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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
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Bethesda, Maryland 20014

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FOREWORD: This report presents the results of the bioasay of sulfisoxazole 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 greater incidence of cancer than control animals, do not necessarily mean that the test chemical is not a carcinogen, inasmuch as 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 that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

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

The NCI project officers who were responsible for selecting the protocols used in this bioassay were Drs. N. P. Page (1,2) and C. Cueto (1). The principal investigators were Drs. M. B. Powers (3) and R. W. Voelker (3). Ms. K. J. Petrovics (3) was responsible for data management, and Mr. G. Najarian (3) for animal care. Histopathologic examinations were performed by Drs. B. W. Ulland (3) and D. A. Banas (3) and reviewed by Dr. Voelker, and the diagnoses included in this report represent their interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (4). Statistical analyses were

performed by Dr. J. R. Joiner (5) and Ms. P. L. Yong (5), using methods selected for the bioassay program by Dr. J. J. Gart (6).

Chemicals used in this bioassay were analyzed at Midwest Research Institute under the direction of Dr. E. Murrill (7), and feed mixtures containing the test chemical were analyzed at Hazleton Laboratories by Dr. C. L. Guyton (3) and Mr. E. Missaghi (3). The results of these analyses were reviewed by Dr. C. W. Jameson (5).

This report was prepared at Tracor Jitco (5) in collaboration with Hazleton Laboratories and NCI. Those responsible for the report at Tracor Jitco were Dr. L. A. Campbell, Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Mr. W. D. Reichardt, and Ms. L. A. Waitz, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley and Ms. P. J. Graboske.

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

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SUMMARY

A bioassay of sulfisoxazole for possible carcinogenicity was conducted by administering the chemical by gavage to Fischer 344 rats and B6C3F1 mice.

Groups of 50 rats of each sex and 50 mice of each sex were administered sulfisoxazole suspended in aqueous 0.5% carboxymethyl cellulose 7 days per week at one of two doses, either 100 or 400 mg/kg body weight for the rats and either 500 or 2,000 mg/kg for the mice. Vehicle controls consisted of groups of 50 rats of each sex and 50 mice of each sex that were administered only the aqueous 0.5% carboxymethyl cellulose. Untreated controls consisted of groups of 50 rats of each sex and 50 mice of each sex. The dosed groups of the rats and mice were administered the chemical by gavage for 103 weeks, then observed for 1 to 3 additional weeks; the vehicle-control groups were similarly administered 0.5% carboxymethyl cellulose alone. All surviving rats and mice were killed at weeks 104 to 106.

Mean body weights of high-dose male rats and female mice were slightly lower than those of corresponding vehicle controls during the last 40 to 50 weeks of the bioassay; mean body weights of dosed female rats and male mice were unaffected. Survival rates were unaffected by the test chemical, and adequate numbers of animals were at risk for the development of late-appearing tumors.

No tumors occurred in the dosed groups of rats or mice of either sex at incidences that were significantly higher than those of the vehicle-control groups.

It is concluded that under the conditions of this bioassay, sulfisoxazole was not carcinogenic for either Fischer 344 rats or B6C3F1 mice.

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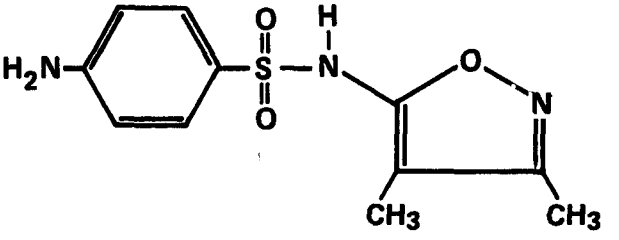
I. INTRODUCTION



Sulfisoxazole

Sulfisoxazole (CAS 127-69-5; NCI C50022) is an antimicrobial drug that is a derivative of sulfanilamide; the chemical name is N^1-(3,4-dimethyl-5-isoxazolyl)sulfanilamide (Koralkovas and Burckhalter, 1976). The sulfanilamide part of the molecule is a structural analog and an effective antimetabolite of p-aminobenzoic-acid (PABA), one of the components of folic acid. The incorporation of sulfanilamides into folic acid precursors inhibits the synthesis of folic acid in susceptible microorganisms and hence, by indirectly inhibiting the formylation of 5'-phosphoribosyl-4-carboxamide-5-aminoimidazole, prevents the biosynthesis of purine (Lehninger, 1975). Susceptible microorganisms are those that must synthesize their own folic acid; thus, bacteria that do

not require folic acid or that can utilize preformed folic acid are not affected (Weinstein, 1975). While some toxic effects may be produced by sulfanilamides in mammals, these are not due to folic acid deficiency, since mammalian cells do not synthesize folic acid and depend on the diet as a source of this material.

Sulfisoxazole was patented in 1947 (Stecher, 1968) and was first used clinically in 1949 (Hayton et al., 1976). It is a broad-spectrum antibacterial agent, effective against both gram-positive and gram-negative organisms (Weinstein, 1975). The foremost clinical use of this drug is in the treatment of urinary tract infections such as cystitis, pyelitis, and pyelonephritis (Stanford Research Institute, 1973). Other uses include the treatment of trachoma, inclusion conjunctivitis, nocardiosis, chancroid, certain types of meningococcal meningitis, and otitis media as well as adjunctive therapy for malaria (American Medical Association, 1971). The normal adult dose is 1 gram, given orally every 4 to 6 hours. The parenteral dose is 100 mg/kg/day, given in divided doses (Weinstein, 1975).

Sulfisoxazole is available in 500 mg tablets; as acetyl sulfisoxazole in a pediatric suspension; as the diolamine salt for injection; as the diolamine salt in a 4% solution and 4% ointment for eye, ear, and nose applications; and as a 10%

vaginal cream. Sulfisoxazole is also marketed in combination with phenazopyridine, the latter providing pain relief from urinary tract infections (Physician's Desk Reference, 1977; Kastrup and Schwach, 1977; Weinstein, 1975).

Although the use of sulfonamide drugs has declined in the past few years due to the emergence of drug-resistant strains of bacteria and the development of newer antimicrobial drugs with fewer side effects (American Medical Association, 1971; Weinstein, 1975), these compounds are still widely prescribed on a chronic basis for the treatment of recurrent urinary tract infections and certain other infectious diseases (American Medical Association, 1971). For 1977, approximately 990,000 new prescriptions for sulfisoxazole tablets, suspensions, or syrups from a single manufacturer were written (National Disease and Therapeutic Index, 1977). Sulfisoxazole was selected for study in the Carcinogenenesis Testing Program because of its extensive clinical use in humans.

II. MATERIALS AND METHODS

A. Chemical

Sulfisoxazole was obtained as the USP-grade chemical in two different lots from Hoffmann-LaRoche, Inc., Nutley, New Jersey. Lot No. 414034 was used for the subchronic study and Lot No. 466094 for the chronic study. USP specifications require 99 to 101% purity on a dry basis with a melting range of 194 to 199°C (USP, 1975).

The identity and purity of both lots of sulfisoxazole were confirmed in analysis at Midwest Research Institute. The melting range for Lot No. 414034 was 196 to 199°C and for Lot No. 466094, 194 to 199°C, with decomposition. Titration of the sulfamide acid group with tetrabutyl ammonium hydroxide indicated a purity of 98.0 $\pm$ 0.3% for Lot No. 414034 and 99.3 $\pm$ 0.6% for Lot No. 466094. High-pressure liquid chromatography showed one homogeneous peak for both lots. Elemental analyses (C, H, N, S) for both lots were correct for $C_{11}H_{13}N_3O_3S$, the molecular formula of sulfisoxazole. Nuclear magnetic resonance and infrared spectra were consistent with spectra for sulfisoxazole given in the literature (Sadtler Standard Spectra, Sadtler

Research Laboratories, Philadelphia, Pennsylvania; Turczan and Medwick, 1972).

The bulk chemical was stored at room temperature.

B. Dosage Preparation

Sulfisoxazole was suspended in an aqueous 0.5% carboxymethyl cellulose (Sigma, St. Louis, Mo.) solution for administration during these studies. Suspensions were prepared at desired concentrations once per week and stored at $4^{\circ}C$ for up to 1 week. To ensure the uniformity of the suspension, it was stirred continuously during the dosing time using a magnetic stirring bar.

Due to problems encountered in the analytical method that was used and to the 1- to 5-month lag period between preparation and analysis, analyses of the suspensions varied considerably (i.e., greater than $\pm$ 10%) from the concentrations established for use in the bioassay during the first year of the study. A modification in the analytical procedures and prompt performance of the analyses resulted in an improvement in the recoveries obtained from subsequent samples, which were shown to be within a $\pm$ 10% tolerance limit.

C. Animals

Fischer 344 rats and B6C3F1 mice were obtained through a National Cancer Institute contract from the Frederick Cancer Research Center Animal Farm, Frederick, Maryland, through contracts with the Division of Cancer Treatment, NCI. They were received at the test lab at 4 weeks of age, and housed within the test facilities. Animals determined to be free from observable disease were assigned to the various dosed and control groups based on initial individual body weights so that a homogeneous distribution of mean weights and weight ranges was obtained between groups. Rats were approximately 5 weeks of age and mice were approximately 7 weeks of age when placed on study.

D. Animal Maintenance

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

The rats and mice were housed in polycarbonate cages covered with

stainless steel cage lids and nonwoven fiber filter bonnets (Filtek, Appleton, Wis.). The rats were initially housed five per cage; at week 52, however, the males were divided into groups of two or three per cage. The mice were housed five per cage throughout the study.

All cages were furnished with heat-treated hardwood chip bedding (Sani-Chips®, Shurfire Products Corporation, Beltsville, Md.); the bedding was changed twice per week. Diets and well water were provided ad libitum. Feed hoppers and water bottles were refilled twice per week.

Cages and water bottles were sanitized at 81°C twice per week, feed hoppers once per week, and cage racks once per month. An industrial dishwasher was used for the water bottles; a cage and rack washer was used for the feed hoppers, cages, and racks. The detergent used was Super Soilax®. When racks were washed, clean racks containing cages of animals were randomly repositioned in the rooms.

The rats and mice were housed in separate rooms. Control animals were housed in the same room as the respective dosed animals.

Rats administered sulfisoxazole by gavage were maintained in the

same room as rats being administered the following chemicals:

Feed Studies

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

Gavage Studies

(CAS 108-60-1) bischloroisopropyl ether
(CAS 7488-56-4) selenium disulfide

Drinking Water Studies

(CAS 108-95-2) phenol

At week 48, the rats fed titanium dioxide, dl-menthol, or benzoin were moved to a separate room for the remainder of the bioassay.

Mice administered sulfisoxazole by gavage were maintained in the same room as mice being administered the following chemicals:

Feed Studies

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

Gavage Studies

(CAS 108-60-1) bischloroisopropyl ether
(CAS 7488-56-4) selenium disulfide

Drinking Water Studies

(CAS 108-95-2) phenol

E. Subchronic Studies

Subchronic oral gavage studies were conducted to estimate the maximum tolerated doses (MTD's) of sulfisoxazole, on the basis of which two concentrations (hereinafter referred to as "low" and "high" doses) were selected for administration in the chronic studies. Groups of ten males and ten females of each species were administered sulfisoxazole by gastric intubation 7 days per week. Ten animals of each sex and species received only the 0.5% aqueous carboxymethyl cellulose solution. Animals were observed daily for deaths and weighed once per week. Table 1 shows the number of animals in each dosed group that survived during the course of administration and the week on study when the last death occurred. The table also shows the mean body weights of the dosed animals at week 13, expressed as percentages of mean body weights of controls.

