NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 457

TOXICOLOGY AND CARCINOGENESIS STUDIES OF SALICYLAZOSULFAPYRIDINE

(CAS NO. 599-79-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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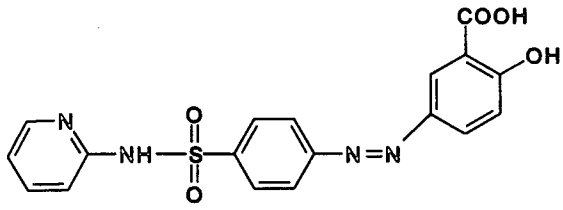
ABSTRACT



SALICYLAZOSULFAPYRIDINE

CAS No. 599-79-1

Chemical Formula: $C_{18}H_{14}N_4O_5S$ Molecular Weight: 398.39

Synonyms: 2-Hydroxy-5-[[4-[2-(pyridinylamino)sulfonyl]phenyl]azo]benzoic acid; 4-(pyridyl-2-amidosulfonyl)-3′-carboxy-4′-hydroxyazobenzene; 5-[4-(2-pyridylsulfamoyl)phenylazo]-2-hydroxybenzoic acid; 5-[*p*-(2-pyridylsulfamoyl)phenylazo]salicylic acid; salazosulfapyridine; sulfasalazine; sulphasalazine

Trade names: Azopyrin, Azulfidine, Benzosulfa, Colo-Pleon, Reupirin, Salazopyrin

Salicylazosulfapyridine is widely used for the treatment of ulcerative colitis and Crohn's disease. It has been beneficial in the treatment of psoriasis and rheumatoid arthritis, and it has been used in veterinary medicine for the treatment of granulomatous colitis. Salicylazosulfapyridine was nominated for toxicity and carcinogenicity testing by the National Cancer Institute on the basis of its widespread use in humans and because it is a representative chemical from a class of aryl sulfonamides. Salicylazosulfapyridine is a suspect carcinogen because reductive cleavage of the azo linkage yields a *p*-amino aryl sulfonamide (sulfapyridine), and a related *p*-amino aryl sulfonamide (sulfamethoxazole) has been shown to produce thyroid neoplasms in rats. Toxicology and carcinogenicity studies were conducted in F344/N rats and B6C3F$_1$ mice. Rats and mice were administered salicylazosulfapyridine (96% to 98% pure) in corn oil by gavage for 16 days, 13 weeks, or 2 years. The gavage route of administration was selected for these studies because it approximates the typical route of human exposure to the chemical. Genetic toxicology studies were conducted *in vitro* in *Salmonella typhimurium* and cultured Chinese hamster ovary cells and *in vivo* in rat and mouse bone marrow and mouse peripheral blood cells.

16-Day Study in Rats

Groups of five male and five female rats were administered 0, 675, 1,350, or 2,700 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for 16 days excluding weekends. All rats survived to the end of the study. With the exception of the 675 mg/kg male group, the final mean body weights of all dosed groups of males and females were significantly lower than those of controls. Mean body weight gains of all dosed groups were less than those of controls. Clinical findings included ruffled fur and distended abdomens in male and female rats receiving 2,700 mg/kg.

Hypothyroidism, evidenced by decreased serum triiodothyronine and thyroxine concentrations and increased thyroid-stimulating hormone concentrations, occurred in 2,700 mg/kg male and female rats. The absolute and relative thymus weights of male rats receiving 1,350 or 2,700 mg/kg and female rats

receiving 2,700 mg/kg were significantly lower than those of controls.

At necropsy, all dosed rats had enlarged cecae/large intestines. Male rats receiving 1,350 mg/kg and male and female rats receiving 2,700 mg/kg had red, enlarged thyroid glands. Chemical-related microscopic lesions were present in the forestomach, thymus, thyroid gland, and pituitary gland. Minimal to mild hyperplasia of the forestomach mucosa was present in the 1,350 and 2,700 mg/kg male and female groups. Lymphoid depletion was observed in the thymus of three male and three female rats in the 2,700 mg/kg groups. Male and female rats receiving 1,350 and 2,700 mg/kg had thyroid gland follicular cell hyperplasia and an increase in thyroid-stimulating hormone producing cells in the pars distalis of the pituitary gland.

16-Day Study in Mice

Groups of five male and five female mice were administered 0, 675, 1,350, or 2,700 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for 16 days excluding weekends. There were no chemical-related deaths, and final mean body weights of dosed mice were similar to those of controls. No chemical-related clinical findings were noted for male or female mice. There were no differences in triiodothyronine, thyroxine, or thyroid-stimulating hormone concentrations between dosed and control mice. There were no biologically significant differences in absolute or relative organ weights between dosed and control male and female mice. At necropsy, male mice receiving 2,700 mg/kg had enlarged cecae/large intestines. There were no biologically significant histopathologic lesions attributed to salicylazosulfapyridine administration.

13-Week Study in Rats

Groups of 10 male and 10 female rats were administered 0, 84, 168.8, or 337.5 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for 13 weeks. All rats survived to the end of the study. The final mean body weights of dosed male rats were similar to those of controls; the final mean body weights and body weight gains of dosed females were significantly lower than those of controls. No chemical-related clinical findings were noted in dosed male or female rats during the 13-week study. No significant differences in hematology or urinalysis parameters between control and dosed rats were observed. The absolute and relative right kidney weights of 337.5 mg/kg females were significantly greater than those of controls.

At necropsy, some 337.5 mg/kg male rats had red, enlarged thyroid glands. Histopathologic changes were noted primarily in the thyroid gland and pituitary gland of males and females in the 337.5 mg/kg groups. The thyroid gland lesions observed were similar to those present in the 16-day study. Nine male rats receiving 168.8 mg/kg and ten male and seven female rats receiving 337.5 mg/kg had minimal but consistent changes in thyroid gland follicular cells. In the pituitary gland of 337.5 mg/kg males and females, the thyroid-stimulating hormone producing cells were enlarged and contained pale-staining cytoplasm and prominent Golgi complexes. Decreased serum triiodothyronine and thyroxine concentrations and increased thyroid-stimulating hormone concentration, similar to differences observed in the 16-day study, occurred in 337.5 mg/kg male rats; thyroid hormone concentrations were not affected in female rats.

Sperm motility of all dosed groups of males was significantly lower than that of controls. Vaginal cytology parameters of dosed groups of females were similar to those of controls.

13-Week Study in Mice

Groups of 10 male and 10 female mice were administered 0, 675, 1,350, or 2,700 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for 13 weeks. All mice survived to the end of the study. The final mean body weights of dosed male and female mice were similar to those of controls. The mean body weight gains of 1,350 and 2,700 mg/kg male mice were less than that of controls. No chemical-related clinical findings were noted in dosed male or female mice during the 13-week study.

There was minimal evidence of a responsive anemia in mice in the 13-week study. The anemia was probably related to a methemoglobinemia. There were minimal decreases in thyroxine concentration in all dosed groups of male and female mice in the 13-week

study. There were, however, no differences in triiodothyronine and thyroid-stimulating hormone concentrations between dosed and control animals.

Absolute and relative liver weights of all groups of dosed male and female mice were significantly greater than those of controls. There were no chemical-related gross lesions. Microscopic evaluation of the liver revealed centrilobular hypertrophy in five 1,350 mg/kg and all 2,700 mg/kg male mice.

The right cauda weight of the 1,350 mg/kg group and the right epididymis weights of all dose groups were significantly lower than those of controls. There was no evidence of chemical-related alteration in the vaginal cytology parameters of female mice.

2-Year Study in Rats

Groups of 60 male and 60 female rats were administered 84, 168, or 337.5 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for up to 105 weeks. Groups of 70 male and 60 female rats were administered the corn oil vehicle by gavage for up to 105 weeks. A stop-exposure group of 70 male rats was administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 6 months, after which animals received the corn oil vehicle by gavage for the remainder of the 2-year study. Ten animals from the vehicle control male group and 10 animals from the 337.5 mg/kg stop-exposure group were evaluated at 6 months; 10 animals from each core-study group were evaluated at 15 months.

Survival, Body Weights, and Clinical Chemistry

Survival of 337.5 mg/kg male core-study rats was significantly lower than that of controls; survival of 84 and 168 mg/kg core-study males, all groups of dosed females, and the stop-exposure male group was similar to controls. Mean body weights of core-study males and stop-exposure males were similar to controls throughout the study. From week 45 to the end of the study, females in the 337.5 mg/kg group had mean body weights that were lower than those of controls. The serum thyroxine concentration in 337.5 mg/kg core-study males at study termination was minimally lower than that of controls; the serum thyroid-stimulating hormone, triiodothyronine, and reverse triiodothyronine concentrations of dosed males and females were similar to those of controls.

Pathology Findings

Administration of salicylazosulfapyridine for 2 years was associated with transitional epithelial papilloma in the urinary bladder of male rats and may have been associated with transitional epithelial papilloma of the kidney and of the urinary bladder of female rats. Nonneoplastic effects in the urinary bladder and kidney of male and female rats and in the spleen of male rats were also observed. Dosed male and female rats had increased incidences of grossly and microscopically observed urinary bladder concretions (diagnosed grossly as calculi at necropsy); male and female rats that developed transitional epithelial papillomas of the urinary bladder had grossly observed concretions (calculi) in the urinary bladder at necropsy. The microscopic neoplastic and nonneoplastic urinary bladder and kidney effects observed in dosed male rats during the 2-year continuous study did not occur in dosed rats during the 2-year stop-exposure study, nor were there gross observations of concretions (calculi) at necropsy. The incidences of mononuclear cell leukemia in male and female rats were decreased. The thyroid gland hyperplasia seen in the 13-week study was not observed in the 2-year study, and there was no evidence of chemical-related thyroid gland follicular cell adenomas or carcinomas.

2-Year Study in Mice

Groups of 60 male and 60 female mice were administered 0, 675, 1,350, or 2,700 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for up to 104 weeks. Ten animals from each group were evaluated at 15 months.

Survival, Body Weights, and Clinical Chemistry

Survival of all the dosed groups of male and female mice was similar to that of controls. Mean body weights of 675 and 1,350 mg/kg male and female mice were similar to controls throughout the study. From week 12 to the end of the study, 2,700 mg/kg male mice had mean body weights that were lower than those of controls. From week 14 to the end of the study, the 2,700 mg/kg female mice had mean body weights that were lower than those of controls.

There were no chemical-related differences in triiodothyronine, reverse triiodothyronine, thyroxine, or thyroid-stimulating hormone concentrations between dosed and control mice at the 15-month evaluation.

Pathology Findings

Exposure of mice to salicylazosulfapyridine in corn oil by gavage for 2 years was associated with increased incidences of hepatocellular neoplasms in males and females. Nonneoplastic effects in the liver and spleen were also observed in male and female mice. The incidences of forestomach squamous cell papilloma in females and forestomach hyperplasia in males and females were decreased.

GENETIC TOXICOLOGY

Salicylazosulfapyridine was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These *in vitro* assays were performed with and without S9 metabolic activation enzymes.

Results from *in vivo* mouse bone marrow chromosomal aberration tests were uniformly negative, while results of micronucleus assays performed on male or female mice exposed to salicylazosulfapyridine for periods ranging from 3 days to 13 weeks were positive. Micronucleus tests in male mice for shorter exposure times (1 to 2 days) yielded negative or very weakly positive results. A three-treatment (72-hour exposure time) micronucleus test performed in male rats yielded equivocal results. Overall, results of these *in vivo* assays indicate that salicylazosulfapyridine is capable of inducing chromosomal damage, possibly in the form of aneuploidy, in mouse bone marrow cells after multiple administrations.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of salicylazosulfapyridine in male and female F344/N rats based on increased incidences of neoplasms in the urinary tract. There was an increased incidence of transitional epithelial papilloma of the urinary bladder in males and a low incidence of rare transitional epithelial papillomas of the kidney and of the urinary bladder in females. There was *clear evidence of carcinogenic activity* of salicylazosulfapyridine in male and female B6C3F_1 mice based on increased incidences of hepatocellular neoplasms.

Increased incidences of nonneoplastic lesions of the urinary bladder and kidney in male and female rats and of the spleen in male rats were observed. Increased incidences of nonneoplastic lesions of the liver and spleen in male and female mice were observed.

Decreased incidences of mononuclear cell leukemia in male and female rats were related to salicylazosulfapyridine administration. Decreased incidences of forestomach squamous cell papilloma in female mice and forestomach hyperplasia in male and female mice were related to salicylazosulfapyridine administration.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Salicylazosulfapyridine

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 84, 168, or 337.5 mg/kg, or 337.5 mg/kg stop-exposure	0, 84, 168, or 337.5 mg/kg	0, 675, 1,350, or 2,700 mg/kg	0, 675, 1,350, or 2,700 mg/kg
Body weights	Dosed groups similar to controls	337.5 mg/kg group lower than controls	2,700 mg/kg group lower than controls	2,700 mg/kg group lower than controls
Survival rates	35/50, 33/50, 31/50, 23/50, 30/50	35/50, 34/50, 31/50, 26/50	40/50, 41/50, 41/50, 46/50	41/50, 41/50, 37/50, 38/50
Nonneoplastic effects	Urinary bladder: mucosal hyperplasia (0/50, 0/49, 14/50, 41/50, 1/47); concretion (0/50, 0/49, 1/50, 10/50, 0/47); dilatation (0/50, 1/49, 2/50, 7/50, 0/47) Kidney: concretion (0/50, 1/50, 13/50, 33/50, 0/50); transitional epithelial hyperplasia (10/50, 10/50, 20/50, 43/50, 4/50); hydronephrosis (0/50, 1/50, 1/50, 28/50, 0/50); mineralization (3/50, 10/50, 11/50, 13/50, 3/50); renal tubule dilatation (0/50, 1/50, 1/50, 11/50, 3/50) Spleen: hemosiderin pigment (14/50, 15/50, 15/50, 30/50, 13/50); hematopoietic cell proliferation (14/50, 15/50, 17/50, 23/50, 14/50)	Urinary bladder: mucosal hyperplasia (2/49, 0/50, 4/50, 12/50) Kidney: concretion (0/50, 9/50, 34/50, 37/50); transitional epithelial hyperplasia (3/50, 7/50, 23/50, 43/50); hydronephrosis (0/50, 0/50, 3/50, 10/50); nephropathy (34/50, 36/50, 41/50, 44/50)	Liver: eosinophilic foci (6/50, 19/50, 20/50, 22/50) Spleen: hematopoietic cell proliferation (11/50, 16/50, 20/49, 13/50); hemosiderin pigment (2/50, 25/50, 32/49, 47/50)	Liver: eosinophilic foci (5/50, 17/50, 15/50, 19/49) Spleen: hematopoietic cell proliferation (7/50, 21/50, 19/50, 23/49); hemosiderin pigment (14/50, 37/50, 39/50, 46/49)
Neoplastic effects	Urinary bladder: transitional epithelial papilloma (0/50, 0/49, 2/50, 6/50, 0/47)	Kidney: transitional epithelial papilloma (0/50, 0/50, 0/50, 2/50) Urinary bladder: transitional epithelial papilloma (0/49, 0/50, 2/50, 0/50)	Liver: hepatocellular adenoma (13/50, 32/50, 28/50, 42/50); hepatocellular adenoma or carcinoma (24/50, 38/50, 38/50, 44/50)	Liver: hepatocellular adenoma (12/50, 28/50, 25/50, 28/49); hepatocellular carcinoma (2/50, 10/50, 10/50, 9/49); hepatocellular adenoma or carcinoma (14/50, 32/50, 28/50, 29/49)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Salicylazosulfapyridine (continued)

