppm for female mice. After the 78-week period of chemical administration, there was an additional observation period of 25 to 26 weeks for dosed rats, 33 weeks for control rats, and 12 to 13 weeks for dosed and control mice.

There were significant positive associations between increased sulfallate concentration and accelerated mortality in both sexes of rats and in female mice. However, adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

Statistical analyses of the incidences of mammary adenocarcinomas in female rats, stomach neoplasms (i.e., combination of papillomas NOS, squamous-cell papillomas, and squamous-cell carcinomas) in male rats, combined alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas in male mice, and adenocarcinomas of the mammary gland in female mice revealed a significant positive association between dosage and incidence. These associations were all supported by at least one significant Fisher exact comparison.

The incidence of toxic tubular nephropathy observed in male rats and in mice of both sexes increased with the concentration of the compound administered. This nonneoplastic lesion was not observed in control animals.

Under the conditions of this bioassay dietary administration of sulfallate was carcinogenic to Osborne-Mendel rats and to B6C3F1 mice, inducing mammary gland tumors in females of both species, tumors of the forestomach in male rats, and lung tumors in male mice.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

LIST OF TABLES (Concluded)

I. INTRODUCTION

Sulfallate (Figure 1) (NCI No. C00453), a chlorinated dithiocarbamate derivative used as a preemergence herbicide on vegetable crops, was selected for bioassay by the National Cancer Institute because of its structural relationship to the known tumorigens selenium diethyldithiocarbamate and potassium bis(2-hydroxyethyl) dithiocarbamate and to a number of suspected tumorigens containing the diethyldithiocarbamate or dimethyldithiocarbamate moieties (Innes et al., 1969).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is diethylcarbamodithioic acid 2-chloro-2-propenyl ester.* It is also called 2-chloro-2-propenyl diethylcarbamodithioate; 2-chloroallyl diethyldithiocarbamate; diethyldithiocarbamic acid 2-chloroallyl ester; CDEC; and CP4742.

Sulfallate is a selective preemergence herbicide used to control annual grasses and broadleaf weeds in vegetable and fruit crops. It is also used to control weeds among shrubbery and ornamental plants (Farm Chemicals Handbook, 1976). Sulfallate is especially suited to sandy soils, but it is also effective on peat muck soil-types (Farm Chemicals Handbook, 1976). Established plants, or those which are vegetatively propagated, are not effectively eradicated by sulfallate administration (Martin and Worthing, 1977).

*The CAS registry number is 95-06-7

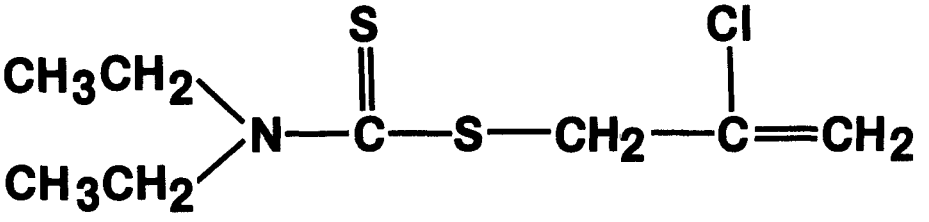


FIGURE 1
CHEMICAL STRUCTURE OF SULFALLATE

Sulfallate is currently produced in commercial quantities (in excess of 1000 pounds or $1000 in value annually) by only one U.S. company (Stanford Research Institute, 1977); consequently, recent production data are considered proprietary and are withheld from the public.

The potential for exposure to sulfallate is greatest for agricultural workers, but may also be considerable for workers in sulfallate production facilities. Residents of agricultural communities may be exposed to airborne residues following spraying operations. The herbicide is readily taken up by plant roots (Martin and Worthing, 1977) and the general population may be exposed via ingestion of residues in food crops. Ingestion is unlikely, however, since sulfallate is hydrolyzed in aqueous solution with a half-life of 47 days at pH 5 and 30 days at pH 8 (Martin and Worthing, 1977).

Chronic and acute toxicity data in humans are not available; however, sulfallate is considered a moderate skin and eye irritant (Gosselin et al., 1976).

II. MATERIALS AND METHODS

A. Chemicals

Technical-grade sulfallate was purchased from Monsanto Chemical Company, St. Louis, Missouri, and analyzed by Hazleton Laboratories America, Inc., Vienna, Virginia. Gas-liquid chromatography (GLC) utilizing the internal standard method demonstrated that the purity was greater than 90 percent. This was in agreement with the manufacturer's specification of purity. GLC total-area analysis revealed the presence of 14 minor components with the major component accounting for over 90 percent of the area. Internal standard and total-area analyses performed 12 months later provided similar results, although total-area analysis indicated the presence of only 7 minor components. The similarity in the results using both methods of GLC analysis over the period of one year indicated a relatively high stability for the compound. Studies performed 24 months after the initial analyses reconfirmed these results.

Throughout this report the term sulfallate is used to represent this technical-grade material.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of 2 percent Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) by weight added to Wayne Lab-Blox® meal (Allied Mills, Inc., Chicago, Illinois). Fresh mixtures of sulfallate in corn oil were prepared each week and stored in the dark. The mixtures of sulfallate

in corn oil were incorporated into the appropriate amount of basal laboratory diet in a twin-shell blender fitted with an accelerator bar.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts with the Division of Cancer Treatment, National Cancer Institute. The Osborne-Mendel rats were procured from the Battelle Memorial Institute, Columbus, Ohio, and the B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, observed for visible signs of disease or parasites, and assigned to the various dosed and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at

a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors. Mice were housed by sex in groups of ten in solid-bottom, polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Pinewood Sawdust Company, Moonachie, New Jersey) were provided once each week for mice. Rats received sanitized cages with no bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles and sipper tubes were provided three times a week. Food and water were available ad libitum.

Dosed rats were housed in a room with other rats receiving diets containing* chlorobenzilate (510-15-6); DDT (50-29-3); and TDE (72-54-8). Control rats were housed in a room with other rats receiving diets containing trifluralin (1582-09-8); dioxathion (78-34-2); dicofol (115-32-2); nitrofen (1836-75-5); endosulfan (115-29-7); and mexacarbate (315-18-4).

All mice, including controls, used in the sulfallate chronic bioassay were housed in the same room as other mice receiving diets containing trifluralin (1582-09-8); dioxathion (78-34-2); methoxychlor (72-43-5); DDE (72-55-9); TDE (72-54-8); dicofol (115-32-2);

*CAS registry numbers are given in parentheses.

chlorobenzilate (510-15-6); acetylaminofluorene (53-96-3); clonitralid (1420-04-8); DDT (50-29-3); pentachloronitrobenzene (82-68-8); nitrofen (1836-75-5); endosulfan (115-29-7); mexacarbate (315-18-4); amitrole (61-82-5); and safrole (94-59-7).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of sulfallate for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. Sulfallate was premixed with a small amount of the laboratory diet. The mixture was then incorporated into the laboratory diet with 2 percent corn oil and fed ad libitum to five of the six rat groups and five of the six mouse groups in concentrations of 215, 464, 1000, 2150, and 4640 ppm. The sixth group of each species served as a control group, receiving only the basal laboratory diet. The dosed dietary preparations were administered for a period of 6 weeks, followed by a 2-week observation period during which all animals were fed the basal laboratory diet.

A concentration inducing no mortality and resulting in a depression in mean group body weight of approximately 20 percent relative to controls was selected as the high concentration for administration in the chronic study. When weight gain criteria were not applicable, mortality data alone were utilized.

Mean body weight depression was observed at the lowest administered concentration in male rats and at 464 ppm and above in female rats. At a level of 464 ppm the depression in mean body weight as compared to controls was 5 percent in male rats and 19 percent in female rats. At 1000 ppm the depression in mean body weight was 42 percent in males, and 40 percent in females. No deaths were observed at these levels. The high concentration selected for administration to both male and female rats in the chronic bioassay was 500 ppm.

In the 8-week mouse subchronic study, weight gain patterns were erratic. At a concentration of 464 ppm mean body weight gain in the male mice was only 19 percent of that gained by the controls. In the female mice receiving 464 ppm, mean body weight gain was 177 percent of that gained by controls. At 1000 ppm an increase in the mean body weight gain of 244 percent in male mice, and 168 percent in the female mice was observed. At 2150 ppm mean body weight gain in male mice was only 56 percent of that in controls, while in females receiving the same concentration no increase or depression in mean body weight was noted when compared to controls. No deaths were observed at any of these concentrations. The high concentrations selected for administration to male and female mice in the chronic bioassay were 2000 and 1200 ppm, respectively.

F. Experimental Design

The experimental design parameters for the chronic bioassay (species, sex, group size, actual concentrations administered, duration

of treated and untreated observation periods, and the time-weighted average concentrations) are summarized in Tables 1 and 2.

The dosed and control rats were all approximately 6 weeks old at the time they were placed on test. The dosed rats were approximately 3 weeks younger than the controls and were started on test approximately 3 weeks after the controls. The concentrations of sulfallate initially utilized for male and female rats were 500 and 250 ppm. Throughout this report those rats initially receiving the former concentration are referred to as the high dose groups, while those initially receiving the latter concentration are referred to as the low dose groups. In week 8 of the study, administration of sulfallate to the high dose female rats ceased for 1 week, followed by 4 weeks of feeding at the previous concentration of 500 ppm. This cyclic pattern of administration continued for the remainder of the dosing period. This same method of total sulfallate intake reduction was employed for the high dose male rats beginning in week 12. The dosing period was 78 weeks followed by an observation period during which the rats received only the basal laboratory diet and water. Although a 32-week final observation period was originally planned, surviving rats were sacrificed after 25 to 26 weeks of observation.

The dosed and control mice were all approximately 6 weeks old at the time the experiment began. The concentrations initially administered to the male mice were 2000 and 1000 ppm. Throughout this report those males initially receiving the former concentration are

TABLE 1

DESIGN SUMMARY FOR OSBORNE MENDEL-RATS
SULFALLATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	SULFALLATE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION OVER A 78-WEEK PERIOD[b]
MALE					
CONTROL	50	0	0	111	0
LOW DOSE	50	250	78		250
		0		26	
HIGH DOSE	50	500	11		410
		500[c]	53	14	
		0		25	
FEMALE					
CONTROL	50	0	0	111	0
LOW DOSE	50	250	78		250
		0		26	
HIGH DOSE	50	500	7		404
		500[c]	56	15	
		0		26	

[a] Concentrations given in parts per million.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{78 \text{ weeks}}$

[c] These dosages were cyclically administered with a pattern of 1 dose-free week followed by 4 weeks (5 days per week) of administration at the dosage indicated.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
SULFALLATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	SULFALLATE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION OVER A 78-WEEK PERIOD[b]
MALE					
CONTROL	20	0	0	91	0
LOW DOSE	50	1000	62		949
		1000[c]	12	4	
		0		13	
HIGH DOSE	50	2000	62		1897
		2000[c]	12	4	
		0		13	
FEMALE					
CONTROL	20	0	0	91	0
LOW DOSE	50	600	8		908
		1000	54		
		1000[c]	12	4	
		0		12	
HIGH DOSE	50	1200	8		1815
		2000	54		
		2000[c]	12	4	
		0		12	

[a] Concentrations in parts per million.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{78 \text{ weeks}}$

[c] These dosages were cyclically administered with a pattern of 1 dose-free week followed by 4 weeks (5 days per week) of administration at the dosage indicated.

referred to as the high dose group, and those initially receiving the latter concentration are referred to as the low dose group. Female mice received initial concentrations of 1200 and 600 ppm. Throughout this report those female mice initially receiving the former concentration are referred to as the high dose group, while those initially receiving the latter concentration are referred to as the low dose group. During week 9, the high and low concentrations administered to the female mice were increased to 2000 and 1000 ppm, respectively. In week 63 of the study, administration of sulfallate to both males and females ceased for 1 week followed by 4 weeks of dietary administration. This cyclic pattern of sulfallate administration continued for the remainder of the dosing period. The 78-week dosing period was followed by a 12- to 13-week observation period during which the mice received only the basal laboratory diet and water.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. From the first day, all animals were inspected daily for mortality. The presence of tissue masses was determined by observation and palpation of each animal.

During the course of this bioassay several pathology protocols were in effect, each for different periods of time. The minimum protocol required that, if possible, certain tissues were to be taken and examined histopathologically from all control animals, from any animal in which a tumor was observed during gross examination, and from at least 10 grossly normal males and 10 grossly normal females from each dosed group. In addition, any tissues showing gross abnormalities were to be taken and examined histopathologically. Under later protocols, some tissues were taken from additional dosed animals. The number of animals in each group from which a tissue was examined is indicated in Appendices A through D.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by exsanguination under sodium pentobarbital anesthesia, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

Slides were prepared from the following tissues from selected animals: brain, pituitary, spinal cord, eye, adrenal, thyroid,

mesenteric lymph node, heart, lung, spleen, liver, kidney, stomach, small intestine, large intestine, pancreas, urinary bladder, prostate or uterus, testis with epididymis or ovary, skin with mammary gland, muscle, bone marrow, and tissue masses.

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

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

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

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

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals.