After 13 weeks of administration of the test chemical, the animals were observed for 1 additional week and then killed and necropsied. The footnotes to table 1 indicate the number of animals having clinical signs and the degree of the finding.

Based on these data, the doses selected for the chronic studies

Table 1. Sulfisoxazole Subchronic Oral Gavage Studies in Rats and Mice

Dose (mg/kg/day)	Male			Female		
	Survival(a)	Week on Study when Last Animal Died	Mean Weight at week 13 as % of Control	Survival(a)	Week on Study when Last Animal Died	Mean Weight at Week 13 as % of Control
RATS						
100	5/5		103	5/5		100
215	5/5		102	5/5		100
464	5/5		97	5/5		99
1,000(b)	5/5		94	5/5		102
2,160(c)	1/5	13	91	5/5		98
MICE(d)						
100	5/5		104	5/5		104
215	5/5		104	5/5		104
464	5/5		108	5/5		100
1,000	5/5		104	5/5		100
2,160	3/5	3	104	5/5		104

(a) Numbers surviving/number in group.

(b) Two males had slight interstitial nephritis.

(c) Two males had severe interstitial nephritis; eight males and four females had tubular nephrosis.

(d) No dose-related histopathologic findings were reported for the mice.

were 100 and 400 mg/kg for the rats and 500 and 2,000 mg/kg for the mice.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 2 and 3.

G. Clinical and Pathologic Examinations

All animals were observed twice per day for deaths. Clinical signs and the presence of palpable masses were recorded every week. Mean body weights were recorded every 2 weeks for the first 12 weeks and monthly thereafter.

Animals that were moribund and those that survived to the termination of the study were killed by exsanguination under sodium pentobarbital anesthesia (Diabutal®, Diamond Laboratories, Inc., Des Moines, Iowa). The Diabutal®, containing 60 mg/ml sodium pentobarbital, was injected intraperitoneally at a volume of 0.3 to 0.5 ml for the rats and 0.03 to 0.05 ml for the mice.

Table 2. Chronic Gavage Studies with Sulfisoxazole in Rats

Sex and Test Group	Initial No. of Animals(a)	Sulfisoxazole Dose (b) (mg/kg)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Male				
Untreated-Control	50	0		106-107
Vehicle-Control(c)	50	0	103	3
Low-Dose	50	100	103	3
High-Dose	50	400	103	2
Female				
Untreated-Control	50	0		106-107
Vehicle-Control(c)	50	0	103	3
Low-Dose	50	100	103	3
High-Dose	50	400	103	3

(a) Rats were approximately 5 weeks of age when placed on study.

(b) Dosed rats were administered a suspension of sulfisoxazole in 0.5% aqueous carboxymethyl cellulose by gavage 7 days per week. A volume of 1 ml/kg body weight was administered, based on the group mean weight and adjusted at weighing periods.

(c) Vehicle controls received a volume of the 0.5% carboxymethyl cellulose solution equal to the highest volumetric dose of test solution given.

Table 3. Chronic Gavage Studies with Sulfisoxazole in Mice

Sex and Test Group	Initial No. of Animals(a)	Sulfisoxazole Dose (b) (mg/kg)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Male				
Untreated-Control	50	0		104
Vehicle-Control(c)	50	0	103	1
Low-Dose	50	500	103	1
High-Dose	50	2,000	103	1-2
Female				
Untreated-Control	50	0		104
Vehicle-Control(c)	50	0	103	1
Low-Dose	50	500	103	2
High-Dose	50	2,000	103	2

(a) Mice were approximately 7 weeks of age when placed on study.

(b) Dosed mice were administered a suspension of sulfisoxazole in 0.5% aqueous carboxymethyl cellulose by gavage 7 days per week. A volume of 10 ml/kg body weight was administered, based on the group mean weight and adjusted at weighing periods.

(c) Vehicle controls received a volume of the 0.5% carboxymethyl cellulose solution equal to the highest volumetric dose of test solution given. Vehicle-control groups were started approximately 1 week before other groups.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder (mice), pancreas, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Occasionally, additional tissues were also examined microscopically. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few tissues from some animals were not examined, particularly from those animals that may have died early, been missing, or been in advanced states of cannibalization or autolysis. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

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 appropriate 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) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is 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 is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The 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) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each

dose level. When results for a number of dosed 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) 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), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is 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 an animal died naturally or was 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 less than 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 dosed 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 dosed 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 dosed 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% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero) 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. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of the dosed male rats were slightly lower than those of corresponding vehicle controls during the last 40 weeks of the bioassay (figure 1); mean body weights of the females were unaffected. Other clinical signs occurred at comparable frequencies in dosed and control groups and included hunched or thin appearance, body sores, alopecia, urine stains, respiratory involvements, and various lesions of the eyes. The eye lesions were noted in all groups at increasing frequency from week 10 to termination of the study.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered sulfisoxazole by gavage at the doses of this bioassay, together with those of the vehicle controls, are shown in figure 2. Two control groups, a vehicle-control and an untreated-control, were used in this study. However, in the statistical analysis, only the

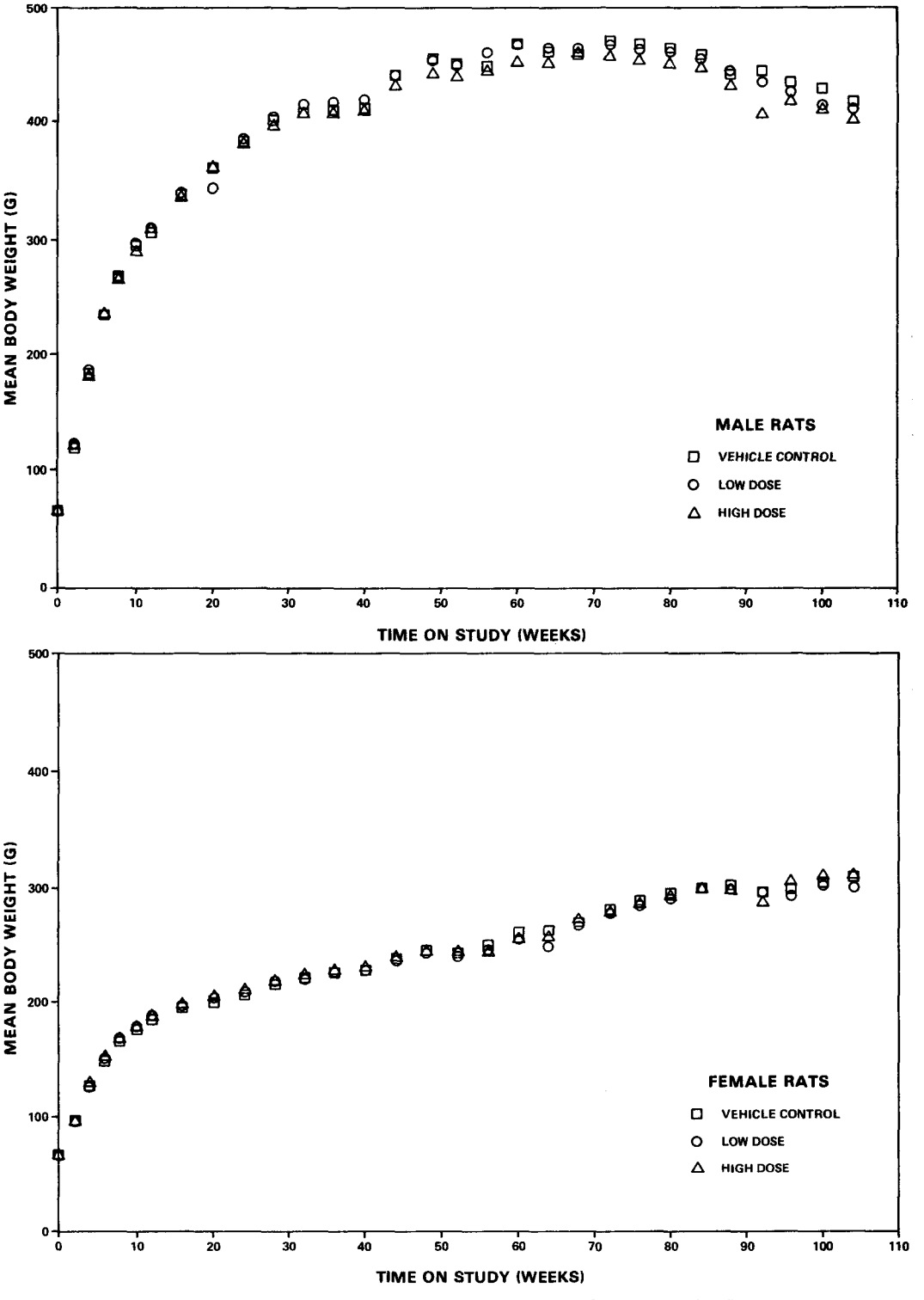


Figure 1. Growth Curves for Rats Administered Sulfisoxazole by Gavage

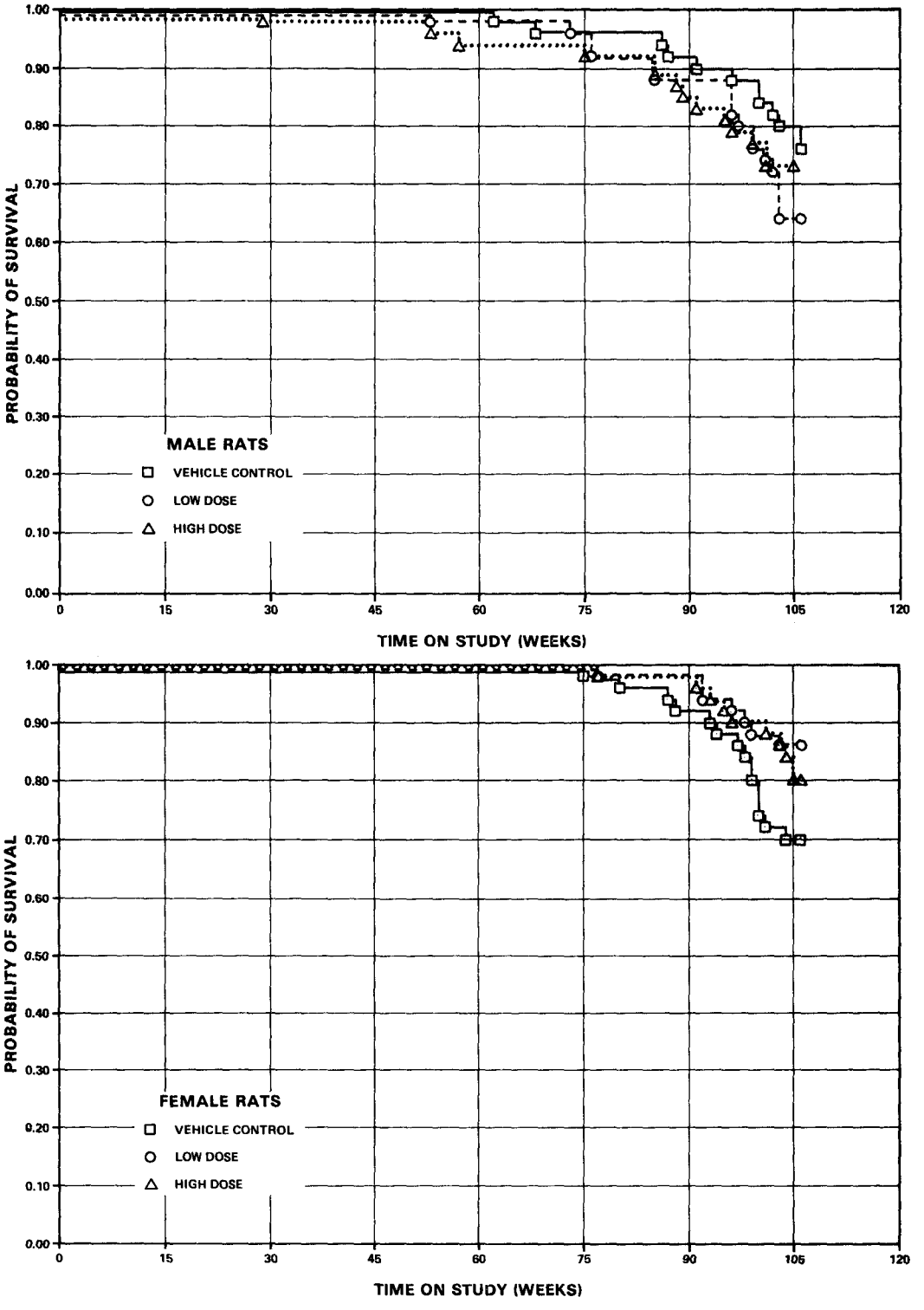


Figure 2. Survival Curves for Rats Administered Sulfisoxazole by Gavage

vehicle-control group is used, because the test conditions of the vehicle-control group more closely resemble those of the dosed groups. The result of the Tarone test for dose-related trend in mortality is not significant in either sex.