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Decreased incidences	Multiple organs: mononuclear cell leukemia (13/50, 18/50, 12/50, 3/50, 10/50)	Multiple organs: mononuclear cell leukemia (14/50, 9/50, 8/50, 3/50)	Forestomach: hyperplasia (18/50, 11/50, 11/49, 10/50)	Forestomach: squamous cell papilloma (5/50, 1/50, 1/50, 0/50); hyperplasia (12/50, 6/49, 4/50, 4/49)
Level of evidence of carcinogenic activity	Some evidence	Some evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA97, TA98, TA100, and TA1535			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Mouse bone marrow *in vivo*:	Negative in standard and nonstandard protocols			
Micronucleated erythrocytes				
Mouse bone marrow *in vivo*:	Positive in two standard protocol assays and in kinetochore assay			
Rat bone marrow *in vivo*:	Equivocal			
Mouse peripheral blood *in vivo*:	Positive			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on salicylazosulfapyridine on 20 June 1995 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

Arnold L. Brown, M.D., Chairperson
University of Wisconsin Medical School
Madison, WI

Thomas L. Goldsworthy, Ph.D., Principal Reviewer
Department of Environmental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Meryl H. Karol, Ph.D.
Department of Environmental Occupational Health
University of Pittsburgh
Pittsburgh, PA

Curtis D. Klaassen, Ph.D.
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Claudia S. Miller, M.D.
University of Texas Health Sciences Center
San Antonio, TX

Janardan K. Reddy, M.D.
Department of Pathology
Northwestern University Medical School
Chicago, IL

Irma Russo, M.D., Principal Reviewer
Fox Chase Cancer Center
Philadelphia, PA

Louise Ryan, Ph.D.
Division of Biostatistics
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D.
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Mary Jo Vodicnik, Ph.D.
Lilly MSG Development Center
Belgium

Jerrold M. Ward, D.V.M., Ph.D., Principal Reviewer
National Cancer Institute
Frederick, MD

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 20 June 1995, the Technical Report on the toxicology and carcinogenesis studies of salicylazosulfapyridine received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. F.W. Kari, NIEHS, introduced the toxicology and carcinogenesis studies of salicylazosulfapyridine by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. Dr. Kari reported that the gross and morphological evidence of thyroid gland hyperplasia in the 16-day and 13-week studies in rats was confirmed by clinical chemistry and indicated a derangement of the pituitary-thyroid axis. As a result, a stop-exposure study was designed in male rats, which were exposed to the highest dose of salicylazosulfapyridine for six months and given the corn oil vehicle for the remainder of the 2-year term. The expected thyroid gland lesions were not seen in any of the animals carried to 2 years. The proposed conclusions for the 2-year studies were *some evidence of carcinogenic activity* in male and female F344/N rats and *clear evidence of carcinogenic activity* in male and female B6C3F$_1$ mice.

Dr. Ward, a principal reviewer, agreed with the proposed conclusions. He thought that male rats might have tolerated a higher dose. Dr. Kari agreed. Dr. Ward said the stop-exposure studies had limited significance in that neither preneoplastic nor neoplastic lesions were shown to have occurred at 26 weeks. Dr. M.R. Elwell, NIEHS, commented that based on the hyperplasia and thyroid gland effects at 13 weeks, it was reasonable to expect that they would be present at 26 weeks.

Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions but had concerns with the dose selection for mice. Given that liver weight changes and centrilobular hypertrophy were observed in all doses in the 13-week studies, he questioned why a dose at which changes had not been seen was not chosen for the 2-year studies. Dr. Elwell said that at the low dose in the 13-week studies, hypertrophy could not be detected morphologically in female mice, and there was only a 10% to 15% increase in liver weight in males. Dr. Goldsworthy commented that the same rationale given for stop-exposure studies in rats could have been applied to the mouse and mouse liver neoplasms. Dr. Kari reported that at the time the studies were designed, the thyroid gland hyperplasia appeared to be the predominant effect from salicylazosulfapyridine, and further, there was great interest in the role of goitrogenic compounds such as the aryl sulfonamides in endocrine disruption and thyroid gland neoplasia.

Dr. Russo, the third principal reviewer, agreed with the proposed conclusions. She noted that review of the literature indicated the probability of fetal damage in humans from salicylazosulfapyridine, as well as transplacental transport and secretion in milk. Lack of data on absorption and disposition of salicylazosulfapyridine in pregnant experimental animals suggests that future studies of transplacental effects would be desirable.

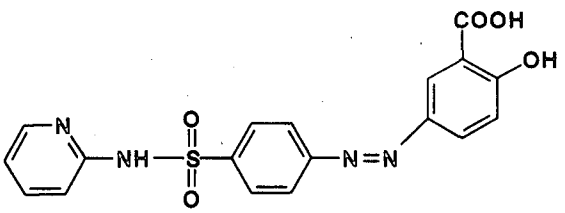
A discussion ensued about the renal neoplasms and their association with bladder calculi (concretions) in rats. Dr. J.R. Bucher, NIEHS, noted that this association was strongly supported by the fact that every animal with a bladder or kidney papilloma also had grossly observable calculi. Dr. Reddy inquired as to the nature of the concretions. Dr. Kari responded that they were spiculated in nature, but were not chemically analyzed. The calculi were presumed to be precipitated drug and/or metabolites. Dr. Russo asked how these findings could be extrapolated to humans when the doses in animals were so much greater. Dr. Kari said the experiments in rodents were designed to maximize the probability for identifying toxicity and carcinogenicity. He pointed out that blood levels in the rodents used in these and other studies were discussed in this Technical Report and allow comparison with blood levels reported after maintenance doses in humans. At least for some of the doses, comparable blood levels were observed between the species.

Dr. A. Imondi, Director of Toxicology and Safety Assessment, Pharmacia, Inc., stated that after many

years of extensive clinical use as a therapeutic agent in inflammatory bowel disease and rheumatoid arthritis, there is no evidence that salicylazosulfapyridine causes neoplasia in humans. With regard to positive micronucleus tests observed in mice by the NTP, he cited unpublished studies that indicate folic acid deficiency is involved and increased incidences of micronuclei could be reduced or reversed by folic acid supplements to drug treatment. Dr. Imondi described other unpublished studies showing that salicylazosulfapyridine did not produce increases in DNA adduct formation in target tissues. He concluded that clinical experience indicated no relevance of the NTP neoplasm findings to humans.

Dr. Ward moved that the Technical Report on salicylazosulfapyridine be accepted with the revisions submitted by the panelists and with the conclusions as written. Dr. Russo seconded the motion, which was accepted unanimously with ten votes.

INTRODUCTION



SALICYLAZOSULFAPYRIDINE

CAS No. 599-79-1

Chemical Formula: $C_{18}H_{14}N_4O_5S$ Molecular Weight: 398.39

Synonyms: 2-Hydroxy-5-[[4-[2-(pyridinylamino)sulfonyl]phenyl]azo]benzoic acid; 4-(pyridyl-2-amidosulfonyl)-3′-carboxy-4′-hydroxyazobenzene; 5-[4-(2-pyridylsulfamoyl)phenylazo]-2-hydroxybenzoic acid; 5-[*p*-(2-pyridylsulfamoyl)phenylazo]salicylic acid; salazosulfapyridine; sulfasalazine; sulphasalazine

Trade names: Azopyrin, Azulfidine, Benzosulfa, Colo-Pleon, Reupirin, Salazopyrin

CHEMICAL AND PHYSICAL PROPERTIES

Salicylazosulfapyridine is manufactured as minute, brownish-yellow, odorless crystals. It is slightly soluble in alcohol and practically insoluble in water, benzene, chloroform, and ether. Salicylazosulfapyridine decomposes at 240° to 245° C and has absorption maxima at 237 and 359 nm (*Merck Index*, 1976).

PRODUCTION, USE, AND HUMAN EXPOSURE

Salicylazosulfapyridine is synthesized by coupling diazotized 2-sulfanilamidopyridine with salicylic acid (U.S. Patent No. 2,396,145). Two American firms (American Cyanamid and Salisbury Labs, Inc.) and one Swedish firm (Pharmacia, Inc.) account for all production of this drug. In 1977, United States production was estimated to be greater than 420 kg, and imports in 1978 were 74,000 kg (Pharmacia, Inc., unpublished data). It is estimated that Pharmacia, Inc., produces 80% of all salicylazosulfapyridine used in the United States. Salicylazosulfapyridine has not been found in United States industrial effluents (USEPA, 1979), in drinking water (NAS, 1977), or in European water supplies (Commission of the European Communities, 1976).

National Formulary grade salicylazosulfapyridine contains 93% to 103% active ingredient calculated on a dry weight basis, with a maximum of 0.5% ignitable residue, 0.4% sulfate, 0.014% chloride, 0.002% heavy metals, and 10% maximum weight loss on drying. Salicylazosulfapyridine was approved as a drug (sulfasalazine) by the FDA in June 1950 for the treatment of ulcerative colitis. It has been marketed since then as National Formulary grade sulfasalazine tablets (500 mg) or as an oral suspension (50 mg/mL) containing 95% to 105% of the labeled amount of the active ingredient (PDR, 1992). Enteric-coated tablets are also available.

Salicylazosulfapyridine is widely used for the treatment of ulcerative colitis and Crohn's disease (Badley, 1975; Caprilli *et al.*, 1975; *Goodman and Gilman's*, 1975; Van Hees *et al.*, 1981). In the treatment of mild to moderate ulcerative colitis it is used by itself,

whereas in severe ulcerative colitis and Crohn's disease it is used as an adjunct therapy (Gardner, 1976; Goldstein *et al.*, 1976). Recently, a new topical (enema) preparation of 5-aminosalicylic acid (mesalazine) has been introduced for the treatment of ulcerative colitis (Bruckstein, 1990). The effective therapeutic dose in the active/acute phase of these ailments is 3 to 6 grams per day, while the usual maintenance dose is 2 grams per day (Davies and Rhodes, 1978; Dronfield and Langman, 1978; Riis *et al.*, 1979). Salicylazosulfapyridine has also been beneficial in the treatment of psoriasis (Farr *et al.*, 1990; Gupta *et al.*, 1990), rheumatoid arthritis (McConkey *et al.*, 1980; Bird *et al.*, 1982), and in veterinary medicine for the treatment of granulomatous colitis (*Merck Index*, 1989). Neither age nor gender influences the efficacy of salicylazosulfapyridine for treatment of rheumatoid arthritis (Capell *et al.*, 1993; Wilkieson *et al.*, 1993). In 1982, 1.3 million prescriptions were written for salicylazosulfapyridine; 40% of these were for ulcerative colitis, 21% were for regional enteritis, 18% were for gastroenteritis in humans at least 2 years old, and 9% were for diverticulitis. The cumulative oral exposure in the United States population is estimated to be 33,997 kg/year (NCI/SRI Database, 1983).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

In Sprague-Dawley rats given salicylazosulfapyridine in feed, the majority of the compound is reductively cleaved by gut bacteria to two biologically active moieties: 5-aminosalicylic acid and sulfapyridine (Peppercorn and Goldman, 1972). Riboflavin has been shown to stimulate the azoreduction of orally administered salicylazosulfapyridine and thus increase the bioavailability of these metabolites in male CD rats (Chungi *et al.*, 1989). Sulfapyridine is well absorbed and eventually excreted via urine, but 5-aminosalicylic acid is poorly absorbed and excreted mainly in feces (Bachrach, 1988).

In male and female B6C3F$_1$ mice, salicylazosulfapyridine rapidly disappeared from blood following intravenous administration of a 5 mg/kg dose with a mean residence time of 0.45 to 0.78 hours (Zheng *et al.*, 1993). The toxicokinetics of salicylazosulfapyridine were also determined following gavage administration of 67.5, 675, 1,350, or 2,700 mg/kg to male and female mice. Bioavailability was 16% to 18% at a dose of 67.5 mg/kg and approximately 3% to 9% for doses of 675 to 2,700 mg/kg. Following oral administration of salicylazosulfapyridine, both sulfapyridine and *N*-acetylsulfapyridine were identified in plasma. The areas under the plasma concentration-time curves of sulfapyridine at all four oral doses were 21- to 32-fold higher than those of salicylazosulfapyridine in male mice and 5- to 25-fold higher in female mice. The maximum plasma concentration (C_{max}) of sulfapyridine was 6 to 8 times higher than C_{max} of salicylazosulfapyridine in male mice and up to 4 times higher in female mice. Elimination rate constants were greater for salicylazosulfapyridine; thus, sulfapyridine was eliminated more slowly than the parent compound, and sulfapyridine accumulated in male and female mice following multiple doses of salicylazosulfapyridine (675, 1,350, and 2,700 mg/kg).

In a companion study with male F344/N rats (NTP, 1994a; Appendix L), plasma elimination rate constants and elimination half lives following a 5 mg/kg intravenous dose were similar to those reported for male B6C3F$_1$ mice. The elimination half-lives ($t_{1/2}$) were 0.53 and 0.54 hours for rats and mice respectively, and the plasma elimination rate constants were 1.47 hr^{-1} and 1.28 hr^{-1} respectively. The area under the plasma concentration-time curve of salicylazosulfapyridine was 2-fold greater in male rats than in male mice, while the systemic body clearance and apparent volume of distribution were 2-fold higher in male mice compared to male rats. These data indicate that male F344/N rats clear salicylazosulfapyridine more slowly and thus retain salicylazosulfapyridine longer than male B6C3F$_1$ mice. Salicylazosulfapyridine and its metabolites were below detectable limits following low dose (67.5 mg/kg) oral administration. Following oral administration of 675 mg/kg salicylazosulfapyridine, the parent compound was detected in plasma at early time points but was undetectable at 12 hours.

No data on salicylazosulfapyridine absorption and disposition in pregnant experimental animals were found in the peer-reviewed literature.