As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

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

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early

tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

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

and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

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

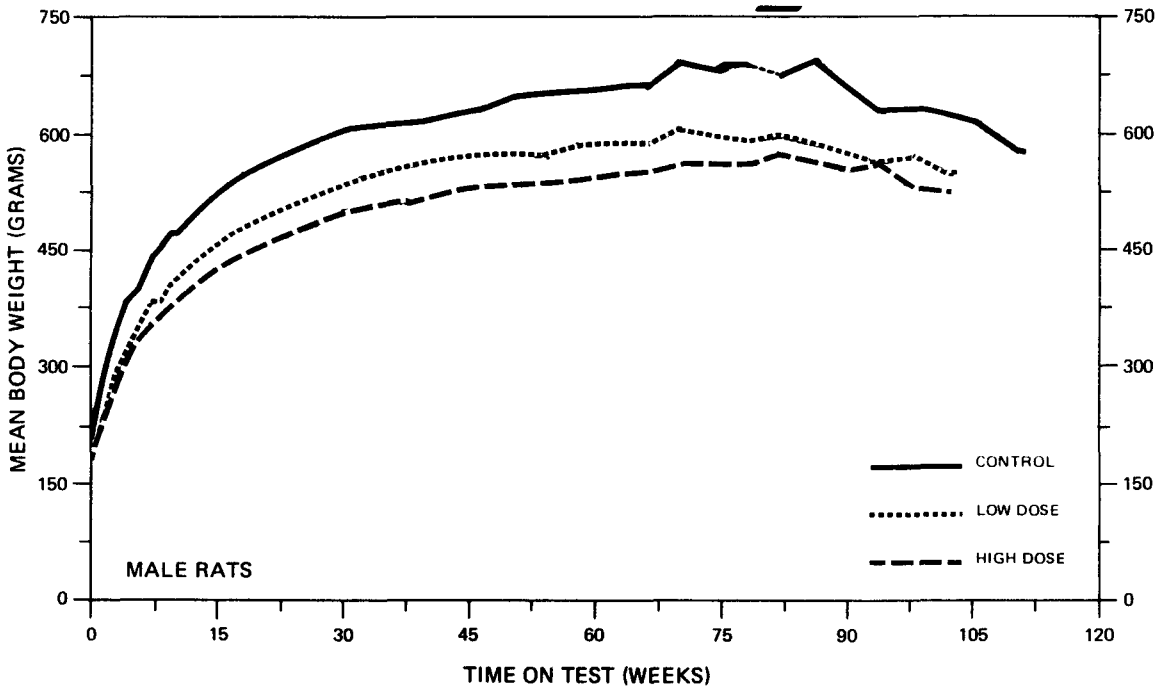
III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

Distinct dose-related mean body weight depression was evident in male and female rats from the beginning of the bioassay and generally continued throughout the study (Figure 2). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

During the first 6 months of the study no clinical signs were observed except for occasional hunched or thin appearance, squinted or reddened eyes, and labored respiration in a few rats in each group. From week 30 to cessation of chemical administration in week 78, an unusually high incidence of signs characteristic of eye irritation (i.e., red-tinged lacrimation; swollen, protruding, or squinted eyes; brown crust around the eyes) were observed in the dosed groups, particularly in the females.

Respiratory signs characterized by labored respiration, wheezing and/or nasal discharge were noted at a low incidence in all groups including the controls. The incidence of this observation increased as the animals aged. Other signs usually associated with aging, which were noted at comparable rates in control and dosed rats, included body sores, alopecia, reddish discharge or brown crust around body orifices, and abdominal urine stains. Observations in one or two rats in each group included transient or sporadic incoordination, salivation, head tilt, and tremors.



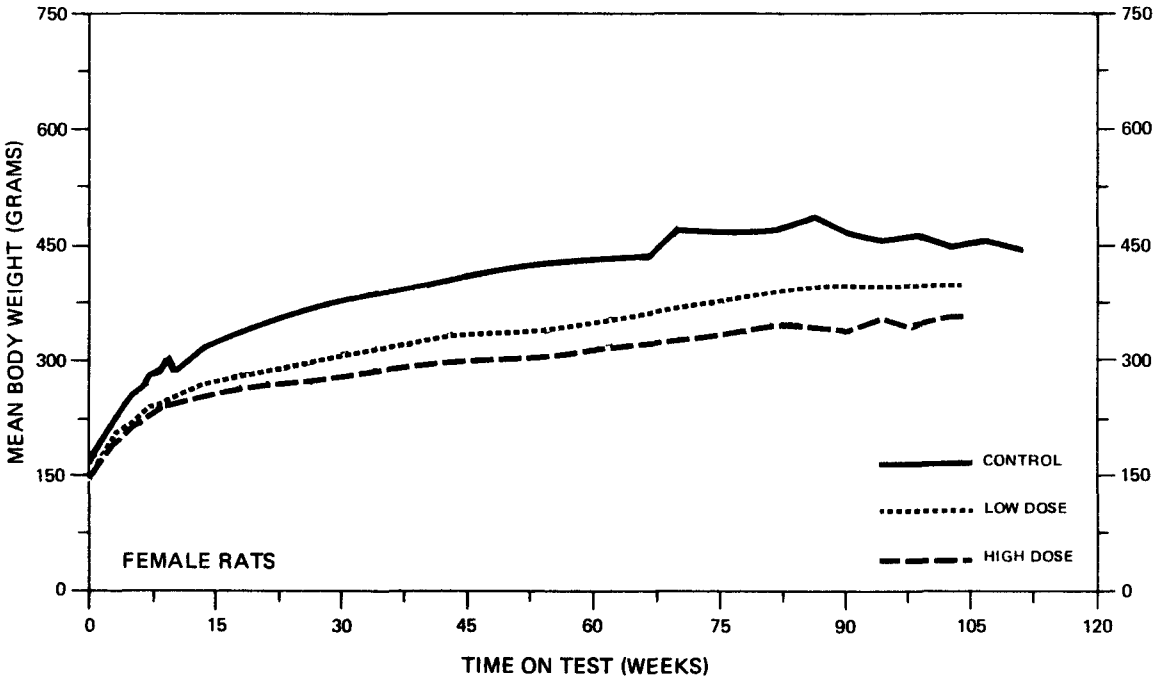


FIGURE 2
GROWTH CURVES FOR SULFALLATE CHRONIC STUDY RATS

Tissue masses, palpable nodules and/or swollen areas were observed at a slightly greater frequency among the dosed rats than among the controls.

B. Survival

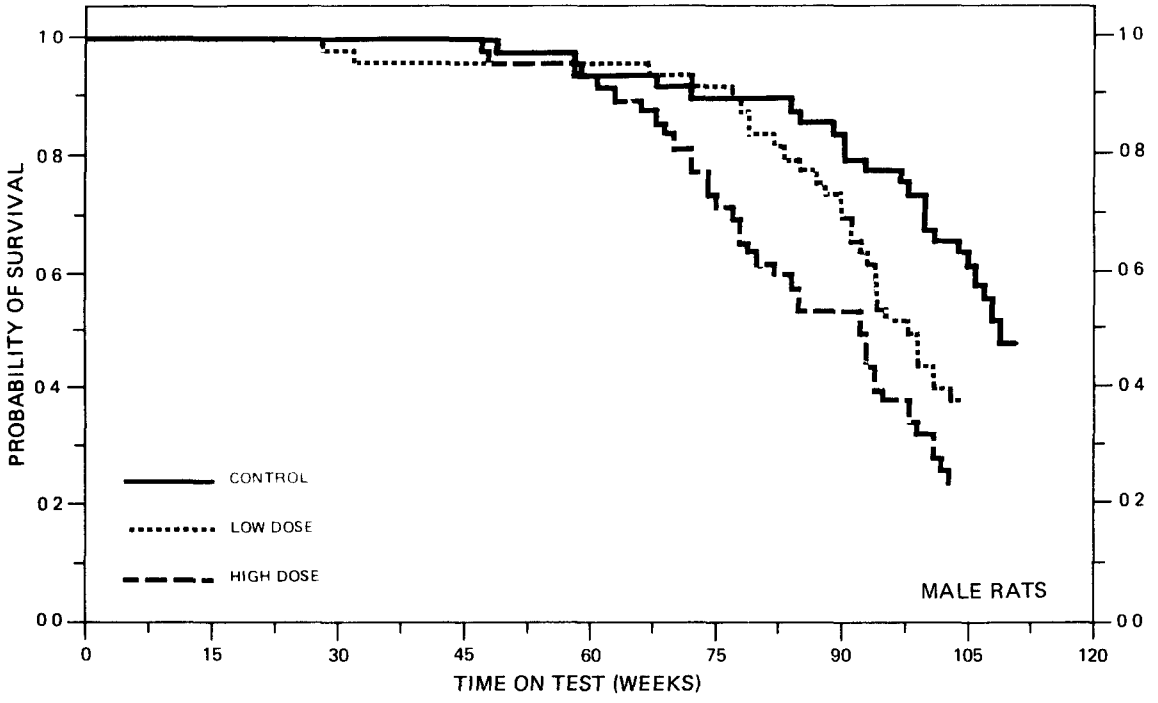
The estimated probabilities of survival for male and female rats in the control and sulfallate-dosed groups are shown in Figure 3. For both males and females the Tarone test indicated a significant ($P < 0.001$) positive association between dosage and mortality.

There were adequate numbers of male and female rats at risk from late-developing tumors. In the males 54 percent (27/50) of the high dose, 74 percent (37/50) of the low dose, and 84 percent (42/50) of the control rats survived on test at least 90 weeks. In the females 60 percent (30/50) of the high dose, 86 percent (43/50) of the low dose, and 90 percent (45/50) of the control group survived on test at least 90 weeks. For both sexes the surviving dosed rats were sacrificed in weeks 103 and 104 while the surviving control rats were sacrificed in week 111.

C. Pathology

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

Long-term dietary intake of sulfallate in rats was associated with increased incidences of neoplasia, especially of squamous-cell



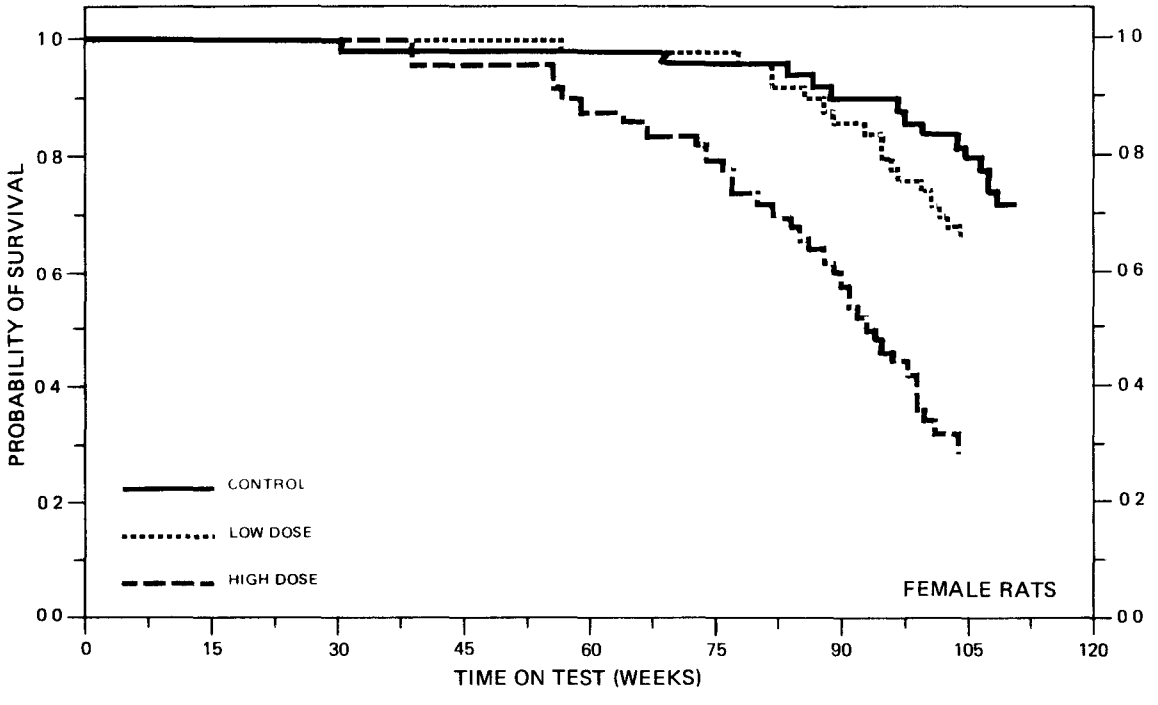


FIGURE 3
SURVIVAL COMPARISONS OF SULFALLATE CHRONIC STUDY RATS

carcinomas, in several organ systems. These tumors were seen in the skin and adnexal tissues, the esophagus and forestomach, and the thyroid gland in both sexes and in the mammary gland in females.

The incidence of esophageal and gastric lesions are tabulated below for dosed rats. None of the neoplasms were observed in control animals.

	Males		Females	
	Low Dose	High Dose	Low Dose	High Dose
Esophagus				
Papilloma	0/26	1/21	0/44	0/28
Squamous-Cell Carcinoma	0/26	1/21	0/44	1/28
Forestomach				
Papilloma	0/30	3/25	0/43	2/35
Squamous-Cell Carcinoma	0/30	2/25	0/43	0/35
Acanthosis	7/30	7/25	1/43	9/35
Hyperkeratosis	7/30	6/25	1/43	6/35

The incidences of acanthosis and hyperkeratosis shown in this table were those in animals without stomach tumors. Microscopically, the papillomas appeared as pedunculated growths showing marked localized acanthosis and hyperkeratosis and projecting into the lumen. The squamous-cell carcinomas, on the other hand, consisted of areas of acanthosis and hyperkeratosis with a downward proliferation of anaplastic basal cells invading lamina propria and submucosa. Basal cells appeared hyperbasophilic with numerous mitotic figures and grew in disorganized sheets of varying-sized cells.

In the integument, squamous-cell carcinomas were observed in 2/48 (4 percent) low dose males, 1/45 (2 percent) high dose males, 1/50 (2 percent) low dose females and 1/48 (2 percent) high dose females. Squamous-cell carcinomas also occurred in the external ear of 1/50 (2 percent) low dose females and 2/48 (4 percent) high dose females. None of these neoplasms occurred in control animals.