In male rats, 36/50 (72%) of the high-dose group, 32/50 (64%) of the low-dose group, and 38/50 (76%) of the vehicle-control group lived to the end of the bioassay. In females, 40/50 (80%) of the high-dose group, 43/50 (86%) of the low-dose group, and 35/50 (70%) of the vehicle-control group lived to the end of the bioassay.

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

C. Pathology (Rats)

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

A variety of neoplastic and nonneoplastic lesions were observed in this study. These were of a type, incidence, and distribution

commonly observed in aged Fischer 344 rats and are therefore considered spontaneous and not related to compound administration.

Based on the pathologic examination, sulfisoxazole was neither carcinogenic nor toxic to Fischer 344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group. Two control groups, a vehicle-control and an untreated-control, were used in this study. However, in the statistical analysis, only the vehicle-control group is used, because the test conditions of the vehicle-control group more closely resemble those of the dosed groups.

In male rats, the result of the Cochran-Armitage test for dose-related trend in the incidences of tumors and those of the Fisher exact test comparing the incidence of tumors in the

vehicle-control group with that in each dosed group are not significant.

In female rats, the results of the Cochran-Armitage test for the incidence of monocytic leukemia and the combined incidence of malignant lymphocytic lymphoma and monocytic leukemia of the hematopoietic system are significant (P = 0.016 and P = 0.033, respectively), but those of the Fisher exact test are not. There is no other incidence of tumors in female rats with significant statistical test results.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by sulfisoxazole, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the high-dose female mice were slightly lower than those of corresponding vehicle controls during the last 50 weeks of the bioassay (figure 3); mean body weights of the males were unaffected. Other clinical signs occurred at comparable rates for dosed and control groups and included hunched or thin appearance, body sores, alopecia, genital irritation and swelling, and distended abdomen.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered sulfisoxazole by gavage at the doses of this bioassay, together with those of the vehicle controls, are shown in figure 4. Two control groups, a vehicle-control and an untreated-control, were used in this study. However, in the statistical analysis, only the vehicle-control group is used, because the test conditions of the vehicle-control group more closely resemble those of the dosed

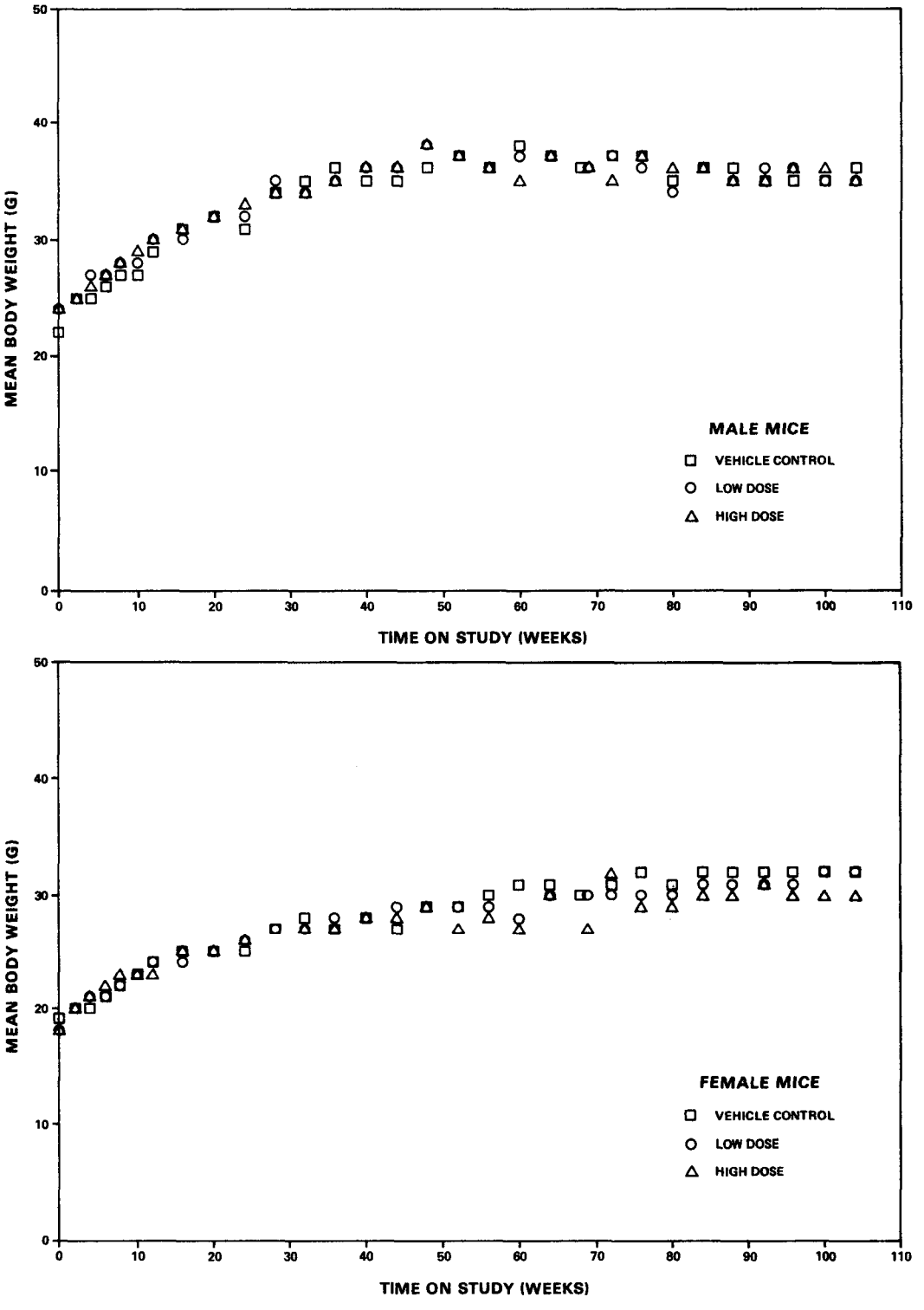


Figure 3. Growth Curves for Mice Administered Sulfisoxazole by Gavage

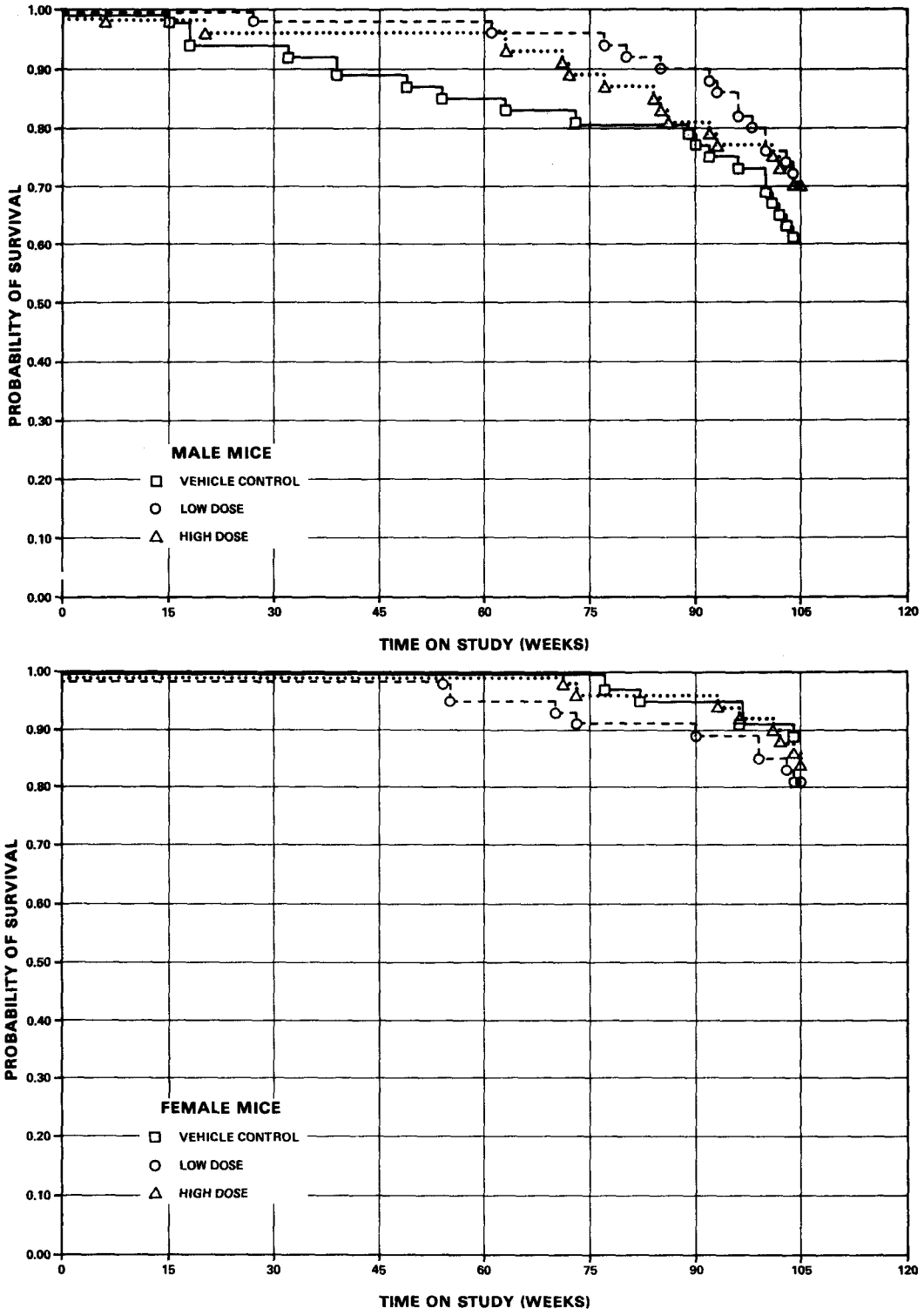


Figure 4. Survival Curves for Mice Administered Sulfisoxazole by Gavage

groups. In each sex of mice, the vehicle-control group was started on study 1 week earlier than the dosed groups; however, the Tarone test for dose-related trend in mortality is applied as if the three groups were started on study at the same time. The Cox test is also used to compare the survival of the vehicle-control group with that of each dosed group. The result of the Tarone test is not significant in either sex. The results of the Cox test comparing the survival of the vehicle-control group with that of each dosed group are also not significant in either sex.