Humans

The clinical pharmacokinetics of salicylazosulfapyridine and its primary metabolites have been reviewed by Tett (1993), and they are summarized here. The metabolism of salicylazosulfapyridine in humans is similar to that previously described in rodents. The metabolic pathway for salicylazosulfapyridine is presented in Figure 1.

Studies in healthy volunteers as well as in patients with ulcerative colitis given single 2 to 4 g oral doses of salicylazosulfapyridine showed detectable blood concentrations of salicylazosulfapyridine within 1.5 hours of dosing and peak concentrations at 3 to 5 hours post-dose (Schröder and Campbell, 1972; Das and Dubin,1976). Both 5-aminosalicylic acid and sulfapyridine (as well as their acetylated derivatives) appear in serum within 3 to 24 hours following a single oral dose. The majority of sulfapyridine is absorbed from the large intestine and is metabolized extensively prior to urinary excretion; in contrast, only a small percentage of 5-aminosalicylic acid is absorbed from the colon, and the remainder is excreted in the feces (Das and Dubin, 1976). 5-Aminosalicylic acid is metabolized to acetylaminosalicylate by *N*-acetylation prior to its urinary excretion (Schröder and Campbell, 1972). The rate at which sulfapyridine is acetylated and hydroxylated is under genetic control (Das and Eastwood, 1975). Patients with a "slow" acetylator phenotype tend to have significantly higher serum concentrations of sulfapyridine and its nonacetylated metabolites. Serum concentrations of sulfapyridine greater than 50 μg/mL appear to be associated with adverse reactions (Azad Khan and Truelove, 1980). In patients with ulcerative colitis, absorption and urinary excretion of salicylazosulfapyridine are not significantly changed compared to healthy controls, while these are reduced for sulfapyridine (Azad Khan *et al.*, 1982).

Salicylazosulfapyridine and its two primary metabolites can cross the placenta as evidenced by detection in umbilical cord blood and amniotic fluids (Azad Kahn and Truelove, 1979; Järnerot *et al.*, 1981). A small amount of salicylazosulfapyridine and sulfapyridine was also detected in breast milk (Järnerot and Into-Malmberg, 1979; Berlin and Yaffe, 1980). No 5-aminosalicylic acid has been detected in maternal plasma or milk or infant urine. Infants have been shown to excrete sulfapyridine and its acetylated and glucuronidated metabolites 1 to 2.5 months after maternal dosing.

Mechanism of Action

The mechanism of action of salicylazosulfapyridine is still under investigation. Originally, it was thought that salicylazosulfapyridine had a particular affinity for colonic connective tissue and serosal membrane (Svartz, 1942). Later, it was shown that both salicylazosulfapyridine and 5-aminosalicylic acid have such an affinity, but sulfapyridine does not (Hanngren *et al.*, 1963). Following identification of the prodrug nature of salicylazosulfapyridine due to its cleavage into active products (Peppercorn and Goldman, 1972), it was proposed that the therapeutic effect was derived from the antibacterial action of sulfapyridine and the anti-inflammatory action of 5-aminosalicylic acid. Even though measurement of sulfapyridine serum concentrations has proven useful in dosage adjustment for salicylazosulfapyridine in patients and the serum concentrations correlate well with beneficial clinical response, the current evidence suggests that 5-aminosalicylic acid is the active therapeutic moiety of salicylazosulfapyridine (Azad Khan *et al.*, 1977; Klotz *et al.*, 1980; Van Hees *et al.*, 1980). There is no evidence for antibacterial action of sulfapyridine because the intestinal microflorae of patients taking salicylazosulfapyridine remain unchanged (*Goodman and Gilman's*, 1975). Ulcerative colitis, the primary indication for salicylazosulfapyridine therapy, is characterized by an acute mucosal inflammation dominated by the random migration and accumulation of polymorphonuclear leukocytes (Hermanowicz and Nawarska, 1981). Because salicylazosulfapyridine and 5-aminosalicylic acid inhibit such random migrations as well as phagocytosis and cellular oxidative metabolism (Molin and Stendahl, 1979), it has been hypothesized that the therapeutic action of 5-aminosalicylic acid could be due to its inhibition of prostaglandin biosynthesis and breakdown (Bakhle, 1980; Hillier *et al.*, 1982) or to its immunosuppressant properties (Molin and Stendahl, 1979; Stenson and Lobos, 1982). Ultimately, salicylazosulfapyridine may be a vehicle that only delivers high concentrations of both 5-aminosalicylic acid and sulfapyridine to the colon (Das and Dubin, 1976; Goldman and Peppercorn, 1973).

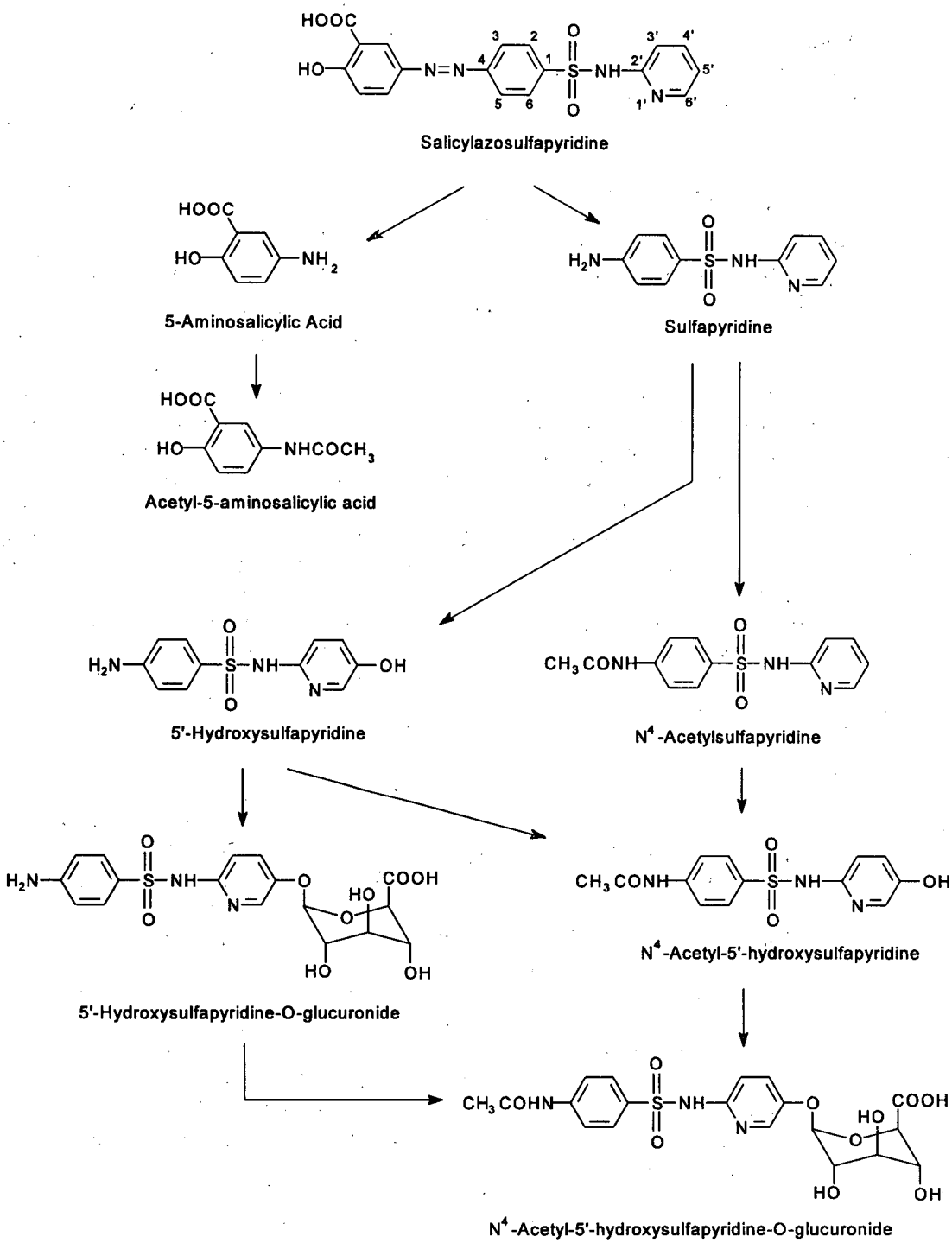


FIGURE 1
Pathways of Salicylazosulfapyridine Metabolism from Das and Dubin (1976)

TOXICITY

Experimental Animals

In mice, the oral LD_{50} for 4-aminosalicylic acid is reported as 4 g/kg body weight and 15 g/kg for sulfapyridine (*Merck Index*, 1976).

Toxic effects of salicylazosulfapyridine therapy in dogs have been reported. Keratoconjunctivitis sicca developed during a 4-year period in 13 dogs; discontinuance of the drug partially resolved the problem (Morgan and Bachrach, 1982).

Humans

It is estimated that more than 25% of patients given 39 mg/kg or more per day of salicylazosulfapyridine develop adverse/toxic effects during therapy. The side effects commonly associated with salicylazosulfapyridine therapy (both in adults and children) have been anorexia, nausea, headache, fever, vomiting, gastric distress, general hypersensitivity reactions (rash, liver function abnormalities), and various hematological abnormalities (Svartz, 1942; Das and Dubin, 1976; Felson *et al.*, 1990). In patients with ulcerative colitis, individuals with the "slow" acetylator phenotype are reported to have increased incidences of salicylazosulfapyridine-induced adverse reactions (Das *et al.*, 1973), whereas in rheumatoid arthritis patients, acetylator phenotype is unrelated to adverse therapeutic outcomes (Chalmers *et al.*, 1990). Several clinical (case) reports have reported other toxic/severe adverse reactions to salicylazosulfapyridine including pancreatitis (Block *et al.*, 1970), renal and hepatic toxicity (Chester *et al.*, 1978), lupus syndrome (Carr-Locke, 1982), folate deficiency (Swinson *et al.*, 1981), male infertility (Toovey *et al.*, 1981), decreased pulmonary function (Eade *et al.*, 1980), neurotoxicity (Smith *et al.*, 1982; Alloway and Mitchell, 1993), lymphadenopathy (Carr-Locke and Ali, 1982), and various hemolytic anemias (aplastic, Heinz body, etc.) (Davies and Palek, 1980; Vilaseca *et al.*, 1980). Most of these adverse reactions were reported to be reversible within a few days to several weeks after the drug was discontinued. Patients with ulcerative colitis or rheumatoid arthritis who benefit from salicylazosulfapyridine therapy but develop hypersensitivity responses are able to resume salicylazosulfapyridine therapy once they have been desensitized via a short withdrawal period (Holdsworth, 1981; Farr *et al.*, 1982; Taffet and Das, 1982; Donovan *et al.*, 1990). Because many of the side effects of salicylazosulfapyridine treatment of inflammatory bowel disease have been associated with the sulfapyridine moiety, 5-aminosalicylic acid was introduced as a new therapeutic agent (mesalazine) (Brimblecombe, 1990).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

When male Sprague-Dawley rats were administered doses up to 617 mg salicylazosulfapyridine/kg body weight per day for 8 weeks, dose-dependent, reversible infertility with a significant reduction in offspring litter size was observed (Ó'Moráin *et al.*, 1984). Male rats exposed to sulfapyridine in feed sired smaller sized litters when mated to untreated virgins than did untreated males. There was no effect on litter size for males exposed to 5-aminosalicylic acid in feed.

No adverse effects on seminal characteristics or libido were observed in 4-year-old beagle dogs during or for 6 weeks after a 6-week oral treatment with 50 mg salicylazosulfapyridine/kg body weight per day (England and Allen, 1993).

Humans

Salicylazosulfapyridine-induced male infertility has been identified (Levi *et al.*, 1979) and confirmed (Toth, 1979; Freeman *et al.*, 1982; Ó'Moráin *et al.*, 1984) in a number of patients being treated for inflammatory bowel diseases. This adverse effect is reversible upon discontinuance of the drug. Although the mechanism of toxicity is not understood, an evaluation of human sperm quality (density, motility, and morphology) in time-course studies indicated that the metabolite sulfapyridine may be directly toxic to developing spermatozoa (Toovey *et al.*, 1981). Embryotoxicity of salicylazosulfapyridine has been suggested in one case in which a young woman given salicylazosulfapyridine during pregnancy delivered (prematurely) an infant with bilateral cleft lip, cleft palate, and severe hydrocephalus (Craxì and Pagliarello, 1980). Other clinical studies, however, have reported no adverse effect of salicylazosulfapyridine on the human fetus following *in utero* exposure (Levy *et al.*, 1981; Mogadam *et al.*, 1981; Vender and Sprio, 1982).

CARCINOGENICITY

Experimental Animals

There is no published literature regarding the evaluation of salicylazosulfapyridine or its metabolites for chronic toxicity or carcinogenicity in rodents, but there are a few carcinogenicity studies of related sulfonamide drugs. In rats, exposure to sulfamethoxazole in feed for 52 or 60 weeks induced thyroid gland neoplasms with lung metastases (Swarm *et al.*, 1973). Withdrawal of sulfamethoxazole from the diet after 6 or 13 weeks of administration resulted in restoration of normal follicular structure in the gland. In contrast, sulfisoxazole was not carcinogenic to Fisher 344 rats or B6C3F$_1$ mice (NCI, 1979). It is believed that various experimental animals (rat, mouse, and dog) are sensitive to a goitrogenic action of sulfonamides, whereas the thyroid gland of monkeys and humans may not be sensitive to this effect (Swarm *et al.*, 1973; Hill *et al.*, 1989; McClain, 1992).

Humans

No epidemiology studies or case reports relating salicylazosulfapyridine to human cancer have been reported in the literature. However, one woman treated with salicylazosulfapyridine and prednisone for ulcerative colitis developed adenocarcinoma of the small intestine 18 years later (Schuringa, 1973). It is known that patients with chronic ulcerative colitis are at increased risk for the development of colon cancer (Reddy *et al.*, 1977).

GENETIC TOXICITY

There have been a limited number of *in vitro* studies conducted with salicylazosulfapyridine and/or its metabolites, and in general, the results indicate that none of these compounds are mutagenic *in vitro*. Neither salicylazosulfapyridine nor its two main metabolites, sulfapyridine and 5-aminosalicylic acid, were active in *Salmonella typhimurium* gene mutation assays, either with or without induced mouse or rat liver S9 enzymes (Voogd *et al.*, 1980; Zeiger *et al.*, 1988). Salicylazosulfapyridine, sulfapyridine, and 5-aminosalicylic acid have also been tested for induction of chromosomal damage in cultured Chinese hamster ovary cells *in vitro*. No increases in sister chromatid exchanges or chromosomal aberrations were observed in cultured Chinese hamster ovary cells treated with salicylazosulfapyridine (Bishop *et al.*, 1990) or 5-aminosalicylic acid (Witt *et al.*, 1992a), either with or without rat liver S9. Sulfapyridine, on the other hand, has been reported to induce small but statistically significant increases in sister chromatid exchanges in the absence of S9; with S9, no increase in sister chromatid exchanges was noted (Witt *et al.*, 1992a). Sulfapyridine did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, either with or without rat liver S9.