Primary squamous-cell carcinomas of the thyroid occurred in 2/21 (10 percent) high dose males. A squamous-cell carcinoma metastasized to the thyroid from the stomach in one high dose male. Microscopically, both tumors were composed of proliferating anaplastic epithelial cells. One was a small discrete lesion consisting of neoplastic cells sequestered in collagenous tissue and the other, a large proliferating structure producing masses of keratin and destroying the normal architecture of the thyroid.

Mammary adenocarcinomas were observed in 0/50 control females, 7/50 (14 percent) low dose females, and 11/48 (23 percent) high dose females. The first mammary carcinoma was observed in the high dose group in week 39. These tumors were characterized microscopically by the presence of irregularly formed acini lined by anaplastic epithelial cells, often several cells in thickness, with papillary projections into the lumen. Some were highly cellular, composed of tightly packed epithelial cells growing in sheets or forming tiny acini and filled with eosinophilic amorphous material. Broad bands

of collagenous connective tissue intersected these tumors and often massive areas of ischemic necrosis were seen containing islands of viable neoplastic tissue around blood vessels. Metastatic lesions were similar in morphology to those observed at the primary site.

A variety of other neoplastic lesions was also observed in the dosed and control animals. These lesions probably represented spontaneously occurring tumors.

The incidence of inflammatory, degenerative, and hyperplastic lesions in the control rats was similar to that of the dosed rats with the exception of the following: in the kidney, minimal changes of toxic tubular nephropathy occurred in 1/31 (3 percent) low dose males, 9/22 (41 percent) high dose males, and 1/28 (4 percent) high dose females. This change was characterized microscopically by the presence of megalocytic tubular epithelial cells having abundant eosinophilic cytoplasm and large hyperchromatic nuclei. These occurred in varying numbers affecting tubules of the inner cortex. Often this change was present in conjunction with spontaneous chronic interstitial nephritis; however, it was felt to be a toxic change rather than part of the spectrum of changes seen in lesions of the kidneys of aging rats.

In the eye, inflammatory and degenerative changes were observed in somewhat greater frequency in dosed rats, especially females, than in control rats.

Based on the results of this histopathologic examination, evidence was provided for the carcinogenicity of sulfallate in Osborne-Mendel rats under the conditions of this study. Administration of the compound was associated with an increased incidence of mammary adenocarcinomas in females and squamous-cell carcinomas of the skin, adnexal tissues, esophagus, and stomach in males and females.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or sulfallate-dosed groups and where such tumors were observed in at least 5 percent of the group.

In females mammary adenocarcinomas were observed in 7/50 (14 percent) of the low dose rats, and in 11/48 (23 percent) of the high dose rats, but not among the control rats. The Cochran-Armitage test indicated a significant ($P = 0.001$) positive association between dosage and the incidence of mammary adenocarcinomas. The results of the Fisher exact tests supported this finding with significant comparisons of both low dose ($P = 0.006$) and high dose ($P < 0.001$) to the control. In historical control data collected by Hazleton Laboratories for the NCI Carcinogenesis Testing Program, only 9/350 (3 percent) of the untreated female Osborne-Mendel rats had mammary adenocarcinomas.

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous-Cell Carcinoma[b]	0/46(0.00)	0/30(0.00)	2/25(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.548
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	66
Stomach: Papilloma NOS, Squamous-Cell Papilloma, or Squamous-Cell Carcinoma[b]	0/46(0.00)	0/30(0.00)	5/25(0.20)
P Values[c]	P = 0.003	N.S.	P = 0.004
Departure from Linear Trend[e]	P = 0.034	---	---
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	2.346
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	66
Kidney: Mixed Tumor Malignant[b]	0/47(0.00)	2/31(0.06)	0/22(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.037	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.450	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	77	---

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	4/41(0.10)	2/30(0.07)	3/20(0.15)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.683	1.538
Lower Limit	---	0.065	0.244
Upper Limit	---	4.406	8.040
Weeks to First Observed Tumor	108	85	103
Thyroid: Follicular-Cell Carcinoma[b]	4/48(0.08)	1/27(0.04)	2/21(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.444	1.143
Lower Limit	---	0.009	0.109
Upper Limit	---	4.158	7.172
Weeks to First Observed Tumor	106	104	103
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	5/48(0.10)	6/27(0.22)	2/21(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.133	0.914
Lower Limit	---	0.593	0.092
Upper Limit	---	7.888	4.987
Weeks to First Observed Tumor	106	95	103

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Squamous-Cell Carcinoma[b]	0/48(0.00)	0/27(0.00)	2/21(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.683
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	59
Thyroid: C-Cell Carcinoma[b]	0/48(0.00)	2/27(0.07)	1/21(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.528	0.123
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	101
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	0/48(0.00)	4/27(0.15)	2/21(0.10)
P Values[c]	P = 0.034	P = 0.014	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.660	0.683
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	101

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Brain: Astrocytoma[b]	0/47(0.00)	2/27(0.07)	1/22(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.520	0.115
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	82
Subcutaneous Tissue: Hemangiosarcoma[b]	4/49(0.08)	0/48(0.00)	0/45(0.00)
P Values[c]	P = 0.014(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.100	1.171
Weeks to First Observed Tumor	72	---	---
Spleen: Hemangiosarcoma[b]	4/47(0.09)	4/29(0.14)	2/20(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.621	1.175
Lower Limit	---	0.324	0.111
Upper Limit	---	7.967	7.334
Weeks to First Observed Tumor	90	101	101

TABLE 3 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 250 or 410 ppm in feed.

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

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

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

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Neoplastic Nodule[b]	1/50(0.02)	3/47(0.06)	2/31(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.191	3.226
Lower Limit	---	0.267	0.176
Upper Limit	---	163.836	183.955
Weeks to First Observed Tumor	111	104	104
Stomach: Papilloma NOS[b]	0/50(0.00)	0/43(0.00)	2/35(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.426
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	91
Pituitary: Chromophobe Adenoma[b]	15/50(0.30)	9/44(0.20)	4/26(0.15)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.682	0.513
Lower Limit	---	0.293	0.135
Upper Limit	---	1.484	1.408
Weeks to First Observed Tumor	100	82	103

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	1/50(0.02)	3/44(0.07)	0/28(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.409	0.000
Lower Limit	---	0.285	0.000
Upper Limit	---	174.727	32.810
Weeks to First Observed Tumor	111	103	---
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	5/50(0.10)	3/44(0.07)	1/28(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.682	0.357
Lower Limit	---	0.111	0.008
Upper Limit	---	3.288	2.942
Weeks to First Observed Tumor	111	104	104
Mammary Gland: Adenocarcinoma NOS[b]	0/50(0.00)	7/50(0.14)	11/48(0.23)
P Values[c]	P = 0.001	P = 0.006	P < 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.944	3.459
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	88	39

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	15/50(0.30)	21/50(0.42)	10/48(0.21)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.039	---	---
Relative Risk (Control)[d]	---	1.400	0.694
Lower Limit	---	0.784	0.310
Upper Limit	---	2.544	1.483
Weeks to First Observed Tumor	87	89	77
Uterus: Endometrial Stromal Polyp[b]	4/49(0.08)	3/46(0.07)	2/28(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.799	0.875
Lower Limit	---	0.122	0.083
Upper Limit	---	4.463	5.631
Weeks to First Observed Tumor	111	104	77
Brain: Astrocytoma[b]	0/50(0.00)	1/45(0.02)	2/26(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.060	0.570
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	103	76

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Hemangiosarcoma[b]	3/50(0.06)	0/50(0.00)	0/48(0.00)
P Values[c]	P = 0.034(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.664	1.730
Weeks to First Observed Tumor	111	---	---
Spleen: Hemangiosarcoma[b]	0/50(0.00)	3/45(0.07)	1/28(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.669	0.096
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	86	104

[a]Treated groups received time-weighted average doses of 250 or 404 ppm in feed.

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

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

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

In male rats when the incidences of C-cell adenomas or C-cell carcinomas of the thyroid were combined, the Cochran-Armitage test indicated a significant (P = 0.034) positive dose-response association. The Fisher exact test comparing low dose to control supported this finding with a significant (P = 0.014) result, but the comparison of high dose to control was not significant. Only 27 thyroids in the low dose group and 21 thyroids in the high dose group were examined microscopically. Squamous-cell carcinomas, follicular-cell adenomas, and follicular-cell carcinomas were also observed, but not in statistically significant proportions. In the historical controls 32/352 (9 percent) of the untreated male Osborne-Mendel rats had either a follicular-cell adenoma or a follicular-cell carcinoma of the thyroid and 12/352 (3 percent) had either a C-cell adenoma or a C-cell carcinoma. No conclusion has been drawn relative to the thyroid C-cell neoplasms in the males because of the difficulty in interpreting the lack of a statistically significant high dose result and the absence of information as to whether the dosed animals selected for histopathologic examination represented a random sampling of the dosed groups.

In males a significant number of stomach neoplasms were observed in the high dose rats. When incidences were combined so that the numerator represented males with either a papilloma NOS, a squamous-cell papilloma, or a squamous-cell carcinoma, the Cochran-Armitage test indicated a significant (P = 0.003) dose-response association.

The departure from linear trend was significant (P = 0.034), principally because the neoplasms were only observed in the high dose rats. The Fisher exact test comparing high dose to control was also significant (P = 0.004). In the historical control data none of the 352 rats had a tumor of these types, compared to the 5/25 (20 percent) observed in the high dose males for this bioassay.

Based upon these statistical results the administration of sulfallate was associated with increased incidences of mammary adenocarcinomas in female rats and of stomach neoplasms in male rats.

The possibility of a negative association between administration and incidence was observed for hemangiosarcomas of the subcutaneous tissue in both males and females, but in both cases the Fisher exact tests were not significant.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

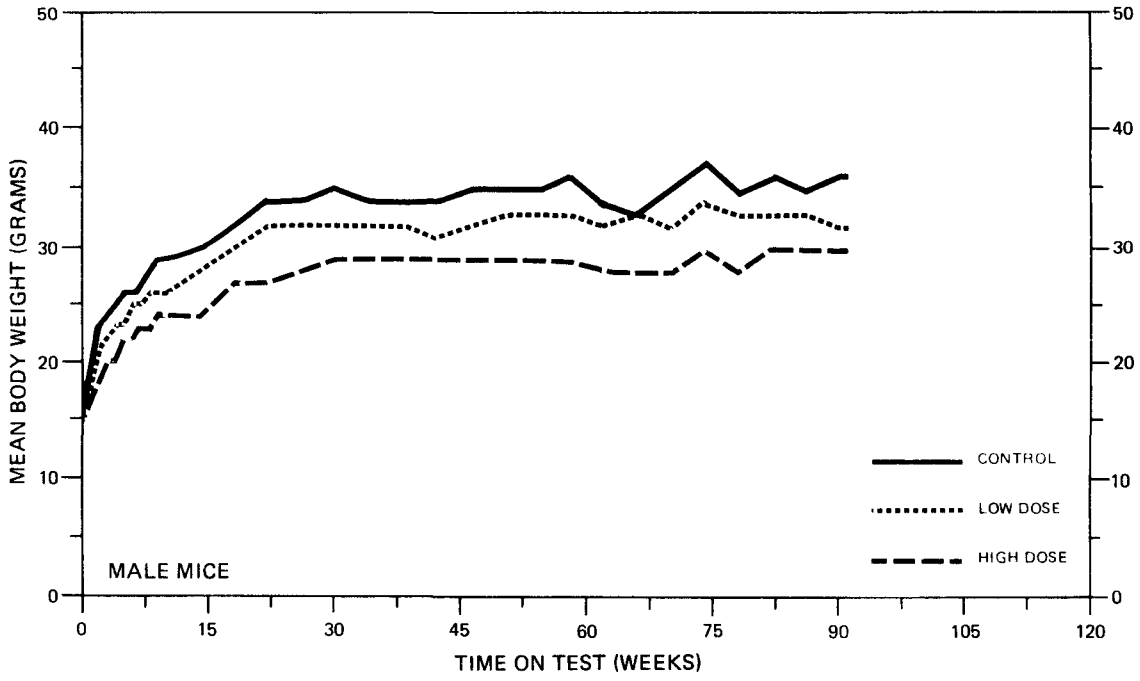
Distinct dose-related mean body weight depression was evident throughout the study for male mice and after week 10 for female mice (Figure 4). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

Physical appearance and behavior of dosed mice during the first year of the study gave no evidence of compound-related effects. Signs often observed in group-housed laboratory mice, particularly in the males, were observed at a comparable rate in dosed and control mice. These common signs included sores on the body and/or extremities; a hunched appearance; localized alopecia; penile, vulvar or anal irritation; and rough or stained fur.

A hunched or thin appearance was observed with greater frequency in the dosed groups than in the controls from week 62 to termination of the study in week 90. The incidence of palpable nodules, tissue masses and/or swollen areas of the body was slightly greater in the dosed mice than in the controls.