In male mice, 34/50 (68%) of the high-dose group, 36/50 (72%) of the low-dose group, and 30/50 (60%) of the vehicle-control group lived to the end of the bioassay. In females, 42/50 (84%) of the high-dose group, 40/50 (80%) of the low-dose group, and 43/50 (86%) of the vehicle-control group lived to the end of the bioassay.

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

C. Pathology (Mice)

Histopathologic findings 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.

There was a high incidence of primary liver tumors in dosed male mice. It was also high in both untreated- and vehicle-control males. This finding is considered to be unrelated to compound administration.

A moderate number of hematopoietic neoplasms and a low incidence of other neoplasms were observed in both control and dosed groups of mice. These neoplasms were of the usual number and type observed in B6C3F1 mice of this age.

Other degenerative, proliferative, and inflammatory lesions observed were also of the usual number and kind observed in aged B6C3F1 mice, and their incidences in control and dosed groups of mice were comparable.

Based on the pathologic examination, sulfisoxazole at the dosage used was neither carcinogenic nor toxic to B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and at an incidence of at least 5% in one or more than one group. Two control groups, a vehicle-control and an untreated-control, were used in this study. However, in the statistical analysis, only the vehicle-control group is used, because the test conditions of the vehicle-control group more closely resemble those of the dosed groups. In each sex of mice, the vehicle-control group was started on study 1 week earlier than the dosed groups; however, the Cochran-Armitage test for dose-related trend in the incidence of tumors is applied as if the three groups were started on study at the same time.

In male mice, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of tumors and the results of the Fisher exact test are not significant. In female mice, the Fisher exact test comparing the incidence of hepatocellular carcinomas in the low-dose and vehicle-control groups indicates a P value of 0.030, which is above the 0.025 level for significance when the Bonferroni inequality criterion is used for multiple comparison. The incidence of this tumor in

the high-dose females is not significant, nor is the result of the Cochran-Armitage test for the females. The result of the Cochran-Armitage test on the incidence of female mice with either alveolar/bronchiolar adenoma or carcinoma is significant (P = 0.006). The Fisher exact comparison of incidences in the high-dose and control groups indicates a P value of 0.030, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison.

Significant results in the negative direction are observed in the incidence of lung tumors in male mice and in the incidence of adenocarcinomas of the mammary gland in female mice.

In most of the 95% confidence intervals for relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals (except that for the incidence of adenocarcinomas of the mammary gland in high-dose female mice) has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by sulfisoxazole, which could not be detected under the conditions of this test.

V. DISCUSSION

Mean body weights of the high-dose male rats and female mice were slightly lower than those of the corresponding vehicle controls during the last 40 to 60 weeks of the bioassay; mean body weights of the dosed female rats and male mice were unaffected. No other clinical signs were observed that could be related to administration of the test compound. Survival rates of both rats and mice were unaffected by the test chemical. All dosed groups of rats and mice could probably have tolerated higher doses. Adequate numbers of rats and mice in dosed and control groups were at risk for the development of late-appearing tumors.

In the male rats and male mice, no tumors occurred in the dosed groups at incidences that were significantly higher than those of the vehicle-control groups.

In the female rats, monocytic leukemia occurred at incidences that were dose related ($P = 0.016$), as did combined monocytic leukemia and lymphocytic lymphoma ($P = 0.033$); however, in direct comparisons, the incidence of these tumors in the individual dosed groups were not significantly higher than those for the vehicle-control groups, and, in addition, there were four animals

with monocytic leukemia among the untreated controls. Thus, the occurrence of these tumors in the dosed groups of female rats cannot be clearly related to administration of the test chemical.

In the female mice, alveolar/bronchiolar adenomas or carcinomas occurred at incidences that were dose related (P = 0.006), and, in a direct comparison, the incidence of the tumors in the high-dose group was higher (P = 0.030) than that for the vehicle-control group. Similarly, hepatocellular carcinomas occurred in the low-dose group at an incidence that was higher (P = 0.030) than that for the vehicle-control group. However, these P values for direct comparisons of dosed groups with control groups are above the level of P = 0.025 required for significance when the Bonferroni inequality criterion is used for multiple comparison. Thus, the occurrence of alveolar/bronchiolar adenomas or carcinomas in the high-dose group and of hepatocellular carcinomas in the low-dose group cannot be clearly related to administration of the test material.

The oral LD_{50} of sulfisoxazole has been reported as 10,000 mg/kg for white rats and albino mice (Schnitzer et al., 1946). When the rats were administered sulfisoxazole in the diet for 26 weeks at daily doses beginning at 2,190 mg/kg and ending at 1,350 mg/kg, they showed no inhibition of growth and no macroscopic or

microscopic change that could be attributed to the chemical. A number of sulfonamides have been reported to induce hyperplasia of the thyroid gland in rats of unspecified strain (Astwood et al., 1943; Mackenzie and Mackenzie, 1943); this effect was believed to be mediated by pituitary thyrotropin (Swarm et al., 1973). When Charles River CD rats were administered sulfamethoxazole, the hyperplasia progressed to adenoma formation and metastases to the lung (Swarm et al., 1973). No evidence of effects on the thyroid is found in reports on sulfisoxazole, including the 26-week chronic study by Schnitzer et al. (1946) and the present 103-week study.

It is concluded that under the conditions of this bioassay, sulfisoxazole was not carcinogenic for either Fischer 344 rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED SULFISOXAZOLE BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED SULFISOXAZOLE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)†	(50)	(50)	(50)
PAPILLOMA, NOS	1 (2%)	1 (2%)	1 (2%)	1 (2%)
SQUAMOUS CELL PAPILLOMA				1 (2%)
SQUAMOUS CELL CARCINOMA	1 (2%)	2 (4%)		
BASAL-CELL CARCINOMA				1 (2%)
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
FIBROMA	1 (2%)	1 (2%)	6 (12%)	2 (4%)
FIBROSARCOMA	2 (4%)	2 (4%)	1 (2%)	
HEMANGIOSARCOMA				2 (4%)
OSTEOSARCOMA			1 (2%)	
NEUROFIBROMA			2 (4%)	
RESPIRATORY SYSTEM				
#TRACHEA	(48)	(50)	(50)	(49)
FOLLICULAR-CELL CARCINOMA, METAS			1 (2%)	
#LUNG	(48)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	1 (2%)		1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		1 (2%)	
INTERSTITIAL-CELL TUMOR, METASTA	1 (2%)			
PHEOCHROMOCYTOMA, METASTATIC				1 (2%)
FIBROSARCOMA, METASTATIC			1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
UNDIFFERENTIATED LEUKEMIA		1 (2%)		
MYELOMONOCYTIC LEUKEMIA	1 (2%)			
MONOCYTIC LEUKEMIA	6 (12%)	8 (16%)	6 (12%)	8 (16%)
*SUBCUT TISSUE/GROIN	(49)	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#SPLEEN	(48)	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC	1 (2%)			
MESOTHELIOMA, METASTATIC			1 (2%)	
ANGIOSARCOMA				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#BRONCHIAL LYMPH NODE	(47)	(50)	(48)	(50)
FIBROSARCOMA, METASTATIC	1 (2%)			
#MESENTERIC L. NODE	(47)	(50)	(48)	(50)
FIBROSARCOMA, METASTATIC	1 (2%)			
#LIVER	(48)	(50)	(50)	(50)
MONOCYTIC LEUKEMIA		1 (2%)		
CIRCULATORY SYSTEM				
#HEART	(48)	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)	
FIBROSARCOMA, METASTATIC			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(48)	(50)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)	2 (4%)	2 (4%)
HEPATOCELLULAR CARCINOMA	2 (4%)		2 (4%)	
#PANCREAS	(48)	(50)	(49)	(50)
FIBROSARCOMA, METASTATIC	1 (2%)			
MESOTHELIOMA, METASTATIC			1 (2%)	
#ESOPHAGUS	(48)	(47)	(46)	(47)
FOLLICULAR-CELL CARCINOMA, METAS			1 (2%)	
#SMALL INTESTINE	(48)	(50)	(48)	(50)
ADENOCARCINOMA, NOS		1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#DUODENUM	(48)	(50)	(48)	(50)
MUCINOUS ADENOCARCINOMA	1 (2%)			
#ILEUM	(48)	(50)	(48)	(50)
ADENOMATOUS POLYP, NOS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(48)	(50)	(50)	(50)
MIXED TUMOR, BENIGN			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(49)	(44)	(50)
CARCINOMA,NOS	1 (2%)			
CHROMOPHOBE ADENOMA	1 (2%)	4 (8%)	4 (9%)	5 (10%)
#ADRENAL	(48)	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)			1 (2%)
PHEOCHROMOCYTOMA	5 (10%)	3 (6%)	10 (20%)	9 (18%)
PHEOCHROMOCYTOMA, MALIGNANT		2 (4%)		1 (2%)
MESOTHELIOMA, METASTATIC			1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)	
#ADRENAL MEDULLA	(48)	(50)	(50)	(50)
GANGLIONEUROMA	1 (2%)			
#THYROID	(48)	(49)	(44)	(48)
FOLLICULAR-CELL ADENOMA		1 (2%)	1 (2%)	
FOLLICULAR-CELL CARCINOMA			1 (2%)	
C-CELL CARCINOMA	2 (4%)	1 (2%)	1 (2%)	2 (4%)
#PARATHYROID	(37)	(37)	(34)	(40)
ADENOMA, NOS			1 (3%)	
#PANCREATIC ISLETS	(48)	(50)	(49)	(50)
ISLET-CELL ADENOMA	3 (6%)	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
FIBROADENOMA	1 (2%)	1 (2%)	2 (4%)	2 (4%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*PREPUTIAL GLAND	(49)	(50)	(50)	(50)
CARCINOMA,NOS	3 (6%)	2 (4%)	4 (8%)	3 (6%)
SQUAMOUS CELL CARCINOMA	1 (2%)			
ADENOMA, NOS			1 (2%)	2 (4%)
*TESTIS	(44)	(48)	(49)	(49)
INTERSTITIAL-CELL TUMOR	39 (89%)	45 (94%)	43 (88%)	46 (94%)
INTERSTITIAL-CELL TUMOR, MALIGNA	1 (2%)			
MESOTHELIOMA, MALIGNANT			1 (2%)	
MESOTHELIOMA, METASTATIC			1 (2%)	
*EPIDIDYMIS	(49)	(50)	(50)	(50)
MESOTHELIOMA, METASTATIC			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*ZYMBAL'S GLAND	(49)	(50)	(50)	(50)
CARCINOMA,NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*BONE/UPPER EXTREMITY	(49)	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)	
BODY CAVITIES				
*MEDIASTINUM	(49)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)	
FIBROSARCOMA			1 (2%)	
*MESENTERY	(49)	(50)	(50)	(50)
FIBROSARCOMA	1 (2%)			
MESOTHELIOMA, MALIGNANT			1 (2%)	
*TUNICA VAGINALIS	(49)	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
MESOTHELIOMA, NOS			2 (4%)	
DIAPHRAGM				
FIBROSARCOMA, METASTATIC			1	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	19	11	16	12
MORIBUND SACRIFICE		1	2	1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				1
TERMINAL SACRIFICE	31	38	32	36
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	43	48	47	49
TOTAL PRIMARY TUMORS	80	81	100	93
TOTAL ANIMALS WITH BENIGN TUMORS	42	47	45	47
TOTAL BENIGN TUMORS	55	59	73	71
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	21	20	18
TOTAL MALIGNANT TUMORS	24	21	23	20
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		5	2
TOTAL SECONDARY TUMORS	5		14	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	4	2
TOTAL UNCERTAIN TUMORS	1	1	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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED SULFISOXAZOLE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
PAPILLOMA, NOS			2 (4%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
FIBROMA	1 (2%)			
FIBROSARCOMA				1 (2%)
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)		
LEUKEMIA,NOS		1 (2%)		
GRANULOCYTIC LEUKEMIA		1 (2%)		
MONOCYTIC LEUKEMIA	4 (8%)	3 (6%)	3 (6%)	9 (18%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(50)	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA		1 (2%)		
URINARY SYSTEM				
NONE				