Mackay *et al.* (1989) tested salicylazosulfapyridine, sulfapyridine, 5-aminosalicylic acid, and four acetylated and/or hydroxylated metabolites of sulfapyridine and 5-aminosalicylic acid for their ability to induce sister chromatid exchanges and micronuclei in cultured human lymphocytes. In contrast to the results obtained in cultured Chinese hamster ovary cells, salicylazosulfapyridine induced both sister chromatid exchanges and micronuclei in human lymphocytes at the same dose concentrations which yielded negative results in cultured Chinese hamster ovary cells in the absence of S9. Furthermore, sulfapyridine and two acetylated sulfapyridine metabolites induced only sister chromatid exchanges, and 5-aminosalicylic acid (along with its acetylated metabolite) induced neither sister chromatid exchanges nor micronuclei. Thus, salicylazosulfapyridine appears to be clastogenic in cultured human cells but not in cultured Chinese hamster ovary cells.

Salicylazosulfapyridine also appears to have clastogenic activity in human lymphocytes *in vivo*, although studies in humans have suffered from various design flaws and the results cannot be considered unequivocal. Mitelman *et al.* (1980, 1982) concluded that patients undergoing salicylazosulfapyridine therapy exhibited evidence of chromosomal damage after one or more months of treatment. However, interpretation of the results from these studies is complicated by concomitant exposures to other drugs such as metronidazole, lack of pretreatment baseline data, and other confounding factors. More recently, Fox *et al.* (1987) reported that salicylazosulfapyridine induced significant increases in the frequency of sister chromatid exchanges and micronuclei in lymphocytes of patients receiving chronic salicylazosulfapyridine therapy compared to healthy controls. Complicating factors were present in this study as well, including considerable interindividual variability in the frequency of micronuclei.

Several studies in mice have provided further evidence of salicylazosulfapyridine-induced chromosomal damage *in vivo*. Specifically, salicylazosulfapyridine has been reported to induce increased frequencies of micronucleated erythrocytes in peripheral blood cells of male and female mice dosed for 13 weeks by gavage (Bishop *et al.*, 1990). Furthermore, it induced dose-related increases in micronuclei in bone marrow cells of male mice dosed for 2 or 3 days by gavage (Bishop *et al.*, 1990; Witt *et al.*, 1992b). The two primary metabolites of salicylazosulfapyridine were also tested for induction of micronuclei in mouse bone marrow erythrocytes; sulfapyridine, but not 5-aminosalicylic acid, induced a strong, dose-related increase in micronucleated polychromatic erythrocytes when administered either by intraperitoneal injection (Witt *et al.*, 1992a) or by gavage (Witt *et al.*, 1992b). The majority of micronucleated erythrocytes induced by salicylazosulfapyridine and sulfapyridine were shown to contain kinetochores (Witt *et al.*, 1992b). The presence of a kinetochore within a micronucleus is presumed to indicate that the micronucleus contains an entire chromosome, resulting from a failure of mitotic chromosomal segregation, rather than a chromosomal fragment resulting from chromosome breakage. These results imply that salicylazosulfapyridine and sulfapyridine induce aneuploidy in mouse bone marrow erythrocytes.

In summary, salicylazosulfapyridine has not been shown to be mutagenic *in vitro*, but it does appear to induce chromosomal damage, perhaps in the form of aneuploidy, in mammalian cells *in vivo*. The genetically active subunit of the salicylazosulfapyridine molecule is sulfapyridine; 5-aminosalicylic acid, the therapeutically active subunit, does not induce genetic alterations *in vitro* or *in vivo*.

Study Rationale

Salicylazosulfapyridine was nominated for study by the National Cancer Institute on the basis of its extended use by a sizable human population and as a representative chemical from a class of aryl sulfonamides. Salicylazosulfapyridine was a suspected carcinogen because reductive cleavage of the azo linkage yields sulfapyridine, a *p*-amino aryl sulfonamide possessing a heterocylic aromatic nitrogen substituent on the sulfonamide nitrogen. Sulfamethoxazole (a related *p*-amino aryl sulfonamide) has been shown to produce thyroid gland neoplasms in rats (Swarm *et al.*, 1973). Accordingly, salicylazosulfapyridine was recommended to the NTP for carcinogenicity testing.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SALICYLAZOSULFAPYRIDINE

Salicylazosulfapyridine was obtained from Salisbury Labs, Inc., (Charles City, IA), in one lot (1089), which was used during the 16-day and 13-week studies. For the 2-year studies, one lot (61838) was obtained from Pharmacia, Inc. (Piscataway, NJ). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory and confirmed by the study laboratories. Reports on analyses performed in support of the salicylazosulfapyridine studies are on file at the National Institute of Environmental Health Sciences. The methods and results of these studies are detailed in Appendix I.

Both lots of the chemical, an orange powder, were identified as salicylazosulfapyridine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of lots 1089 and 61838 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and high-performance liquid chromatography. For both lots, elemental analyses for carbon, hydrogen, nitrogen, and sulfur agreed with theoretical values. Karl Fischer water analysis indicated 0.50% ± 0.04% water in lot 1089 and 0.5% ± 0.1% water in lot 61838. Functional group titration for lot 1089 by two methods indicated purities of 99.3% ± 0.6% and 100.6% ± 0.8%. Functional group titration for lot 61838 by two methods indicated purities of 100.6% ± 0.3% and 101.0% ± 0.4%. For lot 1089, thin-layer chromatography by two systems indicated a major spot and a trace impurity. For lot 61838, thin-layer chromatography indicated a major spot with a trace and two slight trace impurities by one system. A second system indicated a major spot with two trace impurities and a slight trace impurity. Using a detection wavelength of 254 nm, high-performance liquid chromatography revealed a major peak and three impurities with a combined area of 2.3% relative to the major peak area for lot 1089. When using a detection wavelength of 365 nm, two impurities with a combined area of 1.9% relative to the major peak were observed for lot 1089. High-performance liquid chromatography using a detection wavelength of 254 nm resolved a major peak and two impurity peaks with a combined area of 1.7% relative to the major peak area for lot 61838. When 365 nm was used as the detection wavelength, three impurity peaks were observed with a combined area of 1.2% relative to the major peak for lot 61838. The overall purity was determined to be 96% to 97% for lot 1089 and approximately 98% for lot 61838.

The analytical chemistry laboratory analyzed lot 1089 to determine if it met United States Pharmacopeia XX (USP) purity requirements. The complete battery of USP analyses was performed as a supplement to the chemical characterization of salicylazosulfapyridine. The chemical met the USP requirements for the identification tests, which included infrared and visible absorption spectroscopy. The weight loss on drying was 0.30% ± 0.01%, and the residue on ignition was 0.18% ± 0.04%, both of which met the USP requirements. The chemical met the USP requirements of the chloride, sulfate, and heavy metals tests. The USP purity assay indicated that lot 1089 had a purity of 96.5% ± 1.7%, calculated on the anhydrous basis, relative to the USP salicylazosulfapyridine reference standard, which was consistent with USP requirements.

Each lot was concomitantly analyzed with the USP standard for salicylazosulfapyridine content using a high-performance liquid chromatography system. Relative to the USP standard, lot 1089 was determined to contain 96.3% ± 0.7% salicylazosulfapyridine, and lot 61838 was found to contain 97.0% ± 0.9% salicylazosulfapyridine.

Stability studies of the bulk chemical for lot 1089 performed by the analytical chemistry laboratory indicated that salicylazosulfapyridine was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in sealed amber plastic

bags at 5° C during the 16-day and 13-week studies and in metal cans protected from light at room temperature during the 2-year studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing salicylazosulfapyridine with corn oil to give the required concentrations (Table I1). The dose formulations were prepared weekly during the 16-day studies and every 2 weeks during the 13-week and 2-year studies and stored for up to 3 weeks at 0° ± 5° C in clear (16-day studies) or amber-glass (13-week and 2-year studies) bottles.

Periodic analyses of the dose formulations of salicylazosulfapyridine were conducted at the study laboratories and analytical chemistry laboratory using high-performance liquid chromatography. The dose formulations were analyzed at the beginning of the 16-day studies, and all formulations were within 10% of the target concentrations (Table I2). During the 13-week studies, the dose formulations were analyzed at the beginning, midpoint, and end of the studies, and all formulations were within 10% of the target concentrations (Table I3). During the 2-year studies, the dose formulations were analyzed every 6 to 12 weeks. Of the dose formulations analyzed for the 2-year studies, 98% (103/105) were within 10% of the target concentrations (Table I4). The dose formulations differing by more than 10% from the target concentrations were remixed, and the new dose formulations were found to be within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table I5).

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 10 to 14 days and were 6 weeks old on the first day of the studies. Before initiation of the studies, two male and two female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Groups of five male and five female rats and mice received salicylazosulfapyridine in corn oil by gavage for 12 days at doses of 0, 675, 1,350, or 2,700 mg/kg. Feed and water were available *ad libitum*. Rats were housed five per cage and mice were housed individually. Clinical findings were recorded daily for rats and mice. The animals were weighed initially, at 1 week, and at necropsy. Details of the study design and animal maintenance are summarized in Table 1.

At the end of the 16-day studies, animals were anesthetized with an ultra short-acting barbiturate (Bio-Tal), and blood was collected from the external jugular vein of all animals for clinical chemistry analysis. Serum thyroid hormone levels were measured and quantitated using the NML Tri-Tab RIA Kit (Nuclear Medical Laboratories, Dallas, TX). Reagents were provided by the National Institute of Arthritis, Metabolism and Digestive Diseases. The clinical pathology parameters measured are listed in Table 1. The brain, heart, right kidney, liver, lung, right testis, and thymus were weighed. One-half of the pituitary gland and one-half of the thyroid gland were fixed in a cold fixative suitable for electron microscopic evaluation. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A necropsy and complete histopathologic examination was performed on all rats and mice. Table 1 lists the tissues and organs routinely examined.

13-WEEK STUDIES

The 13-week studies were performed to evaluate the cumulative toxic effects of repeated exposure to salicylazosulfapyridine and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA). On receipt, the rats and mice were 4 weeks old. Rats were quarantined for 11 days (males) or 13 days (females); mice were quarantined for 18 days (males) or 20 days (females). Rats were approximately 6 weeks old and mice were approximately 7 weeks old at the start of the studies. Before initiation of the studies, five male and five female rats and mice were

randomly selected for parasite evaluation and gross observation for evidence of disease.

Groups of 10 male and 10 female rats received salicylazosulfapyridine in corn oil by gavage for 13 weeks at doses of 0, 84, 168.8, or 337.5 mg/kg. Groups of 10 male and 10 female mice received salicylazosulfapyridine in corn oil by gavage for 13 weeks at doses of 0, 675, 1,350, or 2,700 mg/kg. Additional groups of 10 male and 10 female mice received salicylazosulfapyridine in corn oil by gavage for 13 weeks at doses of 0, 675, 1,350, or 2,700 mg/kg and were designated for clinical pathology evaluations. Feed and water were available *ad libitum*. Rats were housed five per cage and mice were housed individually. Clinical findings and body weights were recorded weekly for each animal. Details of the study design and animal maintenance are summarized in Table 1.

After 12 weeks of treatment, animals were placed in individual metabolism cages for a 16-hour urine collection period. Hematology analyses were conducted during week 12 for rats and mice. At the end of the 13-week studies, animals were anesthetized with an ultra short-acting barbiturate (Bio-Tal), and blood was collected from the external jugular vein of rats and core study mice and from special study mice for thyroid hormone analyses. Serum thyroid hormone levels were measured and quantitated using the NML Tri-Tab RIA Kit. Reagents were provided by the National Institute of Arthritis, Metabolism and Digestive Diseases. Clinical pathology parameters which were evaluated are listed in Table 1.

At the end of the 13-week studies, samples were collected for sperm morphology and vaginal cytology evaluations from all rats and mice. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's Sperm Morphology and Vaginal Cytology Evaluations Protocol (NTP, 1983a). For 7 consecutive days before the scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). All core study male rats and mice were processed for sperm morphology at necropsy. Male rats and mice were evaluated for sperm morphology, count, and motility. The right epididymis and right testis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. Four sperm morphology slides were prepared for each animal evaluated. An aliquot of killed sperm suspension was stained in a test tube, spread on a microscope slide under a coverslip, and examined.

A necropsy was performed on all core study animals. The brain, heart, right kidney, liver, lung, right testis, and thymus were weighed. One-half of the pituitary gland and one-half of the thyroid gland were fixed in glutaraldehyde for evaluation by electron microscopy. The remaining halves of the pituitary and thyroid glands and all other tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all core study rats and mice. Table 1 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 60 male and 60 female rats were administered 84, 168, or 337.5 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for 103 weeks (males) or 105 weeks (females). Groups of 70 male and 60 female rats were administered the corn oil vehicle by gavage for up to 105 weeks. Groups of 60 male and 60 female mice were administered 0, 675, 1,350, or 2,700 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for 103 weeks

(males) or 104 weeks (females). Ten male and ten female rats and mice from each group were evaluated at 15 months.

Stop-Exposure Evaluation

A group of 70 male rats was administered 337.5 mg salicylazosulfapyridine/kg body weight in corn oil by gavage for 26 weeks; at 26 weeks, the salicylazosulfapyridine was replaced with corn oil for the remainder of the study. Ten vehicle control and ten rats in the 337.5 mg/kg group were evaluated at 6 and 15 months. The stop-exposure evaluation with recovery period was designed to allow for assessment of the potential for salicylazosulfapyridine-induced lesions to progress or regress over the 2-year study.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA), for use in the 2-year studies. On receipt, the animals were approximately 4 weeks old. The animals were quarantined for 11 or 13 days and were approximately 6 weeks old on the first day of the studies. Before the initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At 18 months, five male and three female rats were selected for a similar health check. Up to five male and five female rats and mice were used for serology screening at approximately 6-month intervals. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats were housed five per cage, and mice were housed individually. Feed and water were available *ad libitum*. Rat cages were changed twice weekly, and mouse cages were changed once weekly. Racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

Animals were observed twice daily. Clinical findings and body weights were recorded at the beginning of the 2-year studies, once weekly for the first 14 weeks, monthly thereafter, and at terminal sacrifice.