B. Survival

The estimated probabilities of survival for male and female mice in the control and sulfallate-dosed groups are shown in Figure 5. For males no dose-mortality association was demonstrated, but for females



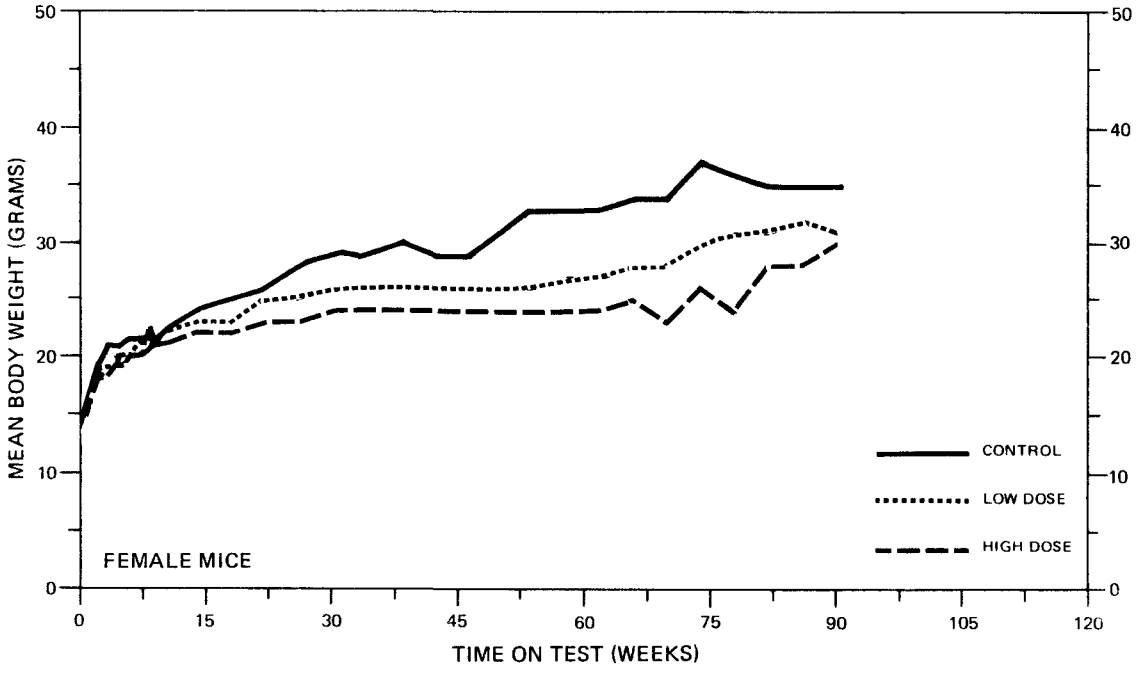


FIGURE 4
GROWTH CURVES FOR SULFALLATE CHRONIC STUDY MICE

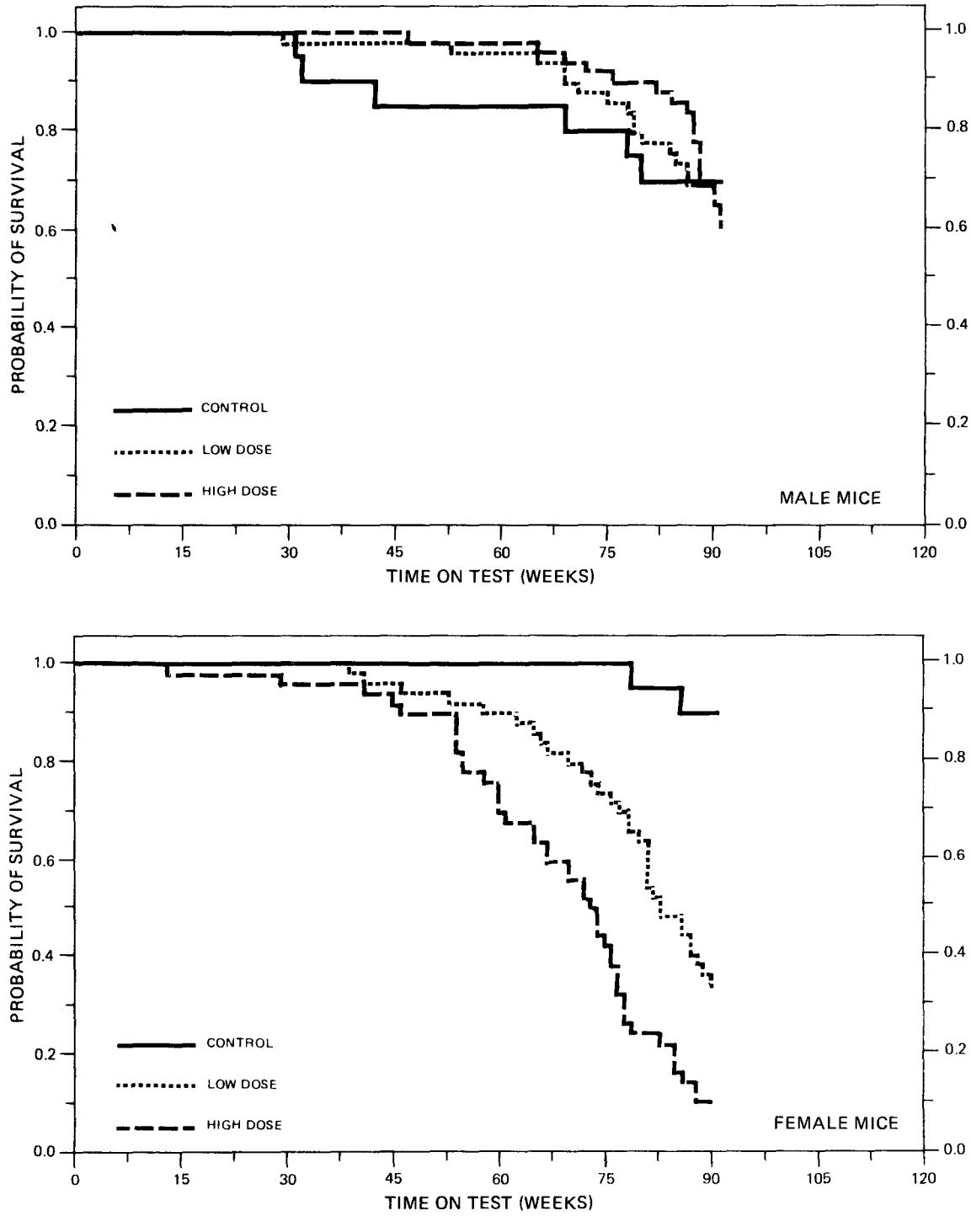


FIGURE 5
SURVIVAL COMPARISONS OF SULFALLATE CHRONIC STUDY MICE

the Tarone test indicated a significant ($P < 0.001$) positive association between dosage and mortality.

For males sufficient numbers survived sufficiently long to be at risk from late-developing tumors, as 92 percent (46/50) of the high dose, 86 percent (43/50) of the low dose, and 80 percent (16/20) of the control mice survived on test at least 75 weeks. For females the survival was also adequate as 44 percent (22/50) of the high dose, 74 percent (37/50) of the low dose, and 20/20 of the control mice survived on test at least 75 weeks.

C. Pathology

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

Long-term dietary administration of sulfallate to mice was associated with increased incidences of neoplastic lesions affecting several organs and tissues (i.e., skin and subcutaneous tissue, lung, liver, stomach, and mammary gland).

Mammary adenocarcinomas occurred in 33/48 (69 percent) low dose females and 27/46 (59 percent) high dose females. In 10 of the 33 low dose females and 16 of the 27 high dose females the adenocarcinomas were accompanied by squamous metaplasia. No mammary adenocarcinomas were observed in the corresponding controls. Microscopically, the morphology of these mammary carcinomas consisted of numerous

irregular acini and papillary structures which were lined by anaplastic epithelial cells sometimes in multiple layers. In a number of mammary tumors, large areas of squamous differentiation were observed. Neoplasms were usually intersected by dense fibrous connective tissue, and large cystic areas of necrosis were noted. When mammary adenocarcinomas metastasized, the metastatic lesions observed in other organs were similar in morphology to the primary tumors.

Squamous-cell carcinomas of the skin or subcutaneous tissue, frequently adjacent to the preputial gland, occurred in 3/46 (7 percent) low dose males, 6/49 (12 percent) high dose males, and 2/48 (4 percent) low dose females. Basal-cell carcinomas of the skin occurred in 1/49 (2 percent) high dose males and 1/46 (2 percent) high dose females. None of these types of tumors were recognized in control mice.

Papillomas of the forestomach occurred in 4/40 (10 percent) low dose males, 3/43 (7 percent) high dose males, and 1/43 (2 percent) low dose females. Squamous-cell carcinomas of the forestomach were observed in 2/40 (5 percent) low dose males, 1/43 (2 percent) high dose males, and 1/38 (3 percent) high dose females. No stomach tumors were observed in control mice. Microscopically, the papillomas occurred as pedunculated growths composed of hyperkeratosis and acanthosis of the superficial epithelium which was supported on a stalk of well-vascularized fibrous connective tissue. The squamous-cell carcinomas demonstrated invasiveness, documented by the presence of small nests of anaplastic epithelial cells in the submucosa and in

some instances, local vascular emboli. A few male and female mice of the high and low dose groups had hyperkeratosis and acanthosis in the forestomach.

Hepatocellular carcinomas occurred in 7/20 (35 percent) control males, 22/45 (49 percent) low dose males, 24/49 (49 percent) high dose males, 0/19 control females, 5/47 (11 percent) low dose females, and 8/46 (17 percent) high dose females. The hepatocellular carcinomas varied greatly in morphology; some were relatively well-differentiated and composed of proliferating basophilic hepatocytes forming liver plates one or more cells in thickness, and these growths compressed adjacent hepatic parenchyma. The anaplastic carcinomas consisted of proliferating large intensely basophilic staining hepatocytes forming pseudoacini and thick blunted liver plates which often projected into ectatic sinusoids. Metastases appeared essentially similar to the primary liver tumor.

Alveolar/bronchiolar adenomas occurred in 11/43 (26 percent) low dose males, 9/45 (20 percent) high dose males, 1/19 (5 percent) control females, 11/45 (24 percent) low dose females, and 2/37 (5 percent) high dose females. Alveolar/bronchiolar carcinomas were observed in 3/43 (7 percent) low dose males, 9/45 (20 percent) high dose males, 4/45 (9 percent) low dose females, and 2/37 (5 percent) high dose females.

Subcutaneous fibrosarcomas occurred in 5/46 (11 percent) low dose males and 2/46 (4 percent) high dose females. Metastatic fibrosarcoma

occurred in the cervical lymph node of 1/41 (2 percent) low dose males. A fibrosarcoma involving muscles of the leg occurred in 1/46 (2 percent) low dose males. None of these tumor types were observed in control mice.

A variety of other neoplastic lesions, apparently unrelated to chemical administration, was seen throughout all groups.

A variety of nonneoplastic lesions was also observed in both dosed and control groups, regardless of experimental regimen. However, 26/42 (62 percent) low dose males, 35/43 (81 percent) high dose males, 10/44 (23 percent) low dose females and 26/37 (70 percent) high dose females had evidence of minimal toxic tubular nephropathy. This change was characterized by the presence of megalocytic tubular epithelial cells, with abundant eosinophilic cytoplasm and large hyperchromatic nuclei. These occurred in varying numbers in the inner renal cortex and in the absence of other changes.

Based on the results of this histopathologic examination, evidence was provided for the carcinogenicity of sulfallate in B6C3F1 mice under the conditions of this experiment. Administration of the compound was associated with an increased incidence of mammary adenocarcinomas in females, squamous-cell carcinomas of the skin, adnexal tissues, and stomach in males and females, lung tumors in males and females, and hepatocellular carcinomas in females.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Skin, Subcutaneous Tissue, or Preputial Gland: Squamous-Cell Carcinoma[b]	0/20(0.00)	3/46(0.07)	6/49(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.272	0.680
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	71	91
Subcutaneous Tissue: Fibroma[b]	2/20(0.10)	3/46(0.07)	0/49(0.00)
P Values[c]	P = 0.043(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.652	0.000
Lower Limit	---	0.083	0.000
Upper Limit	---	7.437	1.372
Weeks to First Observed Tumor	91	91	---
Subcutaneous Tissue: Fibrosarcoma[b]	0/20(0.00)	5/46(0.11)	0/49(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.008	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.571	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	53	---

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/20(0.00)	3/43(0.07)	9/45(0.20)
P Values[c]	P = 0.009	N.S.	P = 0.028
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.291	1.223
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	90	87
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/20(0.00)	14/43(0.33)	17/45(0.38)
P Values[c]	P = 0.004	P = 0.002	P = 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	2.125	2.508
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	79	65
Hematopoietic System: Malignant Lymphoma[b]	0/20(0.00)	3/46(0.07)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.273	0.256
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	47

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Circulatory System: Hemangiosarcoma[b]	0/20(0.00)	1/46(0.02)	6/49(0.12)
P Values[c]	P = 0.024	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.024	0.679
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	69	87
Liver: Hepatocellular Carcinoma[b]	7/20(0.35)	22/45(0.49)	24/49(0.49)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.397	1.399
Lower Limit	---	0.719	0.693
Upper Limit	---	3.275	3.159
Weeks to First Observed Tumor	91	69	69
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	7/20(0.35)	22/45(0.49)	24/49(0.49)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.397	1.399
Lower Limit	---	0.719	0.728
Upper Limit	---	3.275	3.273
Weeks to First Observed Tumor	91	69	69

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous-Cell Carcinoma[b]	0/19(0.00)	2/40(0.05)	1/43(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.147	0.024
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	91
Stomach: Squamous-Cell Carcinoma, Squamous-Cell Papilloma, or Papilloma NOS[b]	0/19(0.00)	6/40(0.15)	4/43(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.796	0.428
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	91
Kidney: Tubular-Cell Adenoma[b]	0/20(0.00)	0/42(0.00)	3/43(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.291
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	86

TABLE 5 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 949 or 1897 ppm in feed.