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(49)	(50)	(50)
ADENOMA, NOS		2 (4%)	1 (2%)	1 (2%)
CHROMOPHOBE ADENOMA	17 (36%)	18 (37%)	19 (38%)	17 (34%)
#ADRENAL	(50)	(49)	(50)	(50)
CORTICAL ADENOMA	1 (2%)	1 (2%)		
PHEOCHROMOCYTOMA		1 (2%)	2 (4%)	
#THYROID	(49)	(47)	(50)	(49)
C-CELL ADENOMA		1 (2%)		
C-CELL CARCINOMA	1 (2%)			2 (4%)
#PARATHYROID	(33)	(32)	(38)	(43)
ADENOMA, NOS		1 (3%)		
#PANCREATIC ISLETS	(50)	(50)	(50)	(49)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)		
ADENOCARCINOMA, NOS	1 (2%)		1 (2%)	
PAPILLARY CYSTADENOMA, NOS		2 (4%)		
FIBROADENOMA	6 (12%)	12 (24%)	16 (32%)	15 (30%)
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)	3 (6%)		1 (2%)
ADENOMA, NOS	2 (4%)			1 (2%)
#UTERUS	(50)	(49)	(49)	(48)
CARCINOMA,NOS	1 (2%)			
PAPILLARY CYSTADENOMA, NOS			1 (2%)	
ENDOMETRIAL STROMAL POLYP	6 (12%)	5 (10%)	6 (12%)	8 (17%)
ENDOMETRIAL STROMAL SARCOMA		1 (2%)		
NERVOUS SYSTEM				
#CEREBRUM	(50)	(50)	(50)	(50)
ASTROCYTOMA			1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
*EYE/CONJUNCTIVA	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	11	15	4	8
MORIBUND SACRIFICE			3	2
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	39	35	43	40
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	30	38	37	35
TOTAL PRIMARY TUMORS	42	56	54	55
TOTAL ANIMALS WITH BENIGN TUMORS	27	32	36	32
TOTAL BENIGN TUMORS	34	45	48	42
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	11	6	11
TOTAL MALIGNANT TUMORS	8	11	6	13
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED SULFISOXAZOLE BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED SULFISOXAZOLE BY GAVAGE

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

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#DUODENUM	(49)	(49)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#THYMUS	(19)	(22)	(22)	(8)
LIPOSARCOMA		1 (5%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(50)	(49)
HEPATOCELLULAR ADENOMA	3 (6%)			1 (2%)
HEPATOCELLULAR CARCINOMA	17 (35%)	15 (30%)	13 (26%)	20 (41%)
HEMANGIOSARCOMA		2 (4%)	1 (2%)	2 (4%)
#BILE DUCT	(49)	(50)	(50)	(49)
CARCINOSARCOMA		1 (2%)		
#PANCREAS	(49)	(50)	(49)	(48)
CORTICAL CARCINOMA, METASTATIC		1 (2%)		
#STOMACH	(49)	(49)	(49)	(49)
CARCINOMA,NOS		1 (2%)		1 (2%)
SQUAMOUS CELL PAPILLOMA	1 (2%)			
ADENOMATOUS POLYP, NOS				1 (2%)
#SMALL INTESTINE	(49)	(49)	(50)	(49)
HEMANGIOSARCOMA, METASTATIC		1 (2%)		
#JEJUNUM	(49)	(49)	(50)	(49)
CARCINOMA,NOS	1 (2%)			
URINARY SYSTEM				
#URINARY BLADDER	(49)	(50)	(50)	(49)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)		
ENDOCRINE SYSTEM				
#ADRENAL	(48)	(49)	(49)	(49)
CORTICAL ADENOMA		1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CORTICAL CARCINOMA		1 (2%)		
PHEOCHROMOCYTOMA		2 (4%)	5 (10%)	
#THYROID	(47)	(47)	(48)	(48)
FOLLICULAR-CELL ADENOMA				1 (2%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(49)	(50)	(50)	(49)
HEMANGIOSARCOMA, METASTATIC		1 (2%)		
#TESTIS	(49)	(50)	(47)	(48)
INTERSTITIAL-CELL TUMOR				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYELID	(49)	(50)	(50)	(49)
SEBACEOUS ADENOCARCINOMA		1 (2%)		
*HARDERIAN GLAND	(49)	(50)	(50)	(49)
CARCINOMA,NOS		1 (2%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(49)
CARCINOSARCOMA, METASTATIC		1 (2%)		
HEMANGIOSARCOMA		1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	12	18	14	14
MORIBUND SACRIFICE		1		
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED	1	1		2
TERMINAL SACRIFICE	36	30	36	34
ANIMAL MISSING	1			
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	29	31	28
TOTAL PRIMARY TUMORS	45	43	41	36
TOTAL ANIMALS WITH BENIGN TUMORS	12	8	9	4
TOTAL BENIGN TUMORS	13	8	12	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	26	25	25	25
TOTAL MALIGNANT TUMORS	32	35	29	32
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	7	3	1
TOTAL SECONDARY TUMORS	3	9	3	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED SULFISOXAZOLE BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	50	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)			
*SUBCUT TISSUE	(50)	(49)	(50)	(50)
FIBROSARCOMA				1 (2%)
HEMANGIOMA		1 (2%)	1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA				2 (4%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(49)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	3 (6%)	6 (12%)	7 (14%)	10 (20%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	10 (20%)	7 (14%)	8 (16%)	10 (20%)
MALIGNANT LYMPHOMA, MIXED TYPE	3 (6%)	3 (6%)	1 (2%)	
GRANULOCYTIC LEUKEMIA	1 (2%)	1 (2%)		
#SPLEEN	(50)	(49)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	
#MESENTERIC L. NODE	(48)	(48)	(50)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)			
CIRCULATORY SYSTEM				
NONE				

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(50)	(50)
HEPATOCELLULAR ADENOMA	1 (2%)			
HEPATOCELLULAR CARCINOMA	2 (4%)		5 (10%)	2 (4%)
#PANCREAS	(50)	(49)	(50)	(50)
CARCINOMA, NOS, METASTATIC	1 (2%)			
#STOMACH	(50)	(49)	(49)	(50)
CARCINOMA,NOS	1 (2%)			
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(45)	(42)	(44)	(31)
CHROMOPHOBE ADENOMA	1 (2%)	2 (5%)	1 (2%)	1 (3%)
#ADRENAL	(50)	(48)	(49)	(50)
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)	
#THYROID	(49)	(48)	(48)	(46)
FOLLICULAR-CELL ADENOMA	1 (2%)		1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(49)	(50)	(50)
ADENOMA, NOS				1 (2%)
ADENOCARCINOMA, NOS	1 (2%)	5 (10%)	1 (2%)	
FIBROADENOMA			1 (2%)	
#UTERUS	(50)	(49)	(50)	(50)
FIBROSARCOMA				1 (2%)
ENDOMETRIAL STROMAL POLYP	1 (2%)	1 (2%)	2 (4%)	
HEMANGIOMA	1 (2%)		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	1 (2%)	1 (2%)
#OVARY	(50)	(49)	(50)	(50)
SERTOLI-CELL TUMOR		1 (2%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#MESOVARIUM	(50)	(49)	(50)	(50)
CARCINOMA, NOS, METASTATIC	1 (2%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(49)	(50)	(50)
ADENOMA, NOS		2 (4%)	2 (4%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(49)	(50)	(50)
FIBROSARCOMA				1 (2%)
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	9	5	9	8
MORIBUND SACRIFICE				
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED		1	1	
TERMINAL SACRIFICE	41	43	40	42
ANIMAL MISSING		1		

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	24	29	31
TOTAL PRIMARY TUMORS	30	31	35	35
TOTAL ANIMALS WITH BENIGN TUMORS	7	7	10	7
TOTAL BENIGN TUMORS	8	8	11	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	20	22	26
TOTAL MALIGNANT TUMORS	22	23	24	28
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1	
TOTAL SECONDARY TUMORS	2		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED SULFISOXAZOLE BY GAVAGE

TABLE C1.