A complete necropsy and microscopic examination were performed on all rats and mice. At the 6-month stop-exposure interim evaluation, the right kidney, liver, spleen, right testis, and thyroid gland were weighed. At the 15-month interim evaluation, the right kidney, liver, spleen, left testis (rats), right testis, and thyroid gland were weighed. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

At the 6-month interim evaluation, blood was collected for thyroid hormone assays from the retroorbital sinus of 10 male control rats and 10 male rats from the 337.5 mg/kg stop-exposure group. Up to 10 male rats and mice from the control and 337.5 mg/kg (rats) and 2,700 mg/kg (mice) groups were evaluated for thyroid hormone alterations at 15 months. Up to 10 male and 10 female rats and mice from each group and 10 male rats from the stop-exposure group were evaluated for thyroid hormone alterations at the end of the study. The groups evaluated are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed selected neoplasms and nonneoplastic lesions.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment

pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of quality assessment pathologists, the PWG chairperson, and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Salicylazosulfapyridine

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)	Southern Research Institute (Birmingham, AL)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Frederick Cancer Research Facility (Frederick, MD)	Simonsen Laboratories, Inc. (Gilroy, CA)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies		
10-14 days	Rats: 11 days (males) or 13 days (females) Mice: 18 days (males) or 20 days (females)	Stop-exposure evaluation: 11 days Core study: Rats: 11 days Mice: 11 or 13 days
Average Age When Studies Began		
6 weeks	Rats: 6 weeks Mice: 7 weeks	Stop-exposure evaluation: 6 weeks Core study: 7 weeks
Date of First Dose		
Rats: 23 September 1985 Mice: 25 September 1985	Rats: 31 March (males) or 2 April (females) 1986 Mice: 7 April (males) or 9 April (females) 1986	Stop-exposure evaluation: 12 December 1988 Core study: Rats: 12 December 1988 Mice: 3 January 1989
Duration of Dosing		
16 days, 5 days/week	13 weeks, 5 days/week	Stop-exposure evaluation: 26 weeks, 5 days/week; then corn oil gavage 5 days/week for the remainder of the study Core study: Rats: 103 weeks (males), or 105 weeks (females), 5 days/week Mice: 103 weeks (males), or 104 weeks (females), 5 days/week
Date of Last Dose		
Rats: 7 October (males) or 8 October (females) 1985 Mice: 9 October (males) or 10 October (females) 1985	Rats: 29-30 June (males) or 1-2 July (females) 1986 Mice: 7-8 July (males) or 9-10 July (females) 1986	Rats: 30 November (males) or 12 December (females) 1990 Mice: 21 December (males) or 28 December (females) 1990

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Salicylazosulfapyridine (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Necropsy Dates		
Rats: 8 October (males) or 9 October (females) 1985 Mice: 10 October (males) or 11 October (females) 1985	Rats: 30 June-1 July (males) or 2-3 July (females) 1986 Mice: 8-9 July (males) or 10-11 July (females) 1986	Stop-exposure evaluation: 26-week interim evaluation: 12 June 1989 Core study: Rats: 15-Month interim evaluation: 12-13 March (males) or 14-15 March (females) 1990 Terminal sacrifice: 10-14 December (males) or 19-21 December (females) 1990 Mice: 15-Month interim evaluation: 3 April (males) or 4 April (females) 1990 Terminal sacrifice: 31 December 1990-4 January 1991 (males) or 7-10 January (females) 1991
Average Age at Necropsy		
9 weeks	Rats: 19 weeks Mice: 20 weeks	Stop-exposure evaluation: 26-week interim evaluation: 32 weeks Core study: Rats: 15-Month interim evaluation: 72 weeks Terminal sacrifice: 110-111 weeks (males) or 111-112 weeks (females) Mice: 15-Month interim evaluation: 72 weeks Terminal sacrifice: 110-111 weeks (males) 111-112 weeks (females)
Size of Study Groups		
5 males and 5 females	10 males and 10 females	Rats: Stop-exposure evaluation: 70 males (337.5 mg/kg) Core study: 70 males and 60 females (0 mg/kg); 60 males and 60 females (84, 168, and 337.5 mg/kg) Mice: 60 males and 60 females

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Salicylazosulfapyridine (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 16-day studies	Same as 16-day studies
Animals per Cage Rats: 5 Mice: 1	Rats: 5 Mice: 1	Rats: 5 Mice: 1
Method of Animal Identification Toe clip	Toe clip	Rats: Tail tattoo Mice: Toe clip
Diet NIH-07 open formula meal diet (Zeigler Brothers Inc., Gardners, PA), available *ad libitum*, changed weekly	Same as 16-day studies	Same as 16-day studies
Water Distribution Tap water (City of Worcester municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 16-day studies	Tap water (City of Birmingham municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*
Cages Polycarbonate (Lab Products Inc., Rochelle Park, NJ), changed twice weekly for rats and weekly for mice	Polycarbonate (Lab Products Inc., Garfield, NJ), changed twice weekly for rats and weekly for mice	Polycarbonate (Lab Products Inc., Maywood, NJ), changed twice weekly for rats and weekly for mice
Bedding BetaChips (Northeastern Products Corp., Warrensburg, NY), changed weekly	BetaChips (Northeastern Products Corp., Warrensburg, NY), changed twice weekly for rats and weekly for mice	Sani-Chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly for rats and weekly for mice
Cage/Rack Filters Nonwoven fiber cage filters (Snow Filtration, Cincinnati, OH), changed every 2 weeks	Same as 16-day studies	Reemay® spun-bonded polyester rack filters (Andico, Birmingham, AL), changed every 2 weeks
Racks Stainless steel (Lab Products Inc., Rochelle Park, NJ), rotated every 2 weeks	Stainless steel (Lab Products Inc., Garfield, NJ), rotated every 2 weeks	Stainless steel (Lab Products Inc., Maywood, NJ), rotated every 2 weeks

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Salicylazosulfapyridine (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Animal Room Environment		
Temperature: 21.7°-22.2° C Relative humidity: 39% to 52% Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour	Temperature: 21.8°-23.1° C Relative humidity: 28% to 60% Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour	Temperature: 13.5°-29.4° C (rats), 13.4°-26.3° C (mice) Relative humidity: 20% to 90% (rats), 15% to 87% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour
Doses		
0, 675, 1,350, or 2,700 mg/kg body weight in corn oil by gavage at a volume of 5 mL/kg for rats or 10 mL/kg for mice	Rats: 0, 84, 168.8, or 337.5 mg/kg body weight in corn oil by gavage at a volume of 5 mL/kg body weight Mice: 0, 675, 1,350, or 2,700mg/kg body weight in corn oil by gavage at a volume of 10 mL/kg body weight	Stop-exposure evaluation: 0 or 337.5 mg/kg body weight in corn oil by gavage at a volume of 5 mL/kg body weight Core study: Rats: 0, 84, 168, or 337.5 mg/kg body weight in corn oil by gavage at a volume of 5 mL/kg body weight Mice: 0, 675, 1,350, or 2,700 mg/kg body weight in corn oil by gavage at a volume of 10 mL/kg body weight
Type and Frequency of Observation		
Observed twice daily; clinical observations were recorded daily; body weights were recorded initially, at 1 week, and at the end of the studies.	Observed twice daily; clinical observations and body weights were recorded weekly.	Observed twice daily; clinical observations and body weights were recorded initially, weekly for the first 14 weeks, monthly thereafter, and at the end of the studies.
Method of Sacrifice		
Carbon dioxide asphyxiation	Same as 16-day studies	Same as 16-day studies
Necropsy		
Necropsy was performed on all animals. Organs weighed were the brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all animals. Organs weighed were the brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all animals. Organs weighed at the 6-month interim evaluation (male rats) were right kidney, liver, spleen, right testis, and thyroid gland. Organs weighed at the 15-month interim evaluation were right kidney, liver, spleen, left testis (rats), right testis, and thyroid gland.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Salicylazosulfapyridine (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Clinical Pathology		
At necropsy, blood was collected from the jugular vein. ***Clinical Chemistry:*** Thyroid-stimulating hormone, triiodothyronine, and thyroxine concentrations.	After 12 weeks of study, 16-hour urine samples were collected and blood was collected from the tail for analysis of hematology parameters. At necropsy, blood was collected from the jugular vein for clinical chemistry. ***Hematology:*** Hematocrit, hemoglobin concentration, erythrocyte and reticulocyte counts, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, leukocyte count and differential, and methemoglobin concentration ***Clinical Chemistry:*** Urea nitrogen, creatinine, glucose, total protein and albumin concentrations, alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase concentrations, thyroid-stimulating hormone, triiodothyronine, and thyroxine concentrations. ***Urinalysis:*** Volume, specific gravity	Stop-exposure evaluation: At 26 weeks and the end of the study, blood was collected from the retroorbital sinus for serum thyroid hormone assays. ***Clinical Chemistry:*** Thyroid-stimulating hormone, triiodothyronine, reverse triiodothyronine, and thyroxine concentrations. Core study: At 15 months (male rats and mice) and the end of the study, blood was collected from the retroorbital sinus for serum thyroid hormone assays. ***Clinical Chemistry:*** Thyroid-stimulating hormone, triiodothyronine, reverse triiodothyronine, and thyroxine concentrations.
Histopathology		
Complete histopathologic examinations were performed on all rats and mice. In addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, brain, clitoral gland (rats), esophagus, femur with marrow, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lungs and mainstem bronchi, lymph nodes, (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testes (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathologic examinations were performed on 0 and 337.5 mg/kg rats and 2,700 mg/kg mice. In addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, brain, clitoral gland (rats), esophagus, femur with marrow, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lungs and mainstem bronchi, lymph nodes, (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testes (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. Additionally, the pituitary gland and thyroid gland from all rats at all dose levels were evaluated, and kidney tissue was evaluated for all rats administered 168.8 mg/kg. Gross lesions in mice administered 675 or 1,350 mg/kg were evaluated microscopically.	Complete histopathologic examinations were performed on all rats and mice. In addition to gross lesions, tissue masses and associated lymph nodes, the tissues examined included: adrenal gland, brain, clitoral gland, esophagus, femur with marrow, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lungs and mainstem bronchi, lymph nodes, (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testes (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Salicylazosulfapyridine (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Sperm Morphology and Vaginal Cytology Evaluation		
None	At terminal sacrifice, sperm samples were collected from all male animals and evaluated for sperm density, morphology, and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal fluid samples were collected for up to 7 consecutive days prior to the end of the studies and evaluated for the relative frequency of estrous stages and estrous cycle length.	None

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have

approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, and epididymal spermatozoa data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973). Because the vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across dose concentrations.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of salicylazosulfapyridine was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, changes in the frequency of micronucleated erythrocytes in mouse peripheral blood and bone marrow (with or without kinetochores) and in rat bone marrow, and chromosomal aberrations in mouse bone marrow cells following *in vivo* treatment. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of salicylazosulfapyridine are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is

currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

RESULTS

RATS

16-DAY STUDY

All rats survived to the end of the study (Table 2). With the exception of 675 mg/kg male rats, the final mean body weights of all dosed groups of males and females were significantly lower than those of controls. Mean body weight gains of all dosed groups were less than those of controls. Clinical findings included ruffled fur and distended abdomens in male and female rats receiving 2,700 mg/kg salicylazosulfapyridine. Female rats receiving 2,700 mg/kg salicylazosulfapyridine appeared to be thinner than controls.

Hypothyroidism, evidenced by decreased serum triiodothyronine and thyroxine concentrations and increased thyroid-stimulating hormone concentrations, occurred in 2,700 mg/kg male and female rats (Table G1). These thyroid hormone changes were consistent with the known goitrogenic effects of sulfonamides.

The absolute and relative thymus weights of male rats receiving 1,350 or 2,700 mg/kg salicylazosulfapyridine were significantly lower than those of controls (Table F1). The absolute and relative thymus weights of 2,700 mg/kg females were lower than those of controls. Absolute liver and heart weights of male rats and absolute lung weights of male and female rats were significantly decreased, and the decreases were considered to be secondary to lower body weights in dosed rats. At necropsy, all dosed rats had enlarged cecae/large intestines. Male rats receiving 1,350 mg/kg and male and female rats receiving 2,700 mg/kg had red and slightly enlarged thyroid glands. Chemical-related microscopic lesions were present in the forestomach, thymus, thyroid gland, and pituitary gland. Minimal to mild hyperplasia of the forestomach mucosa was present in four males and one female in the 1,350 mg/kg groups and in three males and two females in the 2,700 mg/kg groups. Lymphoid depletion was observed in the thymus of three male and three female rats in the 2,700 mg/kg groups. All male and female rats in the 1,350 and 2,700 mg/kg groups had minimal to mild thyroid gland follicular cell hyperplasia. Follicles varied in size and were lined by columnar cells. Colloid (PAS positive) was present in some but not in all follicles. Ultrastructural examination of the thyroid gland from male and female rats receiving 2,700 mg/kg revealed distention of rough endoplasmic reticulum with colloid, decreased numbers of cytoplasmic dense bodies and cytoplasmic colloid droplets, fusion of apical microvilli, increased numbers of dense secretory granules, increased size and numbers of mitochondria, and increased numbers of free ribosomes when compared to controls. Morphometric analysis of the pituitary gland revealed a significant increase in the number ($P < 0.03$) but not the size of thyroid-stimulating hormone producing cells in the pars distalis of the pituitary gland of the 1,350 and 2,700 mg/kg groups. The gross, microscopic, and ultrastructural changes in thyroid glands of dosed rats are suggestive of increased functional activity and are most likely due to the reported goitrogenic effects of salicylazosulfapyridine.

Dose Selection Rationale: Because of the lower mean body weights of male and female rats in each dose group, 337.5 mg/kg was selected as the high dose for the 13-week study.

TABLE 2
Survival and Body Weights of Rats in the 16-Day Gavage Study of Salicylazosulfapyridine

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
Vehicle Control	5/5	135 ± 3	215 ± 5	80 ± 4	
675	5/5	138 ± 3	204 ± 4	66 ± 2*	95
1,350	5/5	133 ± 4	160 ± 4**	26 ± 2**	74
2,700	5/5	137 ± 3	147 ± 4**	9 ± 4**	68
Female					
Vehicle Control	5/5	108 ± 3	147 ± 3	40 ± 1	
675	5/5	111 ± 3	133 ± 2**	21 ± 2**	90
1,350	5/5	109 ± 3	129 ± 4**	20 ± 2**	87
2,700	5/5	110 ± 4	111 ± 3**	1 ± 2**	75

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

13-Week Study

All rats survived to the end of the study (Table 3). The final mean body weights of dosed male rats were similar to that of controls; the final mean body weights and body weight gains of dosed females were significantly lower than those of controls. No chemical-related clinical observations were noted in dosed rats during the 13-week study. No significant differences in hematology or urinalysis parameters between control and dosed rats were observed (Table G2). The absolute and relative right kidney weights of 337.5 mg/kg females were significantly greater than those of controls (Table F2).