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

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

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

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 6

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/19(0.00)	4/45(0.09)	2/37(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.408	0.157
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	73	85
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	1/19(0.05)	13/45(0.29)	4/37(0.11)
P Values[c]	N.S.	P = 0.032	N.S.
Departure from Linear Trend[e]	P = 0.008	---	---
Relative Risk (Control)[d]	---	5.489	2.054
Lower Limit	---	0.942	0.227
Upper Limit	---	226.304	98.234
Weeks to First Observed Tumor	91	73	54
Hematopoietic System: Malignant Lymphoma[b]	5/20(0.25)	4/48(0.08)	3/46(0.07)
P Values[c]	P = 0.038(N)	N.S.	P = 0.049(N)
Relative Risk (Control)[d]	---	0.333	0.261
Lower Limit	---	0.078	0.046
Upper Limit	---	1.439	1.228
Weeks to First Observed Tumor	91	81	54

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Circulatory System: Hemangiosarcoma[b]	1/20(0.05)	0/48(0.00)	3/46(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	1.304
Lower Limit	---	0.000	0.114
Upper Limit	---	7.942	66.966
Weeks to First Observed Tumor	79	---	60
Liver: Hepatocellular Carcinoma[b]	0/19(0.00)	5/47(0.11)	8/46(0.17)
P Values[c]	P = 0.038	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.534	0.990
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	83	67
Mammary Gland: Adenocarcinoma NOS[b]	0/20(0.00)	23/48(0.48)	11/46(0.24)
P Values[c]	N.S.	P < 0.001	P = 0.012
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	3.268	1.506
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	39	46

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenocarcinoma with Squamous Metaplasia[b]	0/20(0.00)	10/48(0.21)	16/46(0.35)
P Values[c]	P = 0.002	P = 0.022	P = 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.292	2.296
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	41	29
Mammary Gland: Adenocarcinoma with Squamous Metaplasia or Adenocarcinoma NOS[b]	0/20(0.00)	33/48(0.69)	27/46(0.59)
P Values[c]	P = 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	4.830	4.061
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	39	29

[a]Treated groups received time-weighted average doses of 908 or 1815 ppm in feed.

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

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

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

[e]The probability level of the test for departure from linear trend is given beneath the control group when P < 0.05.

every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or sulfallate-dosed groups and where such tumors were observed in at least 5 percent of the group.

For males when the incidences were combined so that the numerator of the incidence represented mice with either an alveolar/bronchiolar adenoma or an alveolar/bronchiolar carcinoma, the Cochran-Armitage test indicated a significant (P = 0.004) positive association between dosage and incidence. The Fisher exact test supported these findings with significant comparisons of both high dose (P = 0.001) and low dose (P = 0.002) to control. In historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, 13/386 (3 percent) of the untreated male B6C3F1 mice had an alveolar/bronchiolar adenoma; 2/386 (0.01 percent) had alveolar/bronchiolar carcinomas.

Alveolar/bronchiolar neoplasms were also observed in female mice, but not in statistically significant incidences. The Fisher exact test comparing the combined incidence of 13/45 (29 percent) in the low dose to the 1/19 (5 percent) in the control resulted in a probability level of P = 0.032, a marginal result which was not significant under the Bonferroni criterion. It must be noted, however, that the power of this test was low due to the small sample size in the control and early deaths from tumors in the high dose females. In the historical data, 6/380 (1.5 percent) of the untreated female B6C3F1 mice had alveolar/bronchiolar adenomas, while 4/380 (1 percent) had alveolar/bronchiolar carcinomas.

A high incidence of dosed female mice with an adenocarcinoma accompanied by squamous metaplasia of the mammary gland was noted. These tumors were noted as early as week 29 of the study. The Cochran-Armitage test indicated a significant ($P = 0.002$) dose-response association and the Fisher exact tests indicated significant comparisons of both low dose ($P = 0.021$) and high dose ($P = 0.001$) to control. Additionally, a high incidence of dosed female mice with mammary adenocarcinomas NOS in the absence of glandular squamous metaplasia was observed. The Fisher exact tests were significant in comparing both the low dose ($P < 0.001$) and the high dose ($P = 0.012$) to the control group.

For males the Cochran-Armitage test indicated a significant ($P = 0.024$) positive association between dosage and the incidence of hemangiosarcomas, but the Fisher exact tests were not significant. Similarly, for females the Cochran-Armitage test was significant ($P = 0.038$) for the incidence of hepatocellular carcinomas, but the Fisher exact tests did not support this finding. In the historical data, 8/389 (2 percent) of the untreated males had a hemangiosarcoma or a hemangioma, while 8/411 (2 percent) of the untreated female B6C3F1 mice had a hepatocellular carcinoma.

The Cochran-Armitage test also indicated significant negative associations between dosage and the incidence of malignant lymphomas in females and the incidence of fibromas of the subcutaneous tissue in males. None of these results, however, were supported by Fisher exact tests under the Bonferroni criterion.

Based upon these statistical results the administration of sulfallate was associated with the increased incidence of alveolar/bronchiolar neoplasms in male mice and of mammary adenocarcinomas NOS and of mammary adenocarcinomas with squamous metaplasia in female mice.

V. DISCUSSION

Under the conditions of this bioassay there were significant positive associations between increased sulfallate concentration and accelerated mortality in both sexes of rats and in female mice. In spite of early deaths with tumors, adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

Among female rats, there was a statistically significant positive association between dosage and the incidence of mammary adenocarcinomas. The incidence in each dosed group was significantly higher than the incidence in the control group.

Among male rats, there was a statistically significant positive association between dosage and the incidence of stomach tumors (i.e., combined incidences of squamous-cell carcinomas, squamous-cell papillomas, and papillomas NOS). The incidence of stomach tumors in the high dose group was significantly higher than in the male rat control group.

An increased incidence of thyroid tumors was observed among male rats (i.e., 5/48 [10 percent] controls, 10/27 [37 percent] low dose, and 7/21 [33 percent] high dose). These thyroid tumors included squamous-cell carcinomas (both primary and metastatic), follicular-cell adenomas, follicular-cell carcinomas, C-cell adenomas, and C-cell carcinomas. In historical controls, 8/160 (5 percent) of the untreated male Osborne-Mendel rats had thyroid tumors, all of which

were either follicular-cell adenomas or follicular-cell carcinomas. Statistical calculations based on observed incidences of thyroid tumors are of limited usefulness, however, since there is no indication that the 27 thyroids from low dose rats and 21 thyroids from high dose rats were randomly selected for histopathologic examination. It is evident, nevertheless, that more thyroid tumors did occur among dosed rats than among controls.

The occurrence of rare tumors of the esophagus (i.e., one papilloma and one squamous-cell carcinoma in high dose males and one squamous-cell carcinoma in a high dose female) was observed, supporting the finding of carcinomas of the forestomach. No esophageal tumors were observed in control rats. In addition, a few squamous-cell carcinomas of the skin were observed in dosed but not in control rats.

Among female mice, the incidences of mammary adenocarcinomas were significantly higher in both high and low dose groups than in controls. Many of these adenocarcinomas were accompanied by squamous metaplasia.

When the incidence of alveolar/bronchiolar adenomas was combined with the incidence of alveolar/bronchiolar carcinomas, there was a statistically significant positive association between dosage and tumor incidence for male mice. The combined incidence of these lung tumors was significantly higher in each dosed group than in the male mouse control group. When the incidences of alveolar/bronchiolar

adenomas or alveolar/bronchiolar carcinomas were analyzed separately, the incidence of alveolar/bronchiolar adenomas in the low dose group was significantly higher than that in the male mouse control group, but other comparisons did not indicate statistically significant results. The incidences of these neoplasms in low dose females were also increased but limited survival among high dose females and the small size of the female control group contributed to the lack of statistical significance in the occurrence of these tumors in female mice.

Dietary administration of sulfallate to male and female mice appeared to be associated with increased occurrences of uncommon neoplasms in several organs. These included squamous-cell and basal-cell carcinomas of the skin, squamous-cell papillomas of the stomach and squamous-cell carcinomas of the forestomach. None of these neoplasms occurred in statistically significant incidences.

The incidence of toxic tubular nephropathy observed in male rats and in mice of both sexes increased with the concentration of the compound administered. This nonneoplastic lesion was not observed in control animals.

Under the conditions of this bioassay, dietary administration of sulfallate was carcinogenic to Osborne-Mendel rats and to B6C3F1 mice, inducing mammary gland tumors in females of both species, tumors of the forestomach in male rats, and lung tumors in male mice.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, Chapter 14. J. Wiley & Sons, New York, 1971.

Berenblum, I., editor, Carcinogenicity Testing. International Union Against Cancer, Technical Report Series, Vol. 2. International Union Against Cancer, Geneva, 1969.

Chemical Abstracts Service. The Chemical Abstracts Service (CAS) Ninth Collective Index, Volumes 76-85, 1972-1976. American Chemical Society, Washington, D.C., 1977.

Cox, D.R., Analysis of Binary Data, Chapters 4 and 5. Methuen and Co., Ltd., London, 1970.

Cox, D.R., "Regression Models and Life-Tables." Journal of the Royal Statistical Society, Series "B" 34:187-220, 1972.

Farm Chemicals Handbook, Meister Publishing Company. Willoughby, Ohio, 1976.

Gart, J.J., "The Comparison of Proportions: A Review of Significance Tests, Confidence Limits, and Adjustments for Stratification." International Statistical Institute Review 39:148-169, 1971.

Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason, Clinical Toxicology of Commercial Products, 4th edition. The Williams and Wilkins Company, Baltimore, Maryland, 1976.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, L. Petrucelli, L. Fishbein, E.R. Hart, A.J. Pallotta, R.R. Bates, H.L. Falk, J.J. Gart, M. Klein, I. Mitchell, and J. Peters, "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note." Journal of the National Cancer Institute 42 (6):1101-1114, 1969.

Kaplan, E.L., and P. Meier, "Nonparametric Estimation from Incomplete Observations." Journal of the American Statistical Association 53:457-481, 1958.

Linhart, M.S., J.A. Cooper, R.L. Martin, N.P. Page, and J.A. Peters, "Carcinogenesis Bioassay Data System." Computers and Biomedical Research 7:230-248, 1974.

Martin, H., and C.R. Worthing, editors, Pesticide Manual, Fifth edition. British Crop Protection Council, 1977.

Miller, R.G., Simultaneous Statistical Inference. McGraw-Hill Book Co., New York, 1966.

Reuber, M.D., and E.L. Glover, "Cirrhosis and Carcinoma of the Liver in Male Rats Given Subcutaneous Carbon Tetrachloride." Journal of the National Cancer Institute 44:419-423, 1970.

Saffiotti, U., R. Montesano, A.R. Sellakumar, F. Cefis, and D.G. Kaufman, "Respiratory Tract Carcinogenesis in Hamsters Induced by Different Numbers of Administration of Benzo (a) Pyrene and Ferric Oxide." Cancer Research 32:1073-1079, 1972.

Stanford Research Institute, 1977 Directory of Chemical Producers, U.S.A., Menlo Park, California, 1977.

Tarone, R.E., "Tests for Trend in Life-Table Analysis." Biometrika 62:679-682, 1975.

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

June 29, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, 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 Sulfallate for carcinogenicity.

The reviewer agreed with the conclusion in the report that Sulfallate was carcinogenic in both rats and mice, under the conditions of test. After a brief description of the experimental design, the reviewer noted that the dosages had to be adjusted downward during the course of the chronic study and that the compound had to be administered on an intermittent schedule. She pointed out a number of neoplastic lesions, in both the treated rats and mice, that were found in increased but nonstatistically significant rates. She opined that some of the tumor types may not have been statistically significant because of the small number of control animals. Despite the experimental shortcomings, the reviewer said the conclusion was still valid that Sulfallate was carcinogenic in both sexes of treated rats and mice. She added that Sulfallate would appear to pose a potential carcinogenic risk to humans. The reviewer moved

that the report on the bioassay of Sulfallate be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

---

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

*U.S. GOVERNMENT PRINTING OFFICE:1978 260-899/3199 1-3

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH SULFALLATE

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

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	48	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	38	30
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(48)	(45)
PAPILLOMA, NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA		2 (4%)	1 (2%)
FIBROSARCOMA		1 (2%)	
HEMANGIOPERICYTOMA, MALIGNANT	1 (2%)		
*SUBCUT TISSUE	(49)	(48)	(45)
SQUAMOUS CELL CARCINOMA			1 (2%)
FIBROMA	1 (2%)	1 (2%)	
FIBROSARCOMA	1 (2%)	2 (4%)	1 (2%)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
HEMANGIOSARCOMA	4 (8%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(28)	(21)
CARCINOMA, NOS, METASTATIC		1 (4%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (4%)	
MIXED TUMOR, MALIGNANT	1 (2%)		
HEMANGIOSARCOMA, METASTATIC	2 (4%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(48)	(45)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
#SPLEEN	(47)	(29)	(20)
SARCOMA, NOS			1 (5%)
HEMANGIOMA		1 (3%)	
HEMANGIOSARCOMA	4 (9%)	4 (14%)	2 (10%)
#CERVICAL LYMPH NODE	(45)	(25)	(22)
SQUAMOUS CELL CARCINOMA			1 (5%)

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

TABLE A1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
CIRCULATORY SYSTEM			
#HEART	(47)	(28)	(21)
HEMANGIOSARCOMA	1 (2%)		
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
DIGESTIVE SYSTEM			
#SUBMAXILLARY GLAND		(4)	
SARCOMA, NOS		1 (25%)	
FIBROSARCOMA		1 (25%)	
#LIVER	(49)	(31)	(22)
HEMANGIOSARCOMA			1 (5%)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
#ESOPHAGUS	(1)	(26)	(21)
PAPILLOMA, NOS			1 (5%)
SQUAMOUS CELL CARCINOMA			1 (5%)
#STOMACH	(46)	(30)	(25)
PAPILLOMA, NOS			2 (8%)
SQUAMOUS CELL PAPILLOMA			1 (4%)
SQUAMOUS CELL CARCINOMA			2 (8%)
URINARY SYSTEM			
#KIDNEY	(47)	(31)	(22)
LIPOMA	2 (4%)		
MIXED TUMOR, MALIGNANT		2 (6%)	
HEMANGIOSARCOMA	1 (2%)		
#URINARY BLADDER	(46)	(27)	(21)
PAPILLOMA, NOS	3 (7%)		
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(30)	(20)
CARCINOMA, NOS		1 (3%)	
CHROMOPHOBE ADENOMA	4 (10%)	2 (7%)	3 (15%)
MENINGIOMA			1 (5%)
#ADRENAL	(46)	(28)	(20)
CORTICAL ADENOMA		1 (4%)	1 (5%)