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

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)	3 (6%)	1 (2%)	
HYPERKERATOSIS	1 (2%)			1 (2%)
ACANTHOSIS	1 (2%)	1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
STEATITIS	1 (2%)			
INFLAMMATION, CHRONIC		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(48)	(50)	(50)	(50)
MINERALIZATION		1 (2%)		
HEMORRHAGE	5 (10%)	2 (4%)	6 (12%)	5 (10%)
INFLAMMATION, SUPPURATIVE	1 (2%)			
INFLAMMATION, ACUTE			1 (2%)	
PNEUMONIA, CHRONIC MURINE	39 (81%)	46 (92%)	43 (86%)	44 (88%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(48)	(50)	(50)	(50)
ECTOPIA			2 (4%)	
FIBROSIS		1 (2%)		
FIBROSIS, FOCAL	1 (2%)			
AMYLOIDOSIS	1 (2%)			
HEMOSIDEROSIS		1 (2%)	1 (2%)	
HEMATOPOIESIS	5 (10%)	3 (6%)	1 (2%)	2 (4%)
#SPLENIC CAPSULE	(48)	(50)	(50)	(50)
FIBROSIS, FOCAL			1 (2%)	
#LYMPH NODE	(47)	(50)	(48)	(50)
ATROPHY, NOS	1 (2%)			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#CERVICAL LYMPH NODE	(47)	(50)	(48)	(50)
AMYLOIDOSIS	1 (2%)			
#BRONCHIAL LYMPH NODE	(47)	(50)	(48)	(50)
HEMORRHAGE	1 (2%)			1 (2%)
ATROPHY, NOS		1 (2%)	1 (2%)	
#MESENTERIC L. NODE	(47)	(50)	(48)	(50)
LYMPHANGIECTASIS		1 (2%)	1 (2%)	1 (2%)
AMYLOIDOSIS	1 (2%)			
ATROPHY, NOS		1 (2%)	1 (2%)	
CIRCULATORY SYSTEM				
#HEART/ATRIUM	(48)	(50)	(50)	(50)
THROMBOSIS, NOS	8 (17%)	2 (4%)	4 (8%)	1 (2%)
#MYOCARDIUM	(48)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	6 (13%)	13 (26%)	1 (2%)	2 (4%)
FIBROSIS	23 (48%)	27 (54%)	34 (68%)	32 (64%)
FIBROSIS, FOCAL		2 (4%)	1 (2%)	
DEGENERATION, NOS	11 (23%)	6 (12%)	2 (4%)	9 (18%)
*AORTA	(49)	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)			1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(49)	(49)	(50)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
#LIVER	(48)	(50)	(50)	(50)
FIBROSIS	1 (2%)		1 (2%)	
CIRRHOSIS, PORTAL	3 (6%)			
HEPATITIS, TOXIC	2 (4%)	2 (4%)	1 (2%)	2 (4%)
PELIOSIS HEPATIS			1 (2%)	
NECROSIS, NOS	2 (4%)	2 (4%)	1 (2%)	1 (2%)
METAMORPHOSIS FATTY	1 (2%)	2 (4%)		
HEMOSIDEROSIS			1 (2%)	
FOCAL CELLULAR CHANGE	25 (52%)	28 (56%)	20 (40%)	18 (36%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIESIS		1 (2%)		
#PORTAL TRACT	(48)	(50)	(50)	(50)
FIBROSIS	1 (2%)			
#LIVER/CENTRILOBULAR	(48)	(50)	(50)	(50)
NECROSIS, NOS	5 (10%)	1 (2%)	3 (6%)	2 (4%)
#LIVER/PERIPORTAL	(48)	(50)	(50)	(50)
FIBROSIS	1 (2%)			
#BILE DUCT	(48)	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, CHRONIC	4 (8%)		2 (4%)	
FIBROSIS	3 (6%)	7 (14%)	6 (12%)	10 (20%)
HYPERPLASIA, NOS	33 (69%)	31 (62%)	32 (64%)	36 (72%)
#PANCREAS	(48)	(50)	(49)	(50)
INFLAMMATION, CHRONIC	4 (8%)	3 (6%)		
PERIARTERITIS	3 (6%)	1 (2%)	2 (4%)	3 (6%)
ATROPHY, NOS	6 (13%)	6 (12%)	11 (22%)	13 (26%)
#STOMACH	(48)	(48)	(49)	(48)
HEMORRHAGE	1 (2%)		1 (2%)	
ULCER, NOS			1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)		1 (2%)
NECROSIS, NOS	1 (2%)	2 (4%)	1 (2%)	1 (2%)
NECROSIS, FOCAL	2 (4%)			1 (2%)
ACANTHOSIS			1 (2%)	
#LARGE INTESTINE	(48)	(50)	(49)	(49)
PARASITISM	8 (17%)	7 (14%)	12 (24%)	7 (14%)
INFARCT, NOS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(48)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	42 (88%)	45 (90%)	44 (88%)	45 (90%)
CALCIFICATION, NOS		1 (2%)		
PIGMENTATION, NOS			2 (4%)	
HEMOSIDEROSIS		2 (4%)		
#KIDNEY/TUBULE	(48)	(50)	(50)	(50)
PIGMENTATION, NOS		1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(49)	(44)	(50)
CYST, NOS				1 (2%)
HYPERPLASIA, FOCAL	2 (4%)	1 (2%)	3 (7%)	1 (2%)
#ADRENAL	(48)	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		1 (2%)	
HEMORRHAGE				1 (2%)
NECROSIS, NOS				1 (2%)
NECROSIS, FOCAL	1 (2%)			
METAMORPHOSIS FATTY	4 (8%)		2 (4%)	
#ADRENAL CORTEX	(48)	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)			
DEGENERATION, NOS		4 (8%)		1 (2%)
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL				1 (2%)
#ADRENAL MEDULLA	(48)	(50)	(50)	(50)
HYPERPLASIA, NOS	5 (10%)	6 (12%)	9 (18%)	9 (18%)
#THYROID	(48)	(49)	(44)	(48)
FOLLICULAR CYST, NOS			1 (2%)	
HYPERPLASIA, C-CELL	4 (8%)	1 (2%)	2 (5%)	2 (4%)
#PANCREATIC ISLETS	(48)	(50)	(49)	(50)
HYPERPLASIA, NOS	2 (4%)	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
CYST, NOS		1 (2%)		1 (2%)
CYSTIC DUCTS		5 (10%)		2 (4%)
INFLAMMATION, CHRONIC		1 (2%)		
HYPERPLASIA, CYSTIC				1 (2%)
*PREPUTIAL GLAND	(49)	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, CHRONIC			2 (4%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)	
#PROSTATE	(46)	(49)	(50)	(50)
INFLAMMATION, ACUTE	2 (4%)		11 (22%)	7 (14%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	7 (15%)	17 (35%)	4 (8%)	3 (6%)
NECROSIS, NOS		2 (4%)		
#TESTIS	(44)	(48)	(49)	(49)
HEMORRHAGE	1 (2%)			
ABSCESS, NOS				1 (2%)
INFLAMMATION, CHRONIC		1 (2%)		
PERIARTERITIS	2 (5%)			
DEGENERATION, NOS	11 (25%)	3 (6%)	11 (22%)	
HYPERPLASIA, INTERSTITIAL CELL	10 (23%)	13 (27%)	18 (37%)	19 (39%)
*EPIDIDYMIS	(49)	(50)	(50)	(50)
STEATITIS		1 (2%)		2 (4%)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		2 (4%)	1 (2%)
NECROSIS, NOS		1 (2%)		
NECROSIS, FAT	1 (2%)		1 (2%)	1 (2%)
*SCROTUM	(49)	(50)	(50)	(50)
NECROSIS, FAT		1 (2%)		
NERVOUS SYSTEM				
#CEREBELLUM	(48)	(50)	(49)	(50)
HEMORRHAGE			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(50)	(50)
HEMORRHAGE		3 (6%)		
SYNECHIA, ANTERIOR		1 (2%)		
SYNECHIA, POSTERIOR	1 (2%)	2 (4%)		
CATARACT	1 (2%)	2 (4%)	4 (8%)	
PHTHISIS BULBI		1 (2%)	1 (2%)	
*EYE/RETINA	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)		
DEGENERATION, NOS	1 (2%)	4 (8%)	4 (8%)	
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*MEDIASTINUM	(49)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
*ABDOMINAL CAVITY	(49)	(50)	(50)	(50)
STEATITIS		7 (14%)		
NECROSIS, FAT				1 (2%)
*MESENTERY	(49)	(50)	(50)	(50)
STEATITIS	1 (2%)			2 (4%)
INFLAMMATION, CHRONIC				1 (2%)
PERIARTERITIS			1 (2%)	
NECROSIS, FAT			2 (4%)	
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED				1
AUTO/NECROPSY/HISTO PERF	1			
AUTOLYSIS/NO NECROPSY	1			

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

TABLE C2.

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

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)			
INFLAMMATION, CHRONIC	1 (2%)			
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
NECROSIS, FAT				1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(50)	(49)	(50)	(50)
CALCIFICATION, NOS		1 (2%)		
#LUNG	(50)	(49)	(50)	(50)
HEMORRHAGE	12 (24%)	8 (16%)	7 (14%)	3 (6%)
PNEUMONIA, ASPIRATION	1 (2%)			
ABSCESS, NOS		1 (2%)		
PNEUMONIA, CHRONIC MURINE	46 (92%)	44 (90%)	50 (100%)	47 (94%)
HYPERPLASIA, ALVEOLAR EPITHELIUM				2 (4%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(50)	(50)	(50)	(50)
HYPOPLASIA, NOS			1 (2%)	
#SPLEEN	(50)	(50)	(50)	(49)
ECTOPIA	1 (2%)			
CONGESTION, NOS		1 (2%)		
HEMORRHAGE	1 (2%)			
HEMOSIDEROSIS	9 (18%)	13 (26%)	10 (20%)	4 (8%)
ATROPHY, NOS		1 (2%)		
HEMATOPOIESIS		9 (18%)	3 (6%)	1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(49)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
NECROSIS, NOS		1 (2%)		
#THYMUS	(37)	(10)	(24)	(17)
HEMORRHAGE	2 (5%)			1 (6%)
CIRCULATORY SYSTEM				
#HEART	(50)	(49)	(50)	(50)
PERIARTERITIS		1 (2%)		
#HEART/ATRIUM	(50)	(49)	(50)	(50)
THROMBOSIS, NOS		2 (4%)		
#MYOCARDIUM	(50)	(49)	(50)	(50)
INFLAMMATION, CHRONIC	13 (26%)	3 (6%)	9 (18%)	10 (20%)
FIBROSIS	20 (40%)	5 (10%)		6 (12%)
DEGENERATION, NOS	3 (6%)	5 (10%)	2 (4%)	8 (16%)
CALCIFICATION, NOS		1 (2%)	1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(50)	(50)	(50)	(50)
HEMORRHAGE		2 (4%)		
HEPATITIS, TOXIC	1 (2%)	1 (2%)		
NECROSIS, NOS	1 (2%)	3 (6%)	1 (2%)	1 (2%)
NECROSIS, FOCAL	1 (2%)			
INFARCT, NOS				1 (2%)
METAMORPHOSIS FATTY	2 (4%)	4 (8%)	1 (2%)	5 (10%)
FOCAL CELLULAR CHANGE	38 (76%)	29 (58%)	40 (80%)	39 (78%)
HEMATOPOIESIS		1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(50)	(50)	(50)
NECROSIS, NOS		2 (4%)		1 (2%)
#BILE DUCT	(50)	(50)	(50)	(50)
BILE STASIS			1 (2%)	
INFLAMMATION, CHRONIC	2 (4%)			
FIBROSIS	6 (12%)	5 (10%)		3 (6%)
HYPERPLASIA, NOS	17 (34%)	7 (14%)	7 (14%)	10 (20%)
#PANCREAS	(50)	(50)	(50)	(49)
INFLAMMATION, CHRONIC		1 (2%)		1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PERIARTERITIS			1 (2%)	
ATROPHY, NOS	5 (10%)	2 (4%)	3 (6%)	7 (14%)
ATROPHY, FOCAL	1 (2%)			
#PANCREATIC DUCT	(50)	(50)	(50)	(49)
HYPERPLASIA, FOCAL				1 (2%)
#STOMACH	(50)	(50)	(50)	(49)
CYST, NOS			1 (2%)	
HEMORRHAGE		1 (2%)		
ULCER, NOS				1 (2%)
ULCER, FOCAL	1 (2%)			
INFLAMMATION, CHRONIC		1 (2%)		1 (2%)
NECROSIS, NOS			3 (6%)	
CALCIFICATION, NOS		1 (2%)		
ACANTHOSIS		1 (2%)		
#GASTRIC SUBMUCOSA	(50)	(50)	(50)	(49)
EDEMA, NOS				1 (2%)
#LARGE INTESTINE	(50)	(50)	(50)	(49)
PARASITISM	7 (14%)	7 (14%)	5 (10%)	
#COLON	(50)	(50)	(50)	(49)
PARASITISM				8 (16%)
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	38 (76%)	20 (40%)	22 (44%)	29 (58%)
METAMORPHOSIS FATTY			1 (2%)	
PIGMENTATION, NOS	1 (2%)			
#KIDNEY/TUBULE	(50)	(50)	(50)	(50)
PIGMENTATION, NOS			1 (2%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(49)	(50)	(50)
CYST, NOS	1 (2%)	2 (4%)	5 (10%)	3 (6%)
HEMORRHAGE	2 (4%)	3 (6%)		2 (4%)
HEMATOMA, NOS			2 (4%)	
PIGMENTATION, NOS				1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	1 (2%)	1 (2%)	3 (6%)	1 (2%)
HYPERPLASIA, FOCAL	4 (9%)	5 (10%)	4 (8%)	3 (6%)
ANGIECTASIS		1 (2%)		
#ADRENAL	(50)	(49)	(50)	(50)
THROMBOSIS, NOS	1 (2%)			
HEMORRHAGE	1 (2%)		1 (2%)	
ANGIECTASIS	1 (2%)			1 (2%)
#ADRENAL CORTEX	(50)	(49)	(50)	(50)
THROMBOSIS, NOS			2 (4%)	
DEGENERATION, NOS	4 (8%)	4 (8%)	5 (10%)	5 (10%)
ANGIECTASIS		2 (4%)		
#ADRENAL MEDULLA	(50)	(49)	(50)	(50)
HYPERPLASIA, NOS		3 (6%)	3 (6%)	
#THYROID	(49)	(47)	(50)	(49)
INFLAMMATION, CHRONIC	1 (2%)			
FIBROSIS	1 (2%)			
HYPERPLASIA, C-CELL	3 (6%)	2 (4%)	3 (6%)	8 (16%)
#PANCREATIC ISLETS	(50)	(50)	(50)	(49)
HYPERPLASIA, NOS			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
GALACTOCELE	2 (4%)	1 (2%)		3 (6%)
CYST, NOS	9 (18%)	2 (4%)	22 (44%)	1 (2%)
CYSTIC DUCTS	7 (14%)	22 (44%)		24 (48%)
INFLAMMATION, ACUTE	1 (2%)			
INFLAMMATION, CHRONIC	1 (2%)			
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, CYSTIC			2 (4%)	
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)		
#UTERUS	(50)	(49)	(49)	(48)
HYDROMETRA	1 (2%)	1 (2%)	1 (2%)	
HEMORRHAGE				1 (2%)
PYOMETRA				1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(49)	(49)	(48)
INFLAMMATION, VESICULAR	5 (10%)			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#OVARY/PAROVARIAN	(50)	(49)	(49)	(48)
NECROSIS, FAT	1 (2%)			
#OVARY	(50)	(49)	(49)	(48)
CYST, NOS	1 (2%)	1 (2%)	3 (6%)	
PAROVARIAN CYST		1 (2%)		
HEMORRHAGE		1 (2%)		
NERVOUS SYSTEM				
#BRAIN	(50)	(50)	(50)	(50)
HYDROCEPHALUS, NOS			1 (2%)	
#CEREBELLUM	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
SPECIAL SENSE ORGANS				
*EYE	(50)	(50)	(50)	(50)
SYNECHIA, ANTERIOR	1 (2%)	1 (2%)		
SYNECHIA, POSTERIOR	1 (2%)			
CATARACT	1 (2%)		1 (2%)	
PHTHISIS BULBI				1 (2%)
*EYE/CORNEA	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)			
*EYE/IRIS	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)			
*EYE/RETINA	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)			
DEGENERATION, NOS	1 (2%)	1 (2%)	4 (8%)	1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
STEATITIS		1 (2%)		1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FAT	1 (2%)	3 (6%)	2 (4%)	2 (4%)
*MESENTERY	(50)	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)		1 (2%)	
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/HISTO PERF	1	1		