At necropsy, some 337.5 mg/kg male rats had red, enlarged thyroid glands. Histopathologic changes were noted primarily in the thyroid gland and pituitary gland of males and females receiving 337.5 mg/kg. The thyroid gland lesions observed were similar to those present in the 16-day study. Nine male rats receiving 168.8 mg/kg and ten male and seven female rats receiving 337.5 mg/kg had minimal but consistent changes in thyroid gland follicular cells. There was slight follicular cell hypertrophy and hyperplasia with apparent thickening of the follicular epithelium. A few follicles were enlarged and had apparent ingrowth of the hyperplastic epithelium into the lumen. In addition, the cytoplasm of follicular cells of the dosed rats appeared to be more vacuolated than that of controls. In the pituitary gland of 337.5 mg/kg males and females, the thyroid-stimulating hormone producing cells were enlarged and contained pale-staining cytoplasm and prominent Golgi complexes. Decreased serum triiodothyronine and thyroxine concentrations and increased thyroid-stimulating hormone concentration, similar to that which occurred in the 16-day study, occurred in 337.5 mg/kg male rats; thyroid hormone concentrations were not affected in female rats (Table G2).

Sperm motility of all dosed groups of males was significantly lower than that of controls (Table H1). Vaginal cytology parameters of dosed groups of females were similar to those of controls.

Dose Selection Rationale: Based on the absence of biologically significant body weight differences and of potentially life-threatening thyroid gland lesions in dosed rats, the high dose selected for continuous exposure in the 2-year rat study was 337.5 mg/kg. The 337.5 mg/kg dose was selected for the 6-month stop-exposure evaluation in male rats to examine the progression or regression of thyroid gland lesions.

TABLE 3
Survival and Body Weights of Rats in the 13-Week Gavage Study of Salicylazosulfapyridine

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
Vehicle Control	10/10	124 ± 3	365 ± 7	241 ± 8	
84	10/10	123 ± 4	353 ± 4	231 ± 2	97
168.8	10/10	123 ± 3	354 ± 5	231 ± 3	97
337.5	10/10	123 ± 4	352 ± 6	229 ± 4	97
Female					
Vehicle Control	10/10	103 ± 1	202 ± 3	99 ± 3	
84	10/10	104 ± 1	193 ± 2*	89 ± 2**	96
168.8	10/10	105 ± 1	191 ± 2**	86 ± 3**	95
337.5	10/10	105 ± 1	191 ± 2**	85 ± 2**	94

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier survival curves in Figures 2 (core study) and 3 (stop-exposure males). Survival of 337.5 mg/kg core-study male rats was significantly lower than that of controls, with most deaths occurring during the last 8 weeks of the study. Survival of 84 and 168 mg/kg core-study males, all groups of dosed females, and the stop-exposure male group was similar to controls.

Body Weights, Clinical Findings, and Clinical Chemistry

Mean body weights of core-study males and stop-exposure males were similar to controls throughout the study (Figures 4 and 5 and Table 5). From week 45 to week 89, females in the 337.5 mg/kg group had mean body weights that were 9% to 15% lower than those of controls; the final mean body weight of 337.5 mg/kg females was 7% lower than that of controls (Table 6 and Figure 4). No chemical-related clinical observations were noted in male or female rats. The serum thyroxine concentration in the 337.5 mg/kg core-study males at study termination was minimally lower than that of controls; the serum thyroid-stimulating hormone, triiodothyronine, and reverse triiodothyronine concentrations of dosed male and female rats were similar to those of controls (Table G3).

TABLE 4
Survival of Rats in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg[a] (Stop-Exposure)
Male					
Animals initially in study	70	60	60	60	70
6-Month interim evaluation[b]	10	0	0	0	10
15-Month interim evaluation[b]	10	10	10	10	10
Accidental deaths[b]	1	4	1	2	3
Moribund	13	11	16	15	13
Natural deaths	1	2	2	10	4
Animals surviving to study termination	35	33	31[f]	23	30
Percent probability of survival at end of study[c]	71	72	64	48	65
Mean survival (days)[d]	582	628	630	629	538
Survival analysis[e]	P=0.014	P=1.000N	P=0.424	P=0.036	—[g]
Survival analysis					P=0.416
Female					
Animals initially in study	60	60	60	60	
15-Month interim evaluation[b]	10	10	10	10	
Accidental deaths[b]	1	1	0	9	
Moribund	12	13	14	11	
Natural deaths	2	2	5	4	
Animals surviving to study termination	35[f]	34[f]	31	26	
Percent probability of survival at end of study	72	69	62	65	
Mean survival (days)	696	674	715	625	
Survival analysis	P=0.455	P=0.897	P=0.577	P=0.564	

[a] Ten male rats receiving 337.5 mg/kg salicylazosulfapyridine were evaluated at 6 months. The remaining 70 male rats received the corn oil vehicle until the end of the 2-year study, and 10 male rats were evaluated at 15 months.
[b] Censored from survival analyses
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[e] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with controls are in the dosed columns. A lower mortality in a dose group is indicated by N.
[f] Includes one animal that died the last week of the study
[g] Stop-exposure group is not included in trend test analysis

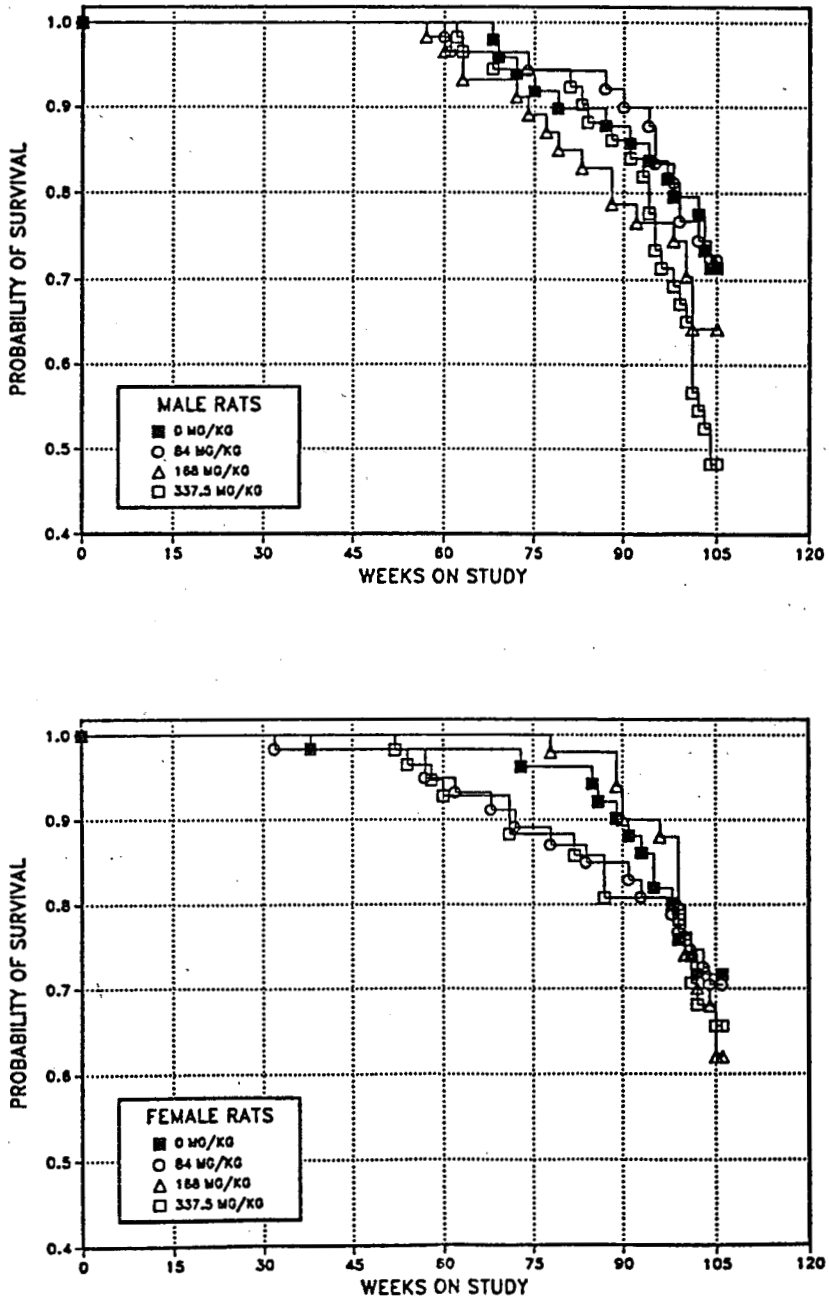


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats
Administered Salicylazosulfapyridine by Gavage for 2 Years

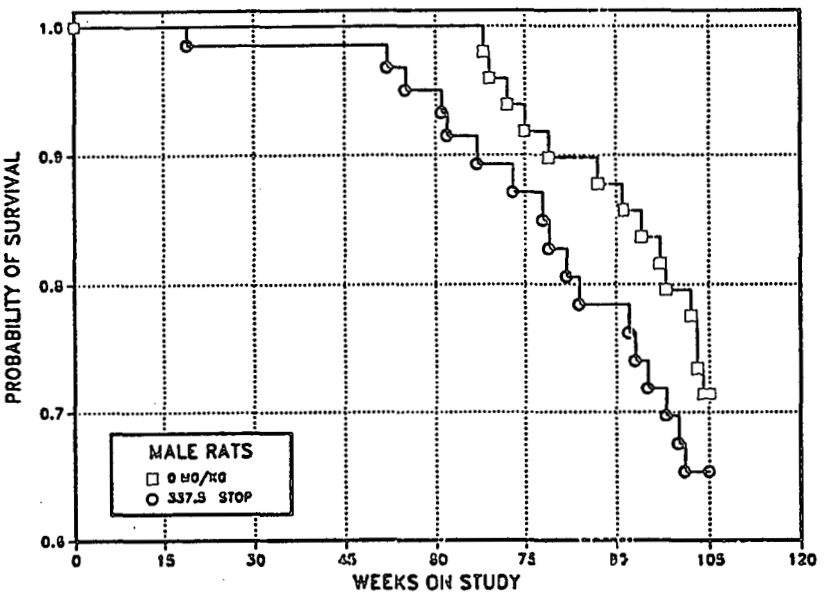
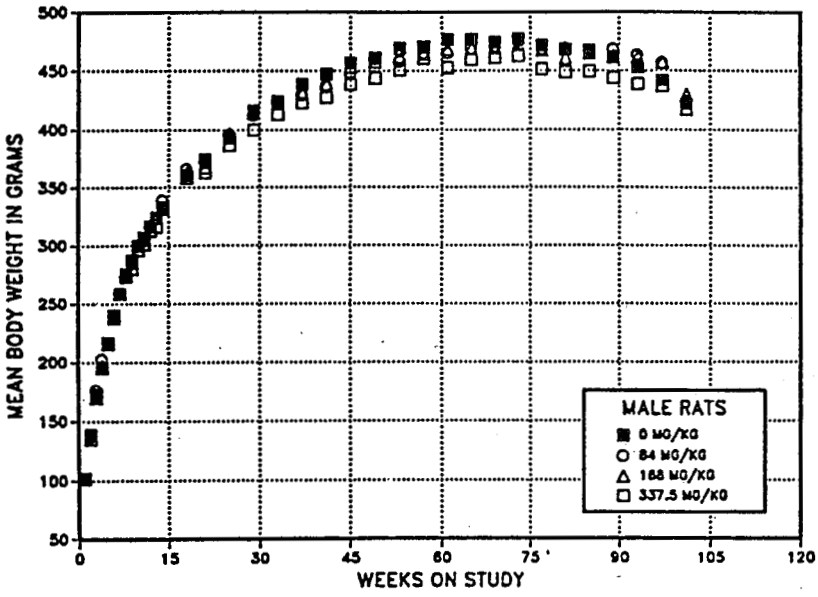


FIGURE 3
Kaplan-Meier Survival Curves for Stop-Exposure Male Rats Administered Salicylazosulfapyridine by Gavage



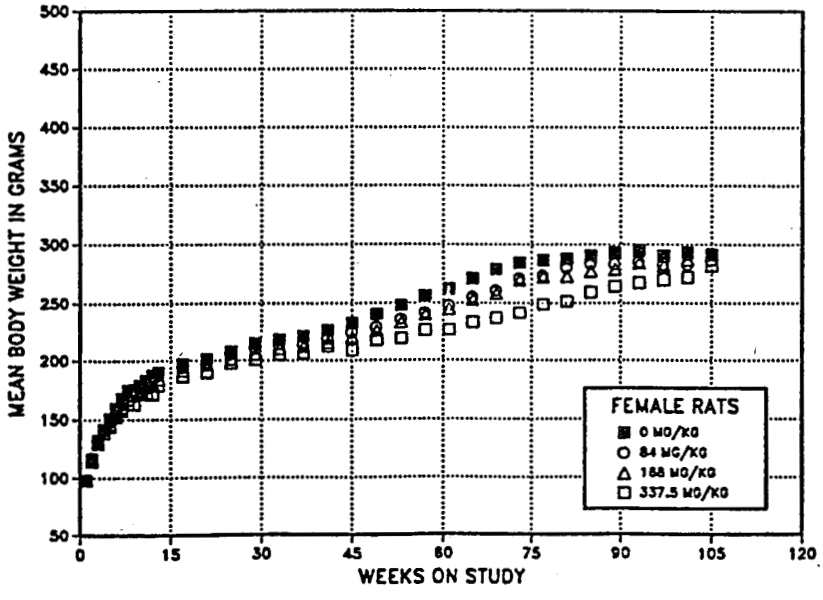


FIGURE 4
Growth Curves for Male and Female Rats
Administered Salicylazosulfapyridine by Gavage for 2 Years

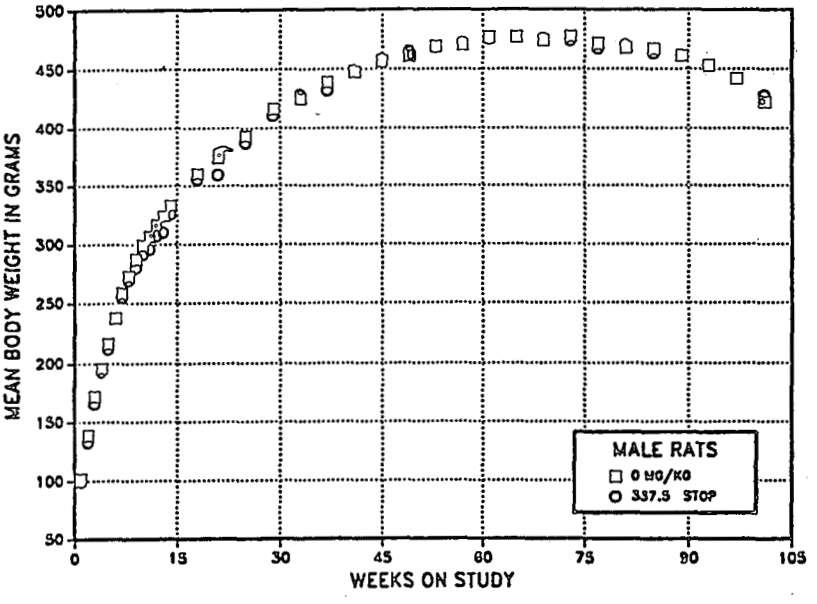


FIGURE 5
Growth Curves for Stop-Exposure Male Rats
Administered Salicylazosulfapyridine by Gavage