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

TABLE A1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
PHEOCHROMOCYTOMA		1 (4%)	1 (5%)
#THYROID	(48)	(27)	(21)
SQUAMOUS CELL CARCINOMA			2 (10%)
SQUAMOUS CELL CARCINOMA, METASTA			1 (5%)
FOLLICULAR-CELL ADENOMA	3 (6%)	5 (19%)	
FOLLICULAR-CELL CARCINOMA	4 (8%)	1 (4%)	2 (10%)
C-CELL ADENOMA		3 (11%)	1 (5%)
C-CELL CARCINOMA		2 (7%)	1 (5%)
#PARATHYROID	(46)	(3)	(1)
ADENOMA, NOS	1 (2%)		
#PANCREATIC ISLETS	(46)	(26)	(21)
ISLET-CELL ADENOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(48)	(45)
ADENOCARCINOMA, NOS	2 (4%)		
FIBROADENOMA	1 (2%)		
#PROSTATE	(34)	(9)	(14)
HEMANGIOSARCOMA, METASTATIC	1 (3%)		
*SEMINAL VESICLE	(49)	(48)	(45)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(47)	(27)	(22)
FIBROSARCOMA		1 (4%)	
GLIOMA, NOS	1 (2%)		1 (5%)
ASTROCYTOMA		2 (7%)	1 (5%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(48)	(45)
FIBROSARCOMA	1 (2%)		

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

TABLE A1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
*MUSCLE OF THORAX	(49)	(48)	(45)
HEMANGIOSARCOMA	1 (2%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(48)	(45)
LIPOMA	1 (2%)		
*TUNICA VAGINALIS	(49)	(48)	(45)
MESOTHELIOMA, NOS		1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(48)	(45)
HEMANGIOSARCOMA	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	24	30	37
MORIBUND SACRIFICE	2	1	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	24	19	12
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	26	19
TOTAL PRIMARY TUMORS	41	38	32
TOTAL ANIMALS WITH BENIGN TUMORS	13	14	9
TOTAL BENIGN TUMORS	17	16	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	19	14
TOTAL MALIGNANT TUMORS	24	21	20
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	1
TOTAL SECONDARY TUMORS	6	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		1	2
TOTAL UNCERTAIN TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

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

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	47	39
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(48)
SQUAMOUS CELL CARCINOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(48)
SQUAMOUS CELL CARCINOMA			1 (2%)
BASAL-CELL CARCINOMA	1 (2%)		
FIBROMA	2 (4%)	2 (4%)	
FIBROSARCOMA		1 (2%) <-	
LIPOMA	1 (2%)	1 (2%)	
HEMANGIOSARCOMA	3 (6%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(44)	(29)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)
ADENOCARCINOMA, NOS, METASTATIC			2 (7%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	1 (2%)
#SPLEEN	(50)	(45)	(28)
SARCOMA, NOS, METASTATIC			1 (4%)
HEMANGIOSARCOMA		3 (7%)	1 (4%)
#CERVICAL LYMPH NODE	(48)	(43)	(26)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
<- MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN TISSUES IS COUNTED ONCE ONLY
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
DIGESTIVE SYSTEM			
#LIVER	(50)	(47)	(31)
NEOPLASTIC NODULE	1 (2%)	3 (6%)	2 (6%)
#ESOPHAGUS		(44)	(28)
SQUAMOUS CELL CARCINOMA			1 (4%)
#STOMACH	(50)	(43)	(35)
PAPILLOMA, NOS			2 (6%)
#DUODENUM	(50)	(43)	(28)
HEMANGIOSARCOMA	1 (2%)		
*ANAL CANAL	(50)	(50)	(48)
HEMANGIOSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(44)	(28)
LIPOMA	1 (2%)		
MIXED TUMOR, MALIGNANT	1 (2%)		
HAMARTOMA+	1 (2%)		
#URINARY BLADDER	(49)	(42)	(28)
FIBROSARCOMA			1 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(44)	(26)
CHROMOPHOBE ADENOMA	15 (30%)	9 (20%)	4 (15%)
#ADRENAL	(50)	(45)	(30)
CORTICAL ADENOMA			1 (3%)
#THYROID	(50)	(44)	(28)
SQUAMOUS CELL CARCINOMA			1 (4%)
ADENOMA, NOS		1 (2%)	
FOLLICULAR-CELL ADENOMA		2 (5%)	
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)	
C-CELL ADENOMA	5 (10%)	2 (5%)	1 (4%)
C-CELL CARCINOMA		1 (2%)	

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
#PANCREATIC ISLETS	(50)	(44)	(28)
ISLET-CELL ADENOMA		2 (5%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(48)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS		7 (14%)	11 (23%)
FIBROADENOMA	15 (30%)	21 (42%)	10 (21%)
#UTERUS	(49)	(46)	(28)
FIBROSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	4 (8%)	3 (7%)	2 (7%)
#OVARY	(49)	(44)	(28)
CARCINOMA,NOS	1 (2%)		
LUTEOMA		1 (2%)	
GRANULOSA-CELL TUMOR	1 (2%)	1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(45)	(26)
ASTROCYTOMA		1 (2%)	2 (8%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(48)
MALIGNANT MELANOMA		1 (2%)	
FIBROSARCOMA			1 (2%)
*EXTERNAL EAR	(50)	(50)	(48)
SQUAMOUS CELL CARCINOMA		1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF HEAD	(50)	(50)	(48)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA			1 (2%)

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

TABLE A2 (CONCLUDED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
BODY CAVITIES			
*ABDOMINAL VISCERA	(50)	(50)	(48)
HEMANGIOSARCOMA	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	14	15	33
MORIBUND SACRIFICE		2	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	33	15
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	36	37	30
TOTAL PRIMARY TUMORS	56	72	46
TOTAL ANIMALS WITH BENIGN TUMORS	31	32	16
TOTAL BENIGN TUMORS	44	45	20
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	18	23
TOTAL MALIGNANT TUMORS	10	23	24
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	4
TOTAL SECONDARY TUMORS		1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	2	4	2
TOTAL UNCERTAIN TUMORS	2	4	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH SULFALLATE

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

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	46	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	46	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(46)	(49)
SQUAMOUS CELL CARCINOMA		3 (7%)	1 (2%)
BASAL-CELL CARCINOMA			1 (2%)
FIBROSARCOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(46)	(49)
SQUAMOUS CELL CARCINOMA			3 (6%)
BASAL-CELL CARCINOMA			1 (2%)
SEBACEOUS ADENOMA			1 (2%)
FIBROMA	2 (10%)	3 (7%)	
FIBROSARCOMA		5 (11%)	
HEMANGIOSARCOMA		1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(43)	(45)
SQUAMOUS CELL CARCINOMA			1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		11 (26%)	9 (20%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		3 (7%)	9 (20%)
HEMANGIOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(46)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	2 (4%)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
#CERVICAL LYMPH NODE	(16)	(41)	(42)
FIBROSARCOMA, METASTATIC		1 (2%)	

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

TABLE B1 (CONTINUED)

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
#MESENTERIC L. NODE	(16)	(41)	(42)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#THYMUS	(14)	(40)	(43)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(45)	(49)
HEPATOCELLULAR CARCINOMA	7 (35%)	22 (49%)	24 (49%)
#STOMACH	(19)	(40)	(43)
PAPILLOMA, NOS			3 (7%)
SQUAMOUS CELL PAPILLOMA		4 (10%)	
SQUAMOUS CELL CARCINOMA		2 (5%)	1 (2%)
*ANUS	(20)	(46)	(49)
FIBROSARCOMA, METASTATIC		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(42)	(43)
HEPATOCELLULAR CARCINOMA, METAST		2 (5%)	
TUBULAR-CELL ADENOMA			3 (7%)
SARCOMA, NOS			1 (2%)
HEMANGIOSARCOMA			3 (7%)
ENDOCRINE SYSTEM			
#ADRENAL	(16)	(40)	(41)
CORTICAL ADENOMA		1 (3%)	
#THYROID	(17)	(38)	(41)
FOLLICULAR-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*PENIS	(20)	(46)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)

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

TABLE B1 (CONTINUED)

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
*PREPUTIAL GLAND	(20)	(46)	(49)
SQUAMOUS CELL CARCINOMA			2 (4%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(20)	(46)	(49)
ADENOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF LEG	(20)	(46)	(49)
FIBROSARCOMA, METASTATIC		1 (2%)	
BODY CAVITIES			
*ABDOMINAL VISCERA	(20)	(46)	(49)
HEMANGIOSARCOMA			1 (2%)
*MESENTERY	(20)	(46)	(49)
SARCOMA, NOS			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	16	19
MORIBUND SACRIFICE		1	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	32	30
ANIMAL MISSING		1	1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	8	37	39
TOTAL PRIMARY TUMORS	9	59	73
TOTAL ANIMALS WITH BENIGN TUMORS	2	16	14
TOTAL BENIGN TUMORS	2	19	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	32	34
TOTAL MALIGNANT TUMORS	7	40	56
TOTAL ANIMALS WITH SECONDARY TUMORS#		5	3
TOTAL SECONDARY TUMORS		6	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH SULFALLATE

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	48	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	48	46
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(48)	(46)
SQUAMOUS CELL CARCINOMA		2 (4%)	
BASAL-CELL CARCINOMA			1 (2%)
FIBROSARCOMA			2 (4%)
HEMANGIOSARCOMA, METASTATIC	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(19)	(45)	(37)
ADENOCARCINOMA, NOS, METASTATIC		3 (7%)	1 (3%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	11 (24%)	2 (5%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		4 (9%)	2 (5%)
ADENOCA/SQUAMOUS METAPLASIA, MET		3 (7%)	3 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(48)	(46)
MALIGNANT LYMPHOMA, NOS		2 (4%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (20%)	1 (2%)	1 (2%)
#SPLEEN	(19)	(45)	(42)
HEMANGIOSARCOMA	1 (5%)		
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#LYMPH NODE	(18)	(42)	(35)
MALIGNANT LYMPHOMA, NOS			1 (3%)
#CERVICAL LYMPH NODE	(18)	(42)	(35)
ADENOCA/SQUAMOUS METAPLASIA, MET		1 (2%)	
OSTEOSARCOMA, METASTATIC		1 (2%)	

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

TABLE B2 (CONTINUED)

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
#KIDNEY	(19)	(44)	(37)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(47)	(46)
HEPATOCELLULAR CARCINOMA		5 (11%)	8 (17%)
HEMANGIOSARCOMA			1 (2%)
#STOMACH	(19)	(43)	(38)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
SQUAMOUS CELL CARCINOMA			1 (3%)
#SMALL INTESTINE	(19)	(45)	(37)
HEPATOCELLULAR CARCINOMA, METAST			1 (3%)
URINARY SYSTEM			
#KIDNEY	(19)	(44)	(37)
HEMANGIOSARCOMA, METASTATIC	1 (5%)		
ENDOCRINE SYSTEM			
NONE			
RFPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(48)	(46)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS		23 (48%)	11 (24%)
ADENOCA/SQUAMOUS METAPLASIA		10 (21%)	16 (35%)
FIBROSARCOMA		1 (2%)	1 (2%)
FIBROADENOMA		1 (2%)	
*VAGINA	(20)	(48)	(46)
SQUAMOUS CELL CARCINOMA		1 (2%)	

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

TABLE B2 (CONTINUED)

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
#UTERUS	(19)	(44)	(37)
LEIOMYOMA	1 (5%)		
ENDOMETRIAL STROMAL POLYP		1 (2%)	1 (3%)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA			1 (3%)
#UTERUS/ENDOMETRIUM	(19)	(44)	(37)
PAPILLOMA, NOS		2 (5%)	
#OVARY	(19)	(44)	(36)
HEMANGIOMA			1 (3%)
HEMANGIOSARCOMA			1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(20)	(48)	(46)
ADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*VERTEBRAL COLUMN	(20)	(48)	(46)
OSTEOSARCOMA		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
THORACIC CAVITY			
NEUROFIBROSARCOMA			1

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

TABLE B2 (CONCLUDED)

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	28	37
MORIBUND SACRIFICE		5	8
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	17	5
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	42	37
TOTAL PRIMARY TUMORS	8	70	54
TOTAL ANIMALS WITH BENIGN TUMORS	2	16	5
TOTAL BENIGN TUMORS	2	18	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	39	37
TOTAL MALIGNANT TUMORS	6	52	49
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	7	5
TOTAL SECONDARY TUMORS	2	8	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

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

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

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	48	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	38	30
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(48)	(45)
EPIDERMAL INCLUSION CYST	1 (2%)		2 (4%)
*SUBCUT TISSUE	(49)	(48)	(45)
ABSCESS, NOS	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(4)	(26)	(21)
INFLAMMATION, NOS	4 (100%)		
#LUNG/BRONCHUS	(49)	(28)	(21)
HYPERPLASIA, LYMPHOID		1 (4%)	3 (14%)
#LUNG	(49)	(28)	(21)
MINERALIZATION		2 (7%)	
EDEMA, NOS		1 (4%)	
INFLAMMATION, NOS		1 (4%)	2 (10%)
INFLAMMATION, NECROTIZING		2 (7%)	
PNEUMONIA, CHRONIC MURINE	20 (41%)	1 (4%)	1 (5%)
HYPERPLASIA, LYMPHOID		20 (71%)	13 (62%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(46)	(27)	(21)
HYPOPLASIA, HEMATOPOIETIC			1 (5%)
#SPLEEN	(47)	(29)	(20)
FIBROSIS	1 (2%)	1 (3%)	
HEMATOPOIESIS	1 (2%)	5 (17%)	2 (10%)
#MESENTERIC L. NODE	(45)	(25)	(22)
CYST, NOS	1 (2%)		