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED SULFISOXAZOLE BY GAVAGE

TABLE D1.

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

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

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
LEUKEMOID REACTION		1 (2%)		
HYPERPLASIA, LYMPHOID	8 (16%)	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIESIS	3 (6%)	2 (4%)	7 (14%)	3 (6%)
#CERVICAL LYMPH NODE	(49)	(50)	(50)	(49)
INFLAMMATION, NOS		1 (2%)		
#MESENTERIC L. NODE	(49)	(50)	(50)	(49)
LYMPHANGIECTASIS	1 (2%)			
CONGESTION, NOS	3 (6%)	11 (22%)	2 (4%)	2 (4%)
INFLAMMATION, NOS	3 (6%)		2 (4%)	
INFLAMMATION, ACUTE	1 (2%)		1 (2%)	
HYPERPLASIA, RETICULUM CELL	1 (2%)			
HYPERPLASIA, LYMPHOID	13 (27%)	5 (10%)	5 (10%)	3 (6%)
HEMATOPOIESIS	1 (2%)		1 (2%)	1 (2%)
CIRCULATORY SYSTEM				
#HEART	(49)	(50)	(50)	(49)
MINERALIZATION			1 (2%)	
DILATATION, NOS	1 (2%)	1 (2%)		
PERIARTERITIS		1 (2%)		
METAPLASIA, OSSEOUS		1 (2%)		
#AURICULAR APPENDAGE	(49)	(50)	(50)	(49)
THROMBOSIS, NOS	1 (2%)			
#MYOCARDIUM	(49)	(50)	(50)	(49)
INFLAMMATION, FOCAL				1 (2%)
DEGENERATION, NOS	1 (2%)			
*AORTA	(49)	(50)	(50)	(49)
INFLAMMATION, NOS		1 (2%)		
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(50)	(49)
CYST, NOS			1 (2%)	
THROMBOSIS, NOS			2 (4%)	1 (2%)
ABSCESS, NOS		1 (2%)		
NECROSIS, NOS	3 (6%)	1 (2%)	2 (4%)	1 (2%)
INFARCT, NOS	3 (6%)			4 (8%)
AMYLOIDOSIS		1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
METAMORPHOSIS FATTY			1 (2%)	
FOCAL CELLULAR CHANGE		1 (2%)		
ANGIECTASIS			2 (4%)	
#LIVER/CENTRILOBULAR	(49)	(50)	(50)	(49)
NECROSIS, NOS		1 (2%)		1 (2%)
#LIVER/PERIPORTAL	(49)	(50)	(50)	(49)
FIBROSIS	1 (2%)			
#BILE DUCT	(49)	(50)	(50)	(49)
CYST, NOS				1 (2%)
HYPERPLASIA, NOS	1 (2%)			
#ESOPHAGUS	(49)	(50)	(49)	(49)
RUPTURE		1 (2%)		1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)
#STOMACH	(49)	(49)	(49)	(49)
ULCER, FOCAL	3 (6%)	2 (4%)	1 (2%)	1 (2%)
HYPERKERATOSIS				2 (4%)
ACANTHOSIS				2 (4%)
#PEYERS PATCH	(49)	(49)	(50)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)		
#LARGE INTESTINE	(49)	(50)	(50)	(47)
INFLAMMATION, ACUTE				1 (2%)
NEMATODIASIS	1 (2%)	2 (4%)	3 (6%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(49)
HYDRONEPHROSIS				2 (4%)
THROMBOSIS, NOS		1 (2%)		
CONGESTION, NOS	1 (2%)			
INFLAMMATION, CHRONIC	6 (12%)	9 (18%)	14 (28%)	14 (29%)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)		
METAPLASIA, OSSEOUS				1 (2%)
#URINARY BLADDER	(49)	(50)	(50)	(49)
INFLAMMATION, CHRONIC	2 (4%)			
HYPERPLASIA, EPITHELIAL				1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(40)	(33)	(46)	(39)
CYST, NOS	2 (5%)			
#ADRENAL	(48)	(49)	(49)	(49)
CONGESTION, NOS				1 (2%)
#ADRENAL MEDULLA	(48)	(49)	(49)	(49)
HYPERPLASIA, NOS		2 (4%)		
#THYROID	(47)	(47)	(48)	(48)
HYPERPLASIA, C-CELL	1 (2%)			
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(49)	(50)	(50)	(49)
DISTENTION				1 (2%)
#PROSTATE	(49)	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)		
INFLAMMATION, ACUTE			1 (2%)	
*SEMINAL VESICLE	(49)	(50)	(50)	(49)
DISTENTION				2 (4%)
ATROPHY, NOS		1 (2%)	1 (2%)	
#TESTIS	(49)	(50)	(47)	(48)
ATROPHY, NOS		2 (4%)	4 (9%)	
HYPOSPERMATOGENESIS				1 (2%)
*EPIDIDYMIS	(49)	(50)	(50)	(49)
GRANULOMA, SPERMATIC	1 (2%)		2 (4%)	1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(50)	(49)
ABSCESS, CHRONIC		1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MEDIASTINUM	(49)	(50)	(50)	(49)
INFLAMMATION, CHRONIC				2 (4%)
*ABDOMINAL CAVITY	(49)	(50)	(50)	(49)
NECROSIS, FAT				1 (2%)
*PERITONEUM	(49)	(50)	(50)	(49)
INFLAMMATION, NOS				1 (2%)
*PLEURA	(49)	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV				1 (2%)
*PERICARDIUM	(49)	(50)	(50)	(49)
INFLAMMATION, CHRONIC				1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(49)
EMBOLUS, SEPTIC	1 (2%)			
LEUKOCYTOSIS, NOS			1 (2%)	
LEUKEMOID REACTION	1 (2%)			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	5	7	8	7
ANIMAL MISSING/NO NECROPSY	1			
AUTOLYSIS/NO NECROPSY				1

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

TABLE D2.

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

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	50	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50	50
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(50)
CONGESTION, NOS	1 (2%)	1 (2%)	1 (2%)	2 (4%)
HEMORRHAGE		4 (8%)		
PNEUMONIA, CHRONIC MURINE	3 (6%)	4 (8%)	1 (2%)	2 (4%)
PIGMENTATION, NOS		1 (2%)		
ALVEOLAR MACROPHAGES		1 (2%)		
LEUKOCYTOSIS, NOS	1 (2%)			
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(50)	(49)	(50)	(50)
FIBROUS OSTEODYSTROPHY			1 (2%)	
HYPERPLASIA, GRANULOCYTIC	1 (2%)			
#SPLEEN	(50)	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID	3 (6%)	7 (14%)	5 (10%)	1 (2%)
HEMATOPOIESIS	1 (2%)		3 (6%)	2 (4%)
#CERVICAL LYMPH NODE	(48)	(48)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)		
#MESENTERIC L. NODE	(48)	(48)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		
HYPERPLASIA, LYMPHOID	4 (8%)	5 (10%)	5 (10%)	4 (8%)
#RENAL LYMPH NODE	(48)	(48)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(29)	(29)	(21)	(20)
HYPERPLASIA, LYMPHOID		1 (3%)		
CIRCULATORY SYSTEM				
#HEART	(50)	(49)	(50)	(50)
PERIARTERITIS	1 (2%)			
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(50)	(50)
CONGESTION, NOS	1 (2%)			
HEMORRHAGE	1 (2%)			
NECROSIS, NOS	1 (2%)		1 (2%)	
#BILE DUCT	(50)	(49)	(50)	(50)
CYST, NOS			1 (2%)	1 (2%)
#PANCREAS	(50)	(49)	(50)	(50)
CYSTIC DUCTS	3 (6%)	3 (6%)	4 (8%)	
#PANCREATIC ACINUS	(50)	(49)	(50)	(50)
ATROPHY, NOS	1 (2%)	1 (2%)		1 (2%)
#STOMACH	(50)	(49)	(49)	(50)
INFLAMMATION, FOCAL				1 (2%)
ULCER, FOCAL		2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)		
#GASTRIC MUCOSA	(50)	(49)	(49)	(50)
HYPERPLASIA, FOCAL			1 (2%)	
#GASTRIC SUBMUCOSA	(50)	(49)	(49)	(50)
EDEMA, NOS			1 (2%)	
#LARGE INTESTINE	(49)	(49)	(50)	(50)
NEMATODIASIS	1 (2%)		1 (2%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(50)	(49)	(50)	(50)
CYST, NOS	1 (2%)			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PYELONEPHRITIS, NOS			1 (2%)	
INFLAMMATION, CHRONIC	5 (10%)		3 (6%)	1 (2%)
PERIARTERITIS	1 (2%)			
GLOMERULOSCLEROSIS, NOS	1 (2%)			
AMYLOIDOSIS	1 (2%)			
METAPLASIA, OSSEOUS				1 (2%)
#KIDNEY/TUBULE	(50)	(49)	(50)	(50)
PIGMENTATION, NOS			1 (2%)	
#URINARY BLADDER	(49)	(48)	(49)	(50)
AMYLOIDOSIS	1 (2%)			
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(50)	(48)	(49)	(50)
DEGENERATION, NOS				1 (2%)
HYPERTROPHY, NOS			1 (2%)	
#THYROID	(49)	(48)	(48)	(46)
CYSTIC FOLLICLES	1 (2%)			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)			
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(49)	(50)	(50)
METAPLASIA, SQUAMOUS		1 (2%)		
#UTERUS	(50)	(49)	(50)	(50)
HYDROMETRA	1 (2%)			1 (2%)
THROMBOSIS, NOS			1 (2%)	
ANGIECTASIS	1 (2%)			
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
HYPERPLASIA, CYSTIC	41 (82%)	45 (92%)	42 (84%)	44 (88%)
#OVARY	(50)	(49)	(50)	(50)
CYSTIC FOLLICLES		2 (4%)		
FOLLICULAR CYST, NOS	4 (8%)	1 (2%)	4 (8%)	8 (16%)
PAROVARIAN CYST	7 (14%)	9 (18%)	5 (10%)	11 (22%)
HEMORRHAGIC CYST			1 (2%)	1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATICN, NOS	1 (2%)			
#RIGHT OVARY	(50)	(49)	(50)	(50)
PAROVARIAN CYST			1 (2%)	
THROMBOSIS, NOS	1 (2%)			
#LEFT OVARY	(50)	(49)	(50)	(50)
THROMBUS, CRGANIZED	1 (2%)			
HEMORRHAGIC CYST			1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(50)	(48)	(50)	(50)
COMPRESSION			1 (2%)	
HEMATOPOIESIS			1 (2%)	
SPECIAL SENSE CRGANS				
*EYE	(50)	(49)	(50)	(50)
INFLAMMATICN, NOS		1 (2%)		
PHTHISIS BULBI		1 (2%)		
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(50)	(49)	(50)	(50)
PARASITISM	1 (2%)			
BODY CAVITIES				
*PERITONEUM	(50)	(49)	(50)	(50)
INFLAMMATICN, NOS	2 (4%)			
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1		2	1