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	84 mg/kg Av. Wt. (g)	84 mg/kg Wt. (% of controls)	84 mg/kg No. of Survivors	168 mg/kg Av. Wt. (g)	168 mg/kg Wt. (% of controls)	168 mg/kg No. of Survivors
1	102	70	102	100	60	102	100	60
2	139	70	137	99	60	138	100	60
3	171	70	176	103	60	170	99	60
4	196	70	203	103	60	198	101	60
5	216	70	217	100	60	216	100	60
6	238	70	240	101	60	241	101	60
7	258	70	259	100	60	259	100	60
8	273	70	273	100	60	274	100	60
9	287	70	285	99	60	280	98	60
10	299	70	300	100	60	296	99	60
11	307	70	304	99	60	301	98	60
12	317	70	316	100	60	312	99	60
13	324	70	324	100	59	324	100	60
14	333	70	339	102	59	333	100	60
18	360	70	366	102	59	363	101	60
21	374	70	372	100	59	367	98	60
25	393	69	396	101	59	397	101	60
29[a]	416	59	412	99	59	414	100	60
33	424	59	423	100	59	423	100	60
37	439	59	430	98	57	431	98	59
41	447	59	437	98	57	439	98	59
45	457	59	448	98	57	453	99	59
49	461	59	460	100	57	458	99	59
53	469	59	458	98	57	463	99	59
57	471	59	465	99	57	464	99	59
61	477	59	465	98	56	468	98	57
65	477	59	469	98	55	469	98	55
69[a]	474	48	471	99	44	470	99	45
73	477	46	475	100	44	473	99	44
77	472	45	468	99	43	468	99	43
81	468	44	469	100	43	461	98	41
85	467	44	467	100	43	465	100	40
89	461	43	468	102	42	463	100	38
93	453	42	464	102	41	462	102	37
97	442	41	457	103	38	457	103	37
101	422	39	424	101	35	430	102	34
Mean for weeks								
1-13	241		241	100		239	99	
14-52	410		408	100		408	100	
53-101	464		463	100		463	100	

(continued)

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine
(continued)

Weeks on Study	337.5 mg/kg			337.5 mg/kg (Stop-Exposure)		
	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	102	100	60	99	97	70
2	135	97	60	133	96	70
3	173	101	60	166	97	70
4	195	100	60	193	98	70
5	215	100	60	212	98	70
6	240	101	60	237	100	70
7	259	100	60	255	99	70
8	275	101	60	270	99	70
9	280	97	60	280	97	70
10	296	99	60	292	97	70
11	301	98	60	296	96	70
12	313	99	60	307	97	70
13	316	97	60	310	96	69
14	331	100	60	325	98	69
18	358	99	60	355	99	68
21	363	97	59	359	96	67
25	386	98	59	387	99	67
29[a]	400	96	59	411	99	57
33	413	97	59	428	101	57
37	423	96	58	432	98	56
41	428	96	58	449	100	56
45	439	96	58	459	100	56
49	444	96	58	465	101	56
53	451	96	58	468	100	55
57	460	98	58	472	100	54
61	453	95	58	475	100	54
65	459	96	56	477	100	52
69[a]	461	97	45	476	100	41
73	463	97	45	474	99	41
77	451	96	45	467	99	40
81	449	96	45	470	101	38
85	450	96	42	463	99	36
89	444	96	41	462	100	36
93	439	97	39	453	100	35
97	437	99	34	442	100	33
101	417	99	31	427	101	31
Mean for weeks						
1-13	238	99		235	98	
14-52	399	97		407	99	
53-101	449	97		464	100	

[a] Interim evaluations occurred during week 27 (vehicle control and 337.5 stop-exposure groups only) and week 66 (vehicle control and all dosed groups).

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	84 mg/kg Av. Wt. (g)	84 mg/kg Wt. (% of controls)	84 mg/kg No. of Survivors	168 mg/kg Av. Wt. (g)	168 mg/kg Wt. (% of controls)	168 mg/kg No. of Survivors	337.5 mg/kg Av. Wt. (g)	337.5 mg/kg Wt. (% of controls)	337.5 mg/kg No. of Survivors
1	98	60	99	101	60	98	100	60	98	100	60
2	116	60	117	101	60	115	99	60	114	98	60
3	132	60	132	100	60	131	99	60	129	98	60
4	142	60	141	99	60	139	98	60	138	98	60
5	151	60	148	98	60	147	97	60	144	95	60
6	159	60	156	98	60	155	97	60	152	95	60
7	167	60	165	98	60	161	96	60	158	94	60
8	174	60	171	98	60	168	97	60	163	94	60
9	175	60	171	98	60	171	97	60	163	93	60
10	179	60	178	99	60	175	98	60	171	96	60
11	183	60	180	99	60	177	97	60	172	94	60
12	187	60	183	98	60	179	96	60	171	91	60
13	190	60	187	99	60	184	97	60	178	94	60
17	197	60	194	98	60	191	97	60	186	94	60
21	201	60	197	98	60	196	98	60	189	94	59
25	208	60	205	99	60	201	97	60	198	95	59
29	215	60	211	98	60	206	96	60	201	94	59
33	218	60	214	98	59	210	96	60	205	94	58
37	221	60	213	97	59	212	96	60	207	93	58
41	226	59	219	97	58	216	95	60	212	94	58
45	233	59	224	96	58	220	95	60	209	90	58
49	240	58	229	95	58	226	94	60	218	91	58
53	248	58	236	95	58	233	94	60	219	88	56
57	256	58	241	94	57	240	94	60	226	88	54
61	262	58	248	95	56	245	93	60	226	86	51
65	271	58	255	94	55	253	93	60	233	86	51
69[a]	279	48	261	93	44	258	93	50	237	85	41
73	284	47	271	95	43	270	95	50	242	85	37
77	287	47	273	95	43	273	95	50	249	87	35
81	287	47	281	98	42	273	95	49	252	88	35
85	290	47	284	98	41	277	96	49	259	89	34
89	293	45	283	97	41	279	95	49	264	90	32
93	295	43	285	97	40	285	96	45	268	91	32
97	290	40	283	97	39	282	97	44	270	93	30
101	293	36	283	97	36	287	98	37	272	93	28
Mean for weeks											
1-13	158		156	99		154	97		150	95	
14-52	218		212	97		209	96		203	93	
53-101	280		268	96		266	95		247	88	

[a] Interim evaluation occurred during week 66.

Pathology and Statistical Analysis

This section describes the statistically significant and biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the urinary bladder, kidney, spleen, and other organs, and in the incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one dose group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Urinary Bladder: In male rats, the incidence of transitional epithelial papilloma in the 337.5 mg/kg core-study group was significantly greater than that in the control group; two of the 337.5 mg/kg core-study males had multiple transitional epithelial papillomas. Two transitional epithelial papillomas occurred in each of the 168 mg/kg male and female groups as well (Tables 7, A1, and B1). There were no transitional epithelial papillomas in the stop-exposure group at any of the evaluation timepoints. The incidences of transitional epithelial papilloma in 168 mg/kg male and female rats and in 337.5 mg/kg core-study male rats exceeded the ranges in historical controls from NTP 2-year corn oil gavage studies (Tables 7, A4, and B4a).

The incidences of mucosal (transitional epithelial) hyperplasia in 168 and 337.5 mg/kg core-study males and in 337.5 mg/kg females were significantly greater than those in controls (Tables 7, A5, and B5). Mucosal hyperplasia was present in one 337.5 mg/kg stop-exposure male at the end of the 2-year study. Concretions were observed grossly at necropsy and diagnosed as calculi. The incidences of grossly observed concretions (calculi) were significantly greater in male rats receiving 168 or 337.5 mg/kg than in controls. However, fewer concretions were diagnosed microscopically than observed grossly at necropsy and were presumed to be lost during tissue processing. The incidence of dilatation in core-study males receiving 337.5 mg/kg was significantly greater than that in controls. The neoplastic and nonneoplastic lesions observed during the 2-year continuous study did not occur during the 2-year stop-exposure study. Urinary bladder transitional epithelial papillomas were single or multiple, discrete masses that protruded from the mucosa into the lumen of the urinary bladder from narrow- or broad-based attachments (Plate 1). Papillomas consisted of a few to several layers of hyperplastic transitional epithelium which formed thick, highly convoluted folds or papillary frond-like structures supported by a core of scant to moderate amounts of fibrovascular stroma (Plates 2 and 3). In general, the hyperplastic cells were cuboidal to polyhedral. However, focal areas of epithelial dysplasia composed of atypical spindle to pleomorphic cells were evident. Papillomas frequently were concurrent with, and appeared to be a neoplastic progression of, mucosal epithelial hyperplasia.

Mucosal (transitional epithelial) hyperplasia was generally a multifocal to diffuse change which varied from minimal to marked. The thickness of the epithelium was increased from the normal one or two cell layers to three to seven cell layers (Plate 4). Often there were focal areas of more prominent plaque-like thickening that exhibited both cellular dysplasia and atypia similar to that of papillomas. With increasing severity, focal areas of the hyperplastic epithelium formed thick complex folds that protruded into the lumen (Plate 5). Along the base of the mucosa in these areas, nodules of hyperplastic epithelium (some of which had central lumina) extended into the subjacent lamina propria. Microscopically, urinary bladder concretions were large, irregular masses composed of mostly amphophilic spiculated material (Plate 6). Dilatation was primarily a gross change which presumably resulted from obstruction of the lower urinary tract by concretions.

TABLE 7
Incidences of Neoplasms and Nonneoplastic Lesions of the Urinary Bladder in Rats in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
Male					
2-Year Study					
Number Examined Microscopically	50	49	50	50	47
Concretion[a]	0	0	1 (4.0)[b]	10** (3.1)	0
Dilatation	0	1 (3.0)	2 (3.5)	7* (3.6)	0
Mucosa Hyperplasia	0	0	14** (2.7)	41** (2.7)	1 (2.0)
Calculus (gross diagnosis)[c]	0	2	12**	28**	0
Transitional Epithelial Papilloma[d]					
Overall rate[e]	0/50 (0%)	0/49 (0%)	2/50 (4%)	6/50 (12%)	0/47 (0%)
Adjusted rate[f]	0.0%	0.0%	6.5%	22.1%	0.0%
Terminal rate[g]	0/35 (0%)	0/33 (0%)	2/31 (6%)	3/23 (13%)	0/30 (0%)
First incidence (days)	—[i]	—	729 (T)	653	—
Logistic regression test[h]	P<0.001	—	P=0.212	P=0.011	—
Female					
15-Month Interim Evaluation					
Number Examined Microscopically	10	10	10	10	
Mucosa Hyperplasia	0	0	0	2 (1.5)	
2-Year Study					
Number Examined Microscopically	49	50	50	50	
Concretion	0	0	1 (4.0)	0	
Mucosa Hyperplasia	2 (2.5)	0	4 (3.3)	12* (1.7)	
Calculus (gross diagnosis)	1	0	4	1	
Transitional Epithelial Papilloma[j]					
Overall rate	0/49 (0%)	0/50 (0%)	2/50 (4%)	0/50 (0%)	

* Significantly different (P≤0.05) from the vehicle control group by the logistic regression test
** P≤0.01
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with grossly observed urinary bladder concretions (diagnosed as calculi at necropsy)
[d] Historical incidence for 2-year NTP corn oil gavage studies with vehicle control groups (mean ± standard deviation): 1/904 (0.1% ± 0.5%), range 0%-2%
[e] Number of animals with neoplasm per number of animals with urinary bladder examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the vehicle control incidence are the P values associated with the trend test (does not include the stop-exposure group). Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 3/903 (0.3% ± 0.8%), range 0%-2%

Kidney: The absolute kidney weight of 337.5 mg/kg females was significantly greater than that of controls at the 15-month interim evaluation (Table F3). Papilloma of the renal pelvis transitional epithelium was observed in two female rats receiving 337.5 mg/kg (Tables 8 and B1). The incidence of transitional epithelial papilloma in 337.5 mg/kg female rats exceeded the incidence in historical controls from NTP 2-year corn oil gavage studies (Tables 8 and B4b).

There were increased incidences of nonneoplastic kidney lesions in dosed male and female rats at 2 years and in 337.5 mg/kg females at 15 months. The incidences of concretion and transitional epithelial hyperplasia in 168 and 337.5 mg/kg core-study male and female rats were significantly greater than those in controls at 2 years as were the incidences in 337.5 mg/kg females at 15 months (Tables 8, A5, and B5). In addition, focal atypical epithelial hyperplasia occurred in three core-study male rats receiving 337.5 mg/kg for 2 years. At 2 years, the incidences of hydronephrosis in 337.5 mg/kg core-study males and females were significantly greater than those in controls. The incidence of renal tubule dilatation in 337.5 mg/kg core-study males was significantly greater than that in controls at 2 years. The incidences of mineralization in 84, 168, and 337.5 mg/kg males were significantly greater than that in controls at 2 years.