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
EDEMA, NOS		1 (4%)	
CIRCULATORY SYSTEM			
#HEART	(47)	(28)	(21)
MINERALIZATION		1 (4%)	
#MYOCARDIUM	(47)	(28)	(21)
INFLAMMATION, NOS	14 (30%)	10 (36%)	6 (29%)
INFLAMMATION WITH FIBROSIS		1 (4%)	
FIBROSIS	1 (2%)	3 (11%)	
FIBROSIS, DIFFUSE		6 (21%)	1 (5%)
#ENDOCARDIUM	(47)	(28)	(21)
ENDOCARDITIS, BACTERIAL		1 (4%)	
METAPLASIA, OSSEOUS		1 (4%)	
*AORTA	(49)	(48)	(45)
PERIARTERITIS			1 (2%)
ARTERIOSCLEROSIS, NOS	4 (8%)		
CALCIFICATION, NOS		2 (4%)	
DIGESTIVE SYSTEM			
#SUBMAXILLARY GLAND		(4)	
EDEMA, NOS		1 (25%)	
ABSCESS, NOS		1 (25%)	
FIBROSIS		1 (25%)	
#LIVER	(49)	(31)	(22)
CYST, NOS	2 (4%)		
INFLAMMATION, NOS	3 (6%)		1 (5%)
NECROSIS, NOS			1 (5%)
METAMORPHOSIS FATTY	3 (6%)	7 (23%)	2 (9%)
CYTOPLASMIC VACUOLIZATION		6 (19%)	
CYTOLOGIC DEGENERATION		1 (3%)	
HYPERPLASIA, NOS	5 (10%)		
HEMATOPOIESIS			1 (5%)
#LIVER/CENTRILOBULAR	(49)	(31)	(22)
DEGENERATION, NOS		2 (6%)	
NECROSIS, NOS		1 (3%)	
#LIVER/HEPATOCYTES	(49)	(31)	(22)
NECROSIS, NOS			1 (5%)

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
HYPERTROPHY, NOS		7 (23%)	3 (14%)
*BILE DUCT	(49)	(48)	(45)
INFLAMMATION, NOS		9 (19%)	11 (24%)
HYPERPLASIA, NOS	3 (6%)	16 (33%)	14 (31%)
#PANCREAS	(46)	(26)	(21)
PERIARTERITIS	5 (11%)	1 (4%)	1 (5%)
ATROPHY, NOS		2 (8%)	3 (14%)
*ESOPHAGUS	(1)	(26)	(21)
INFLAMMATION, NOS	1 (100%)		
#STOMACH	(46)	(30)	(25)
MINERALIZATION		4 (13%)	
THROMBOSIS, NOS			1 (4%)
INFLAMMATION, NOS	1 (2%)		
ULCER, NOS			4 (16%)
REACTION, FOREIGN BODY		1 (3%)	
NECROSIS, FOCAL			1 (4%)
HYPERKERATOSIS		7 (23%)	6 (24%)
ACANTHOSIS		7 (23%)	7 (28%)
#COLON	(46)	(26)	(20)
INFLAMMATION, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(47)	(31)	(22)
MINERALIZATION		3 (10%)	1 (5%)
CONGESTION, NOS		1 (3%)	
PYELONEPHRITIS, NOS	2 (4%)		
PYONEPHROSIS	1 (2%)		
ABSCESS, NOS	1 (2%)	1 (3%)	
INFLAMMATION, CHRONIC	37 (79%)	27 (87%)	15 (68%)
NEPHROPATHY, TOXIC		1 (3%)	9 (41%)
#KIDNEY/CORTEX	(47)	(31)	(22)
CYST, NOS		5 (16%)	
#KIDNEY/PELVIS	(47)	(31)	(22)
DILATATION, NOS		1 (3%)	
INFLAMMATION, NOS		1 (3%)	1 (5%)
#URINARY BLADDER	(46)	(27)	(21)
INFLAMMATION, NOS	1 (2%)		

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(30)	(20)
CYST, NOS	1 (2%)	1 (3%)	1 (5%)
HYPERPLASIA, CHROMOPHOBE-CELL			2 (10%)
#ADRENAL	(46)	(28)	(20)
CYTOLOGIC DEGENERATION		14 (50%)	8 (40%)
ANGIECTASIS	8 (17%)		
#ADRENAL CORTEX	(46)	(28)	(20)
CYTOPLASMIC VACUOLIZATION		1 (4%)	
ATROPHY, NOS		1 (4%)	
HYPERTROPHY, NOS		14 (50%)	6 (30%)
#THYROID	(48)	(27)	(21)
CYST, NOS	1 (2%)		
CYSTIC FOLLICLES			2 (10%)
HYPERPLASIA, C-CELL	1 (2%)	1 (4%)	5 (24%)
HYPERPLASIA, FOLLICULAR-CELL	4 (8%)		
#PARATHYROID	(46)	(3)	(1)
HYPERPLASIA, NOS	2 (4%)	3 (100%)	1 (100%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(43)	(48)	(45)
GALACTOCELE	1 (2%)		
CYST, NOS	1 (2%)		
#PROSTATE	(34)	(9)	(14)
INFLAMMATION, NOS	9 (26%)	4 (44%)	5 (36%)
*SEMINAL VESICLE	(49)	(48)	(45)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
#TESTIS	(44)	(27)	(21)
MINERALIZATION		1 (4%)	
GRANULOMA, SPERMATIC		2 (7%)	
ATROPHY, NOS	9 (20%)	8 (30%)	3 (14%)
*EPIDIDYMIS	(49)	(48)	(45)
MINERALIZATION		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
GRANULOMA, SPERMATIC		1 (2%)	
ATROPHY, NOS		1 (2%)	
NERVOUS SYSTEM			
*BRAIN	(47)	(27)	(22)
ABSCESS, NOS			1 (5%)
SPECIAL SENSE ORGANS			
*EYE	(49)	(48)	(45)
MINERALIZATION		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
CATARACT		1 (2%)	
PHTHISIS BULBI	1 (2%)		
*EYE/CRYSTALLINE LENS	(49)	(48)	(45)
DEGENERATION, NOS			1 (2%)
*EYE/LACRIMAL GLAND	(49)	(48)	(45)
HYPERPLASIA, NOS		1 (2%)	
*HARDERIAN GLAND	(49)	(48)	(45)
INFLAMMATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(48)	(45)
DEGENERATION, NOS	1 (2%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(48)	(45)
NECROSIS, FAT		1 (2%)	
*PERICARDIUM	(49)	(48)	(45)
INFLAMMATION, NOS	5 (10%)		
*MESENTERY	(49)	(48)	(45)
PERIARTERITIS	2 (4%)	1 (2%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE C1 (CONCLUDED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M016	HIGH DOSE 01-M017
SPECIAL MORPHOLOGY SUMMARY			
NECROPSY PERF/NO HISTO PERFORMED		2	12
AUTO/NECROPSY/NO HISTO		8	3
AUTOLYSIS/NO NECROPSY	1	2	5

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

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

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	47	39
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(48)
INFLAMMATION, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(5)	(44)	(28)
INFLAMMATION, NOS	5 (100%)		
#LUNG/BRONCHUS	(50)	(44)	(29)
ABSCESS, NOS		1 (2%)	
#LUNG	(50)	(44)	(29)
CYST, NOS		2 (5%)	
INFLAMMATION, NOS		3 (7%)	2 (7%)
PNEUMONIA, CHRONIC MURINE	15 (30%)		1 (3%)
HYPERPLASIA, LYMPHOID		32 (73%)	12 (41%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(43)	(28)
METAMORPHOSIS FATTY	1 (2%)		
LEUKEMOID REACTION		1 (2%)	
#SPLEEN	(50)	(45)	(28)
LEUKEMOID REACTION		1 (2%)	
HEMATOPOIESIS	5 (10%)	8 (18%)	7 (25%)
#SPLENIC CAPSULE	(50)	(45)	(28)
FIBROSIS		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(44)	(28)
MINERALIZATION			2 (7%)

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
FIBROSIS, DIFFUSE		1 (2%)	1 (4%)
PERIARTERITIS		1 (2%)	
NECROSIS, NOS		1 (2%)	
#MYOCARDIUM	(50)	(44)	(28)
INFLAMMATION, NOS		4 (9%)	2 (7%)
FIBROSIS, DIFFUSE		1 (2%)	
DEGENERATION, NOS	2 (4%)		
#ENDOCARDIUM	(50)	(44)	(28)
HYPERPLASIA, NOS	1 (2%)		
*AORTA	(50)	(50)	(48)
ARTERIOSCLEROSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND			(1)
INFLAMMATION, SUPPURATIVE			1 (100%)
#LIVER	(50)	(47)	(31)
INFLAMMATION, NOS	4 (8%)		
GRANULOMA, NOS		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	5 (11%)	3 (10%)
CYTOPLASMIC VACUOLIZATION		1 (2%)	2 (6%)
FOCAL CELLULAR CHANGE	1 (2%)	4 (9%)	1 (3%)
HYPERTROPHY, NOS			11 (35%)
HYPERPLASIA, NOS			2 (6%)
HEMATOPOIESIS			1 (3%)
#LIVER/CENTRILOBULAR	(50)	(47)	(31)
NECROSIS, NOS		1 (2%)	1 (3%)
#LIVER/PERIPORTAL	(50)	(47)	(31)
NECROSIS, NOS		1 (2%)	
#LIVER/HEPATOCYTES	(50)	(47)	(31)
HYPERTROPHY, NOS		13 (28%)	
*BILE DUCT	(50)	(50)	(48)
DILATATION, NOS	1 (2%)	7 (14%)	18 (38%)
INFLAMMATION, NOS		25 (50%)	19 (40%)
HYPERTROPHY, NOS			1 (2%)
HYPERPLASIA, NOS	2 (4%)	34 (68%)	29 (60%)

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
#PANCREAS	(50)	(44)	(28)
ATROPHY, NOS		1 (2%)	1 (4%)
ATROPHY, FOCAL		1 (2%)	
#STOMACH	(50)	(43)	(35)
ULCER, NOS		2 (5%)	4 (11%)
ULCER, FOCAL	5 (10%)	2 (5%)	3 (9%)
CALCIUM DEPOSIT	1 (2%)		
HYPERKERATOSIS		1 (2%)	6 (17%)
ACANTHOSIS		1 (2%)	9 (26%)
#LARGE INTESTINE	(49)	(43)	(28)
NEMATODIASIS		1 (2%)	
PARASITISM	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(44)	(28)
MINERALIZATION			2 (7%)
HYDRONEPHROSIS		1 (2%)	
PYELONEPHRITIS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	23 (46%)	18 (41%)	12 (43%)
NEPHROPATHY, TOXIC			1 (4%)
HYPERPLASIA, NOS		1 (2%)	
#KIDNEY/PELVIS	(50)	(44)	(28)
INFLAMMATION, NOS		1 (2%)	2 (7%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(44)	(26)
CYST, NOS		2 (5%)	
HYPERPLASIA, CHROMOPHOBE-CELL		1 (2%)	2 (8%)
ANGIECTASIS	1 (2%)		
#ADRENAL	(50)	(45)	(30)
DEGENERATION, NOS			12 (40%)
CYTOLOGIC DEGENERATION		21 (47%)	
HYPERTROPHY, NOS			12 (40%)
ANGIECTASIS	17 (34%)	9 (20%)	11 (37%)
HEMATOPOIESIS			1 (3%)
#ADRENAL CORTEX	(50)	(45)	(30)
HYPERTROPHY, NOS		21 (47%)	

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
#THYROID	(50)	(44)	(28)
CYSTIC FOLLICLES		3 (7%)	2 (7%)
HYPERPLASIA, NOS		2 (5%)	1 (4%)
HYPERPLASIA, PAPILLARY			1 (4%)
HYPERPLASIA, C-CELL	2 (4%)	3 (7%)	4 (14%)
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)	1 (2%)	
#PANCREATIC ISLETS	(50)	(44)	(28)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(48)
GALACTOCELE			1 (2%)
CYST, NOS		2 (4%)	
HYPERPLASIA, NOS	1 (2%)		
*VAGINA	(50)	(50)	(48)
FIBROSIS		1 (2%)	
#UTERUS	(49)	(46)	(28)
HYDROMETRA	9 (18%)	1 (2%)	
INFLAMMATION, NOS	2 (4%)		
PYOMETRA		3 (7%)	2 (7%)
#UTERUS/ENDOMETRIUM	(49)	(46)	(28)
INFLAMMATION, NOS		2 (4%)	
HYPERPLASIA, NOS		7 (15%)	
HYPERPLASIA, CYSTIC	3 (6%)	8 (17%)	5 (18%)
#OVARY	(49)	(44)	(28)
CYST, NOS	2 (4%)	1 (2%)	1 (4%)
FOLLICULAR CYST, NOS		2 (5%)	1 (4%)
NERVOUS SYSTEM			
*PINEAL BODY	(50)	(50)	(48)
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(48)
INFLAMMATION, NOS		2 (4%)	