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL MISSING/NO NECROPSY		1		

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED SULFISOXAZOLE BY GAVAGE

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sulfisoxazole by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	1/50 (2)	6/50 (12)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.026		
Relative Risk (f)		6.000	2.000
Lower Limit		0.768	0.108
Upper Limit		269.891	115.621
Weeks to First Observed Tumor	106	96	85
Hematopoietic System: Monocytic Leukemia (b)	9/50 (18)	6/50 (12)	8/50 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.667	0.889
Lower Limit		0.211	0.325
Upper Limit		1.935	2.382
Weeks to First Observed Tumor	96	101	91

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Hematopoietic System: All Lymphoma or Leukemia (b)	11/50 (20)	7/50 (14)	10/50 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.636	0.909
Lower Limit		0.228	0.381
Upper Limit		1.645	2.140
Weeks to First Observed Tumor	96	101	88
Liver: Hepatocellular Carcinoma or Neoplastic Nodule (b)	1/50 (2)	4/50 (8)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		4.000	2.000
Lower Limit		0.415	0.108
Upper Limit		192.805	115.621
Weeks to First Observed Tumor	106	106	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	4/49 (8)	4/44 (9)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.114	1.225
Lower Limit		0.220	0.280
Upper Limit		5.626	5.833
Weeks to First Observed Tumor	86	99	75
Adrenal: Pheochromocytoma or Malignant Pheochromocytoma (b)	5/50 (10)	10/50 (20)	10/50 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.000	2.000
Lower Limit		0.675	0.675
Upper Limit		6.944	6.944
Weeks to First Observed Tumor	91	97	89

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Preputial Gland: Carcinoma, NOS (b)	2/50 (4)	4/50 (8)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.000	1.500
Lower Limit		0.301	0.180
Upper Limit		21.316	17.329
Weeks to First Observed Tumor	106	103	105
Testis: Interstitial-cell Tumor (b)	45/48 (94)	43/49 (88)	46/49 (94)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.936	1.001
Lower Limit		0.843	0.907
Upper Limit		1.082	1.106
Weeks to First Observed Tumor	87	85	66

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sulfisoxazole by Gavage (a)

(continued)

(a) Dosed groups received 100 or 400 mg/kg.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the vehicle-control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the vehicle-control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sulfisoxazole by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Hematopoietic System:			
Monocytic Leukemia (b)	3/50 (6)	3/50 (6)	9/50 (18)
P Values (c,d)	P = 0.016	N.S.	N.S.
Relative Risk (f)		1.000	3.000
Lower Limit		0.140	0.803
Upper Limit		7.133	16.338
Weeks to First Observed Tumor	98	106	91
Hematopoietic System: Malignant			
Lymphocytic Lymphoma or Monocytic Leukemia (b)	4/50 (8)	3/50 (6)	9/50 (18)
P Values (c,d)	P = 0.033	N.S.	N.S.
Relative Risk (f)		0.750	2.250
Lower Limit		0.115	0.676
Upper Limit		4.206	9.394
Weeks to First Observed Tumor	98	106	91

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Hematopoietic System: All			
Lymphoma or Leukemia (b)	6/50 (12)	3/50 (6)	9/50 (18)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.500	1.500
Lower Limit		0.085	0.517
Upper Limit		2.200	4.749
Weeks to First Observed Tumor	98	106	91
Pituitary: Chromophobe			
Adenoma (b)	18/49 (37)	19/50 (38)	17/50 (34)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.034	0.926
Lower Limit		0.590	0.513
Upper Limit		1.821	1.667
Weeks to First Observed Tumor	75	77	77

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma (b)	12/50 (24)	16/50 (33)	15/50 (30)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.333	1.250
Lower Limit		0.663	0.611
Upper Limit		2.754	2.615
Weeks to First Observed Tumor	88	99	103
Preputial Gland: Carcinoma, NOS (b)	3/50 (6)	0/50 (0)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.333
Lower Limit		0.000	0.006
Upper Limit		1.663	3.983
Weeks to First Observed Tumor	94	--	106

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Preputial Gland: Carcinoma or Adenoma, NOS (b)	3/50 (6)	0/50 (0)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.667
Lower Limit		0.000	0.058
Upper Limit		1.663	5.570
Weeks to First Observed Tumor	94	--	106
Uterus: Endometrial Stromal Polyp (b)	5/49 (10)	6/49 (12)	8/48 (17)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.200	1.633
Lower Limit		0.327	0.509
Upper Limit		4.654	5.913
Weeks to First Observed Tumor	106	106	95

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sulfisoxazole by Gavage (a)

(continued)

(a) Dosed groups received 100 or 400 mg/kg.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the vehicle-control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the vehicle-control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED SULFISOXAZOLE BY GAVAGE

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sulfisoxazole by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Integumentary System:			
Fibrosarcoma of the Subcutaneous Tissue (b)	4/50 (8)	5/50 (10)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.250	0.765
Lower Limit		0.286	0.118
Upper Limit		5.954	4.288
Weeks to First Observed Tumor	100	80	92
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	4/50 (8)	5/50 (10)	0/49 (0)
P Values (c,d)	P = 0.029 (N)	N.S.	N.S.
Relative Risk (f)		1.250	0.000
Lower Limit		0.286	0.000
Upper Limit		5.954	1.100
Weeks to First Observed Tumor	73	104	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Hematopoietic System: All Lymphoma (b)	3/50 (6)	8/50 (16)	5/49 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.667	1.701
Lower Limit		0.685	0.351
Upper Limit		14.816	10.426
Weeks to First Observed Tumor	90	77	104
Hematopoietic System: All Lymphoma or Leukemia (b)	4/50 (8)	8/50 (16)	5/49 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.000	1.276
Lower Limit		0.576	0.292
Upper Limit		8.539	6.070
Weeks to First Observed Tumor	89	77	104

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
All Sites: Hemangiosarcoma (b)	5/50 (10)	1/50 (2)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.200	0.612
Lower Limit		0.004	0.100
Upper Limit		1.699	2.967
Weeks to First Observed Tumor	63	100	63
All Sites: Hemangiosarcoma or Hemangioma (b)	5/50 (10)	2/50 (4)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.400	0.612
Lower Limit		0.040	0.100
Upper Limit		2.313	2.967
Weeks to First Observed Tumor	63	100	63

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	15/50 (30)	13/50 (26)	20/49 (41)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.867	1.361
Lower Limit		0.426	0.755
Upper Limit		1.741	2.493
Weeks to First Observed Tumor	100	93	71
Liver: Hepatocellular Carcinoma or Adenoma (b)	15/50 (30)	13/50 (26)	21/49 (43)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.867	1.429
Lower Limit		0.426	0.802
Upper Limit		1.741	2.592
Weeks to First Observed Tumor	100	93	71

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Adrenal: Pheochromocytoma	2/49 (4)	5/49 (10)	0/49 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.500	0.000
Lower Limit		0.433	0.000
Upper Limit		25.265	3.379
Weeks to First Observed Tumor	104	93	--

(a) Dosed groups received 500 or 2,000 mg/kg.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the vehicle-control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the vehicle-control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Sulfisoxazole by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	0/49 (0)	1/50 (2)	5/50 (10)
P Values (c,d)	P = 0.006	N.S.	P = 0.030
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.053	1.237
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor		105	96
Hematopoietic System: All Lymphoma (b)	16/49 (33)	16/50 (32)	20/50 (40)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.980	1.225
Lower Limit		0.521	0.690
Upper Limit		1.847	2.205
Weeks to First Observed Tumor	77	73	71

F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Hematopoietic System: All			
Lymphoma or Leukemia (b)	17/49 (35)	16/50 (32)	20/50 (40)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.922	1.153
Lower Limit		0.496	0.658
Upper Limit		1.709	2.040
Weeks to First Observed Tumor	77	73	71
Liver: Hepatocellular			
Carcinoma (b)	0/49 (0)	5/50 (10)	2/50 (4)
P Values (c,d)	N.S.	P = 0.030	N.S.
Departure from Linear Trend (e)	P = 0.019		
Relative Risk (f)		Infinite	Infinite
Lower Limit		1.237	0.290
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor		103	105

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	2/42 (5)	1/44 (2)	1/31 (3)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.477	0.677
Lower Limit		0.008	0.012
Upper Limit		8.824	12.354
Weeks to First Observed Tumor	104	105	105
Mammary Gland: Adenocarcinoma, NOS (b)	5/49 (10)	1/50 (2)	0/50 (0)
P Values (c,d)	P = 0.018 (N)	N.S.	P = 0.027 (N)
Relative Risk (f)		0.196	0.000
Lower Limit		0.004	0.000
Upper Limit		1.665	0.777
Weeks to First Observed Tumor	104	105	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Sulfisoxazole by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
All Sites: Hemangioma or Hemangiosarcoma (b)	2/49 (4)	4/50 (8)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.960	0.490
Lower Limit		0.296	0.008
Upper Limit		20.886	9.103
Weeks to First Observed Tumor	104	105	105

(a) Dosed groups received 500 or 2,000 mg/kg.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the vehicle-control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is the indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group when P less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the vehicle-control group.

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

August 31, 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 Sulfisoxazole for carcinogenicity.

The primary reviewer noted that Sulfisoxazole is a widely used antibiotic for urinary tract infections. She agreed with the conclusion in the report that Sulfisoxazole was not carcinogenic, under the conditions of test. She briefly described the experimental design and noted the absence of any unusual highlights in the conduct or results of the study. The primary reviewer remarked on the lack of toxicity displayed in treated rats and mice, suggesting that maximum tolerated doses may not have been achieved.

The secondary reviewer agreed with the conclusion in the report that Sulfisoxazole was not carcinogenic, under the conditions of test. Although the study was adequately conducted, he noted the four-fold difference in dose levels, in both treated rats and mice. He commented on the increased incidence of lung tumors in treated female mice, which appeared to be dose-related, and the negative association for these tumors among treated male rats. The secondary reviewer concluded that the study was a valid test for the carcinogenicity of Sulfisoxazole and that the compound would not appear to pose a risk to humans.

A motion was approved unanimously that the report on the bioassay of Sulfisoxazole be accepted as written.

Members present were:

Arnold Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
(Kenneth Wilcox, Michigan State Health Department, submitted a written review)

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

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