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

TABLE C2 (CONCLUDED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F016	HIGH DOSE 01-F017
SYNECHIA, ANTERIOR			1 (2%)
CATARACT		3 (6%)	1 (2%)
DYSPLASIA, NOS			1 (2%)
*EYE/CORNEA	(50)	(50)	(48)
INFLAMMATION, NOS			1 (2%)
*EYE/IRIS	(50)	(50)	(48)
INFLAMMATION, NOS		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		1
NECROPSY PERF/NO HISTO PERFORMED		3	6
AUTO/NECROPSY/HISTO PERF			1
AUTO/NECROPSY/NO HISTO			3
AUTOLYSIS/NO NECROPSY			2

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

APPENDIX D

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

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

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	46	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	46	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(46)	(49)
EPIDERMAL INCLUSION CYST		3 (7%)	
ULCER, NOS	1 (5%)		
ABSCESS, NOS		1 (2%)	
*SUBCUT TISSUE	(20)	(46)	(49)
EPIDERMAL INCLUSION CYST			1 (2%)
HEMORRHAGIC CYST			1 (2%)
INFLAMMATION, NOS			1 (2%)
ULCER, NOS		1 (2%)	
ABSCESS, NOS	2 (10%)		
RESPIRATORY SYSTEM			
*NASAL MUCOSA	(20)	(46)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#TRACHEA	(18)	(38)	(41)
HYPERPLASIA, PAPILLARY			1 (2%)
#LUNG	(20)	(43)	(45)
CONGESTION, NOS			4 (9%)
HEMORRHAGE		1 (2%)	2 (4%)
INFLAMMATION, NOS		1 (2%)	3 (7%)
PNEUMONIA, CHRONIC MURINE		13 (30%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
HYPERPLASIA, ADENOMATOUS			4 (9%)
METAPLASIA, SQUAMOUS			1 (2%)
HYPERPLASIA, LYMPHOID			5 (11%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(17)	(34)	(44)
AMYLOIDOSIS	4 (24%)	3 (9%)	

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
HYPERPLASIA, LYMPHOID		2 (6%)	
HEMATOPOIESIS		5 (15%)	9 (20%)
#LYMPH NODE	(16)	(41)	(42)
INFLAMMATION, NOS			1 (2%)
HYPERPLASIA, NOS		3 (7%)	
ANGIECTASIS			1 (2%)
HYPERPLASIA, LYMPHOID		2 (5%)	
#CERVICAL LYMPH NODE	(16)	(41)	(42)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(16)	(41)	(42)
CONGESTION, NOS			1 (2%)
INFLAMMATION, NOS	2 (13%)	3 (7%)	
AMYLOIDOSIS		1 (2%)	
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, NOS		6 (15%)	
HYPERPLASIA, LYMPHOID		3 (7%)	1 (2%)
#THYMUS	(14)	(40)	(43)
AMYLOIDOSIS		1 (3%)	
ATROPHY, NOS		1 (3%)	
HYPERTROPHY, NOS		1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(20)	(40)	(43)
PERIARTERITIS	1 (5%)		1 (2%)
#MYOCARDIUM	(20)	(40)	(43)
FIBROSIS		2 (5%)	
#ENDOCARDIUM	(20)	(40)	(43)
INFLAMMATION, NOS		1 (3%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(38)	(36)
INFLAMMATION, NOS		3 (8%)	
#LIVER	(20)	(45)	(49)
THROMBOSIS, NOS			12 (24%)

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
CONGESTION, NOS			3 (6%)
INFLAMMATION, NOS		3 (7%)	5 (10%)
INFLAMMATION, FOCAL		2 (4%)	
INFLAMMATION, ACUTE		1 (2%)	
INFARCT, NOS			1 (2%)
AMYLOIDOSIS	2 (10%)		
METAMORPHOSIS FATTY		2 (4%)	
PIGMENTATION, NOS			1 (2%)
HYPERTROPHY, NOS		1 (2%)	
HYPERTROPHY, FOCAL		2 (4%)	1 (2%)
HYPERPLASIA, NODULAR		4 (9%)	
ANGIECTASIS		2 (4%)	26 (53%)
HEMATOPOIESIS			1 (2%)
#LIVER/CENTRILOBULAR	(20)	(45)	(49)
HYPERTROPHY, NOS			1 (2%)
#LIVER/HEPATOCYTES	(20)	(45)	(49)
HYPERTROPHY, NOS			3 (6%)
*GALLBLADDER	(20)	(46)	(49)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, PAPILLARY			1 (2%)
*BILE DUCT	(20)	(46)	(49)
DILATATION, NOS			1 (2%)
INFLAMMATION, NOS		3 (7%)	
#PANCREAS	(18)	(40)	(42)
INFLAMMATION, NOS		2 (5%)	
FIBROSIS		1 (3%)	
FIBROSIS, FOCAL		1 (3%)	
PERIARTERITIS		1 (3%)	
AMYLOIDOSIS	1 (6%)		
ATROPHY, NOS		1 (3%)	
#STOMACH	(19)	(40)	(43)
INFLAMMATION, NOS		1 (3%)	
ULCER, NOS		1 (3%)	1 (2%)
HYPERPLASIA, EPITHELIAL		3 (8%)	
HYPERKERATOSIS		1 (3%)	2 (5%)
ACANTHOSIS		1 (3%)	2 (5%)
#PEYERS PATCH	(19)	(40)	(42)
HYPERPLASIA, NOS		1 (3%)	

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
#LARGE INTESTINE	(19)	(40)	(43)
NEMATODIASIS	1 (5%)		
*RECTUM	(20)	(46)	(49)
PROLAPSE	5 (25%)	5 (11%)	
*ANUS	(20)	(46)	(49)
ULCER, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(42)	(43)
HYDRONEPHROSIS			4 (9%)
PYELONEPHRITIS, NOS		4 (10%)	
INFLAMMATION, NOS		6 (14%)	
INFLAMMATION, CHRONIC	5 (25%)	14 (33%)	3 (7%)
NEPHROPATHY, TOXIC		26 (62%)	35 (81%)
AMYLOIDOSIS	4 (20%)	1 (2%)	
#KIDNEY/PELVIS	(20)	(42)	(43)
INFLAMMATION, NOS	3 (15%)	3 (7%)	2 (5%)
#URINARY BLADDER	(18)	(40)	(41)
CYST, NOS		1 (3%)	
INFLAMMATION, NOS		5 (13%)	
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(39)	(36)
CYST, NOS	1 (6%)		
#ADRENAL	(16)	(40)	(41)
HYPERPLASIA, FOCAL		1 (3%)	
#THYROID	(17)	(38)	(41)
INFLAMMATION, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(20)	(46)	(49)
ABSCESS, NOS	1 (5%)		1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
#PROSTATE	(16)	(37)	(41)
CYST, NOS		2 (5%)	
INFLAMMATION, NOS		2 (5%)	
INFLAMMATION, VESICULAR		1 (3%)	
HYPERPLASIA, CYSTIC		2 (5%)	
*SEMINAL VESICLE	(20)	(46)	(49)
INFLAMMATION, NOS		1 (2%)	
#TESTIS	(19)	(40)	(43)
CALCIFICATION, NOS		3 (8%)	
ATROPHY, NOS		1 (3%)	1 (2%)
*EPIDIDYMIS	(20)	(46)	(49)
GRANULOMA, SPERMATIC	1 (5%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(40)	(42)
CALCIFICATION, FOCAL		1 (3%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(46)	(49)
INFLAMMATION, NOS		1 (2%)	
FIBROSIS		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE D1 (CONCLUDED)

	CONTROL (VEH) 02-M019	LOW DOSE 02-M020	HIGH DOSE 02-M021
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2		
ANIMAL MISSING/NO NECROPSY		1	1
AUTO/NECROPSY/HISTO PERF	2	1	
AUTOLYSIS/NO NECROPSY		3	

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

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

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	48	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	48	46
INTEGUMENTARY SYSTEM			
#SKIN	(20)	(48)	(46)
HEMATOMA, NOS			1 (2%)
#SUBCUT TISSUE	(20)	(48)	(46)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(45)	(37)
CONGESTION, NOS			7 (19%)
INFLAMMATION, NOS		4 (9%)	1 (3%)
PNEUMONIA, CHRONIC MURINE		22 (49%)	
HYPERPLASIA, ADENOMATOUS			3 (8%)
HYPERPLASIA, LYMPHOID			1 (3%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(45)	(42)
HEMORRHAGIC CYST		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
AMYLOIDOSIS	1 (5%)	1 (2%)	
LEUKEMOID REACTION	2 (11%)		
HYPERPLASIA, LYMPHOID		9 (20%)	
HEMATOPOIESIS		22 (49%)	15 (36%)
#LYMPH NODE	(18)	(42)	(35)
HYPERPLASIA, NOS		2 (5%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#CERVICAL LYMPH NODE	(18)	(42)	(35)
INFLAMMATION, NOS		1 (2%)	

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

TABLE D2 (CONTINUED)

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
CALCIFICATION, METASTATIC		1 (2%)	
#MESENTERIC L. NODE	(18)	(42)	(35)
CONGESTION, NOS			1 (3%)
INFLAMMATION, NOS		3 (7%)	
AMYLOIDOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID		3 (7%)	
#THYMUS	(14)	(43)	(34)
HYPERPLASIA, NOS		4 (9%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(19)	(44)	(36)
INFLAMMATION, NOS		2 (5%)	
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION WITH FIBROSIS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(17)	(38)	(29)
INFLAMMATION, NOS		1 (3%)	
#LIVER	(19)	(47)	(46)
THROMBOSIS, NOS		4 (9%)	1 (2%)
THROMBUS, ORGANIZED			1 (2%)
INFLAMMATION, NOS		3 (6%)	4 (9%)
INFLAMMATION, FOCAL		1 (2%)	
ABSCESS, NOS		1 (2%)	
NECROSIS, NOS			1 (2%)
HYPERTROPHY, NOS		2 (4%)	
HYPERTROPHY, FOCAL		1 (2%)	
HYPERPLASIA, NODULAR		3 (6%)	3 (7%)
ANGIECTASIS		12 (26%)	14 (30%)
#LIVER/CENTRILOBULAR	(19)	(47)	(46)
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS			1 (2%)
#LIVER/HEPATOCYTES	(19)	(47)	(46)
HYPERTROPHY, NOS			2 (4%)
*GALLBLADDER	(20)	(48)	(46)
CYST, NOS			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
*BILE DUCT	(20)	(48)	(46)
INFLAMMATION, NOS		2 (4%)	
#STOMACH	(19)	(43)	(38)
INFLAMMATION, NOS		4 (9%)	
ULCER, NOS		1 (2%)	1 (3%)
#LARGE INTESTINE	(19)	(41)	(37)
INFLAMMATION, HEMORRHAGIC			1 (3%)
NEMATODIASIS			1 (3%)
#COLON	(19)	(41)	(37)
PARASITISM			1 (3%)
URINARY SYSTEM			
#KIDNEY	(19)	(44)	(37)
HYDRONEPHROSIS		1 (2%)	1 (3%)
CONGESTION, NOS		1 (2%)	
PYELONEPHRITIS, NOS		3 (7%)	
INFLAMMATION, NOS		5 (11%)	
INFLAMMATION, CHRONIC	2 (11%)	7 (16%)	2 (5%)
NEPHROPATHY, TOXIC		10 (23%)	26 (70%)
#KIDNEY/PELVIS	(19)	(44)	(37)
INFLAMMATION, NOS		4 (9%)	
#URINARY BLADDER	(16)	(43)	(34)
INFLAMMATION, NOS		8 (19%)	
INFLAMMATION, HEMORRHAGIC			1 (3%)
ENDOCRINE SYSTEM			
#PITUITARY	(15)	(39)	(26)
CONGESTION, NOS		1 (3%)	
HEMORRHAGE		1 (3%)	
INFLAMMATION, NOS		1 (3%)	
#ADRENAL	(19)	(44)	(35)
CONGESTION, NOS		1 (2%)	
INFLAMMATION, NOS		5 (11%)	
#THYROID	(18)	(41)	(32)
HYPERPLASIA, FOLLICULAR-CELL	1 (6%)		

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

TABLE D2 (CONTINUED)

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
REPRODUCTIVE SYSTEM			
*VAGINA	(20)	(48)	(46)
INFLAMMATION, NOS			2 (4%)
#UTERUS	(19)	(44)	(37)
HYDROMETRA		1 (2%)	2 (5%)
INFLAMMATION, NOS		2 (5%)	1 (3%)
INFLAMMATION, SUPPURATIVE	1 (5%)		
PYOMETRA	1 (5%)		
#UTERUS/ENDOMETRIUM	(19)	(44)	(37)
INFLAMMATION, NOS	1 (5%)		1 (3%)
INFLAMMATION, SUPPURATIVE	1 (5%)		
INFLAMMATION, VESICULAR		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, CYSTIC	11 (58%)	17 (39%)	3 (8%)
#OVARY	(19)	(44)	(36)
CYST, NOS	1 (5%)	1 (2%)	4 (11%)
FOLLICULAR CYST, NOS	4 (21%)	2 (5%)	
PAROVARIAN CYST	1 (5%)		
HEMORRHAGIC CYST	1 (5%)		
INFLAMMATION, SUPPURATIVE	3 (16%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(48)	(46)
INFLAMMATION, NOS		3 (6%)	
ABSCESS, NOS		1 (2%)	
PARASITISM	1 (5%)		
CALCIFICATION, NOS		1 (2%)	

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

TABLE D2 (CONCLUDED)

	CONTROL (VEH) 02-F019	LOW DOSE 02-F022	HIGH DOSE 02-F023
BODY CAVITIES			
*PERITONEUM	(20)	(48)	(46)
INFLAMMATION, NOS		2 (4%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		1
AUTO/NECROPSY/HISTO PERF		1	2
AUTO/NECROPSY/NO HISTO	1		
AUTOLYSIS/NO NECROPSY		2	4

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

DHEW Publication No. (NIH) 78-1370