Papillary necrosis was observed in four 337.5 mg/kg core-study males and in one 337.5 mg/kg female (Tables 8, A5, and B5). The average severity of nephropathy was greater in dosed males than in controls. The incidence of nephropathy in 337.5 mg/kg females was significantly greater than that in controls. The

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control		84 mg/kg		168 mg/kg		337.5 mg/kg		337.5 mg/kg (Stop-Exposure)	
Male										
6-Month Interim Evaluation										
Number Examined Microscopically	10								10	
Mineralization[a]	1	(1.0)[b]							1	(1.0)
Nephropathy	8	(1.0)							9	(1.0)
Renal Tubule Dilatation	0								1	(2.0)
15-Month Interim Evaluation										
Number Examined Microscopically	10		10		10		10		10	
Mineralization	0		0		0		0		2	(1.0)
Nephropathy	10	(1.5)	10	(1.0)	10	(1.1)	10	(1.2)	10	(1.1)
Renal Tubule Dilatation	1	(2.0)	0		0		2	(2.0)	0	
Transitional Epithelial Hyperplasia	0		0		0		1	(1.0)	0	
2-Year Study										
Number Examined Microscopically	50		50		50		50		50	
Concretion	0		1	(1.0)	13**	(2.1)	33**	(2.6)	0	
Hydronephrosis	0		1	(2.0)	1	(2.0)	28**	(2.2)	0	
Mineralization	3	(1.0)	10*	(1.2)	11*	(1.5)	13**	(1.8)	3	(1.0)
Nephropathy	48	(1.6)	47	(1.9)	50	(2.0)	48	(2.5)	46	(1.5)
Papillary Necrosis	0		0		1	(3.0)	4	(2.5)	0	
Renal Tubule Dilatation	0		1	(1.0)	1	(3.0)	11**	(2.7)	3	(2.0)
Transitional Epithelial Hyperplasia	10	(1.2)	10	(1.1)	20*	(1.8)	43**	(2.6)	4	(1.0)
Atypical Transitional Epithelial Hyperplasia	0		0		0		3	(3.0)	0	
Calculus (gross diagnosis)[c]	0		0		3		18		0	

(continued)

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
Female					
15-Month Interim Evaluation					
Number Examined Microscopically	10	10	10	10	
Concretion	0	0	1 (1.0)	6** (2.7)	
Mineralization	9 (1.3)	10 (1.9)	8 (1.9)	9 (2.1)	
Nephropathy	4 (1.0)	6 (1.0)	6 (1.0)	10** (1.0)	
Renal Tubule Dilatation	0	0	0	0	
Transitional Epithelial Hyperplasia	0	0	2 (1.5)	8** (2.4)	
2-Year Study					
Number Examined Microscopically	50	50	50	50	
Concretion	0	9** (1.6)	34** (1.9)	37** (2.9)	
Hydronephrosis	0	0	3 (3.0)	10** (2.0)	
Mineralization	44 (1.7)	47 (1.7)	43 (1.9)	41 (1.8)	
Nephropathy	34 (1.1)	36 (1.2)	41 (1.2)	44** (1.4)	
Papillary Necrosis	0	0	0	1 (2.0)	
Renal Tubule Dilatation	2 (2.0)	2 (2.0)	1 (3.0)	6 (2.3)	
Transitional Epithelial Hyperplasia	3 (1.3)	7 (1.3)	23** (1.5)	43** (2.6)	
Calculus (gross diagnosis)	0	0	2	11	
Transitional Epithelial Papilloma[d]	0	0	0	2	

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with grossly observed kidney concretions (diagnosed as calculi at necropsy)
[d] Historical incidence for 2-year NTP corn oil gavage studies with vehicle control groups: 0/920

incidence and severity of nonneoplastic kidney lesions in stop-exposure male rats were similar to those in controls.

Microscopically, concretions consisted of one or more variably sized irregular aggregates of lightly eosinophilic to amphophilic spicules (often radially arranged) or granular material within the lumen of the renal pelvis and/or incorporated within hyperplastic pelvic transitional epithelium (Plate 7). Focal mineralization was often a feature of concretions.

Transitional epithelial papillomas were narrow- or broad-based exophytic masses that protruded into the lumen of the renal pelvis. They consisted of papillary fronds of thickened transitional epithelium supported by a core of scant to moderate amounts of fibrovascular tissue. Transitional epithelial hyperplasia was a multifocal to diffuse change. The hyperplastic epithelium frequently occurred as few to several nodular to papillary projections with scant cores of fibrovascular stroma (Plate 8), and/or as focal or focally extensive areas in which the epithelium was increased in thickness from two to five times the normal thickness due to an increase in the number of cell layers. Less frequently, thickening of the pelvic epithelium was diffuse and relatively uniform and there was concurrent hyperplasia of the epithelium of the proximal ureter. Atypical transitional epithelial hyperplasias were single, epithelial-lined, nodular lesions, 0.5 to 1.0 cm

in diameter, that consisted of densely packed polygonal to spindle cells that projected above or occurred in the submucosa lamina propria immediately beneath the mucosa (Plate 9).

Papillary necrosis was considered an ischemic change most likely the result of pressure from the concretions lodged within the urinary pelvis rather than from precipitation of compound or a metabolite into the collecting tubules. The entire renal papilla was generally affected and appeared hypoeosinophilic with decreased cellular detail and cells that lacked nuclei (Plate 10).

Minimal to mild nephropathy consisted of scattered clusters of small diameter regenerative tubules lined by basophilic cuboidal epithelial cells and often surrounded by a slightly thickened basement membrane, and dilated tubules filled with eosinophilic proteinaceous fluid. With increasing severity, more tubules were involved, and interstitial fibrosis with variable mononuclear cell infiltrates and focal tubule suppuration and variable glomerular sclerosis were widespread. Mineralization consisted of round to irregular particulate and/or laminated bodies that occurred in the inner cortex or near the corticomedullary junction. Mineralization in this location is a common, spontaneous finding in rats, particularly in female rats. The increased incidence of mineralization noted in dosed male rats may be associated with the increased severity of nephropathy noted in these animals. Renal tubule dilatation was characterized by widespread distension of renal tubules to approximately twice the normal diameter. Hydronephrosis was characterized by mild to moderate dilatation of the renal pelvis.

Spleen: The incidences of splenic hematopoietic cell proliferation [vehicle control, 14/50; 84 mg/kg, 15/50; 168 mg/kg, 17/50; 337.5 mg/kg (continuous exposure), 23/50; 337.5 mg/kg (stop-exposure), 14/50] and hemosiderin pigmentation (14/50, 15/50, 15/50, 30/50, 13/50) were significantly greater in core-study male rats receiving 337.5 mg/kg than in controls (Table A5). These increases may be suggestive of increased erythrocyte toxicity and destruction (hemolysis).

Multiple Organs: The incidences of mononuclear cell leukemia in male core-study (13/50, 18/50, 12/50, 3/50, 10/50; Table A3) and female (14/50, 9/50, 8/50, 3/50; Table B3) rats receiving 337.5 mg/kg were significantly less than in controls.

Other Organs: The combined incidences of benign and malignant pheochromocytoma of the adrenal medulla were significantly less in dosed groups of males than that in controls (16/50, 7/49, 7/50, 8/49, 6/50; Table A3). The incidences of mammary gland fibroadenoma (22/50, 9/50, 20/50, 5/50) and pituitary gland (pars distalis) adenoma (26/50, 20/49, 24/50, 13/50) in dosed groups of females were less than in controls (Table B3).

Incidences of pancreatic acinar cell cytoplasmic alteration (1/50, 1/50, 3/50, 15/50, 3/48), forestomach ulcer (1/50, 1/50, 1/50, 7/50, 0/50), and forestomach mucosal hyperplasia (0/50, 0/50, 0/50, 9/50, 0/50) were significantly greater in core-study males administered 337.5 mg/kg than in controls (Table A5). The incidence of mammary gland ectasia was significantly greater in 168 mg/kg females than that in controls (10/50, 10/50, 20/50, 4/50; Table B5).

Incidences of accessory adrenal cortical nodules (19/50, 19/50, 13/50, 8/50, 12/50), chronic inflammation of the preputial gland (24/50, 18/50, 16/50, 9/50, 25/50), and corpora amylacea of the prostate gland (28/50, 28/50, 19/50, 11/50, 25/50) were significantly less in males administered 337.5 mg/kg than in controls (Table A5). Incidences of pituitary gland (pars distalis) cysts in females administered 168 or 337.5 mg/kg were significantly less than in controls (29/50, 26/49, 18/50, 15/50; Table B5).

The biological significance of these incidences is uncertain but may be related to treatment or changes in body weight. In general, 1) the lesions represent usual age-related changes encountered in chronic studies, 2) the increased or decreased incidences were marginal and did not have a clear dose-related trend, or 3) there was usually no similar effect in animals of the other sex.

MICE

16-DAY STUDY

There were no chemical-related deaths, and final mean body weights of dosed mice were similar to those of controls (Table 9). No chemical-related clinical observations were noted for male or female mice. There were no differences between dosed and control mice in triiodothyronine, thyroxine, or thyroid-stimulating hormone concentrations (Table G4). There were no biologically significant differences in absolute or relative organ weights between dosed and control mice (Table F5). At necropsy, male mice receiving 2,700 mg/kg had enlarged cecae/large intestines. There were no biologically significant histopathologic lesions attributed to salicylazosulfapyridine administration.

Dose Selection Rationale: Based on the absence of chemical-related mortality, body weight effects, and lesions, the high dose selected for the 13-week mouse study was 2,700 mg/kg.

TABLE 9
Survival and Body Weights of Mice in the 16-Day Gavage Study of Salicylazosulfapyridine

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
Vehicle Control	5/5	21.0 ± 0.3	23.6 ± 0.4	2.6 ± 0.4	
675	5/5	20.8 ± 0.4	23.0 ± 0.4	2.2 ± 0.4	97
1,350	5/5	21.3 ± 0.2	24.2 ± 0.5	2.9 ± 0.3	102
2,700	5/5	21.3 ± 0.3	24.1 ± 0.4	2.9 ± 0.4	102
Female					
Vehicle Control	5/5	17.2 ± 0.2	19.6 ± 0.3	2.4 ± 0.3	
675	4/5[c]	17.2 ± 0.2	20.8 ± 0.2	3.5 ± 0.4*	106
1,350	5/5	16.8 ± 0.3	20.1 ± 0.3	3.3 ± 0.3	103
2,700	4/5[c]	16.7 ± 0.3	20.3 ± 0.7	3.4 ± 0.3	103

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Day of death: 7

13-Week Study

All mice survived to the end of the study. The final mean body weights of dosed male and female mice were similar to those of controls (Table 10). In 1,350 mg/kg male mice, the mean body weight gain was 86% that of controls, and in 2,700 mg/kg male mice, the body weight gain was 80% that of controls. No chemical-related clinical observations were noted in dosed male or female mice during the 13-week study.

The hematology, clinical chemistry, and urinalysis data for mice in the 13-week study are listed in Table G5. Reticulocytosis, evidenced by increased reticulocyte numbers, occurred in all dosed groups of male and female mice. In general, reticulocytosis indicates an erythropoietic response to anemia. In this study, there was some evidence of anemia, characterized by decreased erythrocyte counts and hematocrit values of dosed groups of females. Methemoglobinemia occurred in 1,350 and 2,700 mg/kg female mice, evidenced by increased methemoglobin concentrations. Sulfonamides can cause methemoglobinemia, and this could explain the minimal responsive anemia. The urine specific gravity values were increased in all male and female dose groups, suggesting an increased need for conservation of body water. The cause of the increased urine concentration was unknown. Increased urine concentration could, however, be related to a mild dehydration which could have masked the severity of the anemia. Leukocytosis, evidenced by increased leukocyte numbers, occurred in 2,700 mg/kg male and female mice. The leukocytosis was characterized by increases in mature neutrophil and lymphocyte numbers. There were no microscopic lesions that could account for the leukocytosis and the significance is unknown. While elevated peripheral neutrophil and lymphocyte numbers can be related to increased production, increases can also occur as a result of altered cell margination or homing, tissue migration, and recirculation. There were minimal increases in alanine aminotransferase and alkaline phosphatase activities in 1,350 and 2,700 mg/kg male mice; these changes may be consistent with the centrilobular hypertrophy observed microscopically in the liver. Minimal decreases in thyroxine concentration occurred in all dosed male and female mice. There were, however, no differences in triiodothyronine and thyroid-stimulating hormone concentrations between dosed and control animals.

Absolute and relative liver weights of all groups of dosed male and female mice were significantly greater than those of controls (Table F6).

There were no chemical-related gross lesions. Microscopic evaluation of the liver revealed centrilobular hypertrophy in five 1,350 mg/kg and all 2,700 mg/kg male mice.

The right cauda weight of the 1,350 mg/kg group and the right epididymis weights of all dose groups were significantly lower than those of controls. There was no evidence of chemical-related alteration in the vaginal cytology parameters of female mice (Table H2).

Dose Selection Rationale: Based on the absence of biologically significant body weight differences and of potentially life-threatening hepatotoxicity in dosed mice, the high dose selected for the 2-year study was 2,700 mg/kg.

TABLE 10
Survival and Body Weights of Mice in the 13-Week Gavage Study of Salicylazosulfapyridine

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
Vehicle Control	10/10	22.3 ± 0.3	31.3 ± 0.6	9.0 ± 0.5	
675	10/10	22.7 ± 0.4	30.9 ± 0.4	8.2 ± 0.6	99
1,350	10/10	22.5 ± 0.3	30.3 ± 0.5	7.7 ± 0.3*	97
2,700	10/10	23.1 ± 0.3	30.3 ± 0.4	7.2 ± 0.3**	97
Female					
Vehicle Control	10/10	18.9 ± 0.3	26.5 ± 0.5	7.6 ± 0.4	
675	10/10	19.0 ± 0.3	26.2 ± 0.3	7.1 ± 0.3	99
1,350	10/10	18.6 ± 0.2	26.4 ± 0.3	7.8 ± 0.3	100
2,700	10/10	18.5 ± 0.3	26.4 ± 0.5	7.8 ± 0.4	100

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 11 and in the Kaplan-Meier survival curves (Figure 6). Survival of all dosed groups of male and female mice was similar to that of controls.

Body Weights, Clinical Findings, and Clinical Chemistry

Mean body weights of 675 and 1,350 mg/kg male and female mice were similar to those of controls throughout the study (Figure 7 and Tables 12 and 13). From week 12 to the end of the study, 2,700 mg/kg male mice had mean body weights that were 6% to 18% lower than those of controls; the final mean body weight of 2,700 mg/kg males was 12% less than that of controls. From week 14 to the end of the study, 2,700 mg/kg female mice had mean body weights that were 5% to 19% lower than those of controls; the final mean body weight of these dosed females was 10% less than that of controls. No chemical-related clinical observations were noted in male or female mice. There were no chemical-related differences in triiodothyronine, reverse triiodothyronine, thyroxine, or thyroid-stimulating hormone concentrations between dosed and control mice at the 15-month evaluation (Table G6).

TABLE 11
Survival of Mice in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	2	0	0	0
Moribund	5	4	3	4
Natural deaths	3	5	6	0
Animals surviving to study termination	40	41	41	46
Percent probability of survival at end of study[b]	84	83	82	93
Mean survival (days)[c]	649	654	664	653
Survival analysis[d]	P=0.251N	P=1.000	P=1.000	P=0.350N
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	2	0	1	2
Moribund	5	6	8	6
Natural deaths	2	3	4	4
Animals surviving to study termination	41	41	37[e]	38
Percent probability of survival at end of study	86	83	77	80
Mean survival (days)	643	656	641	630
Survival analysis	P=0.484	P=0.839	P=0.327	P=0.594

[a] Censored from survival analyses
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.
[e] Includes one animal that died the last week of the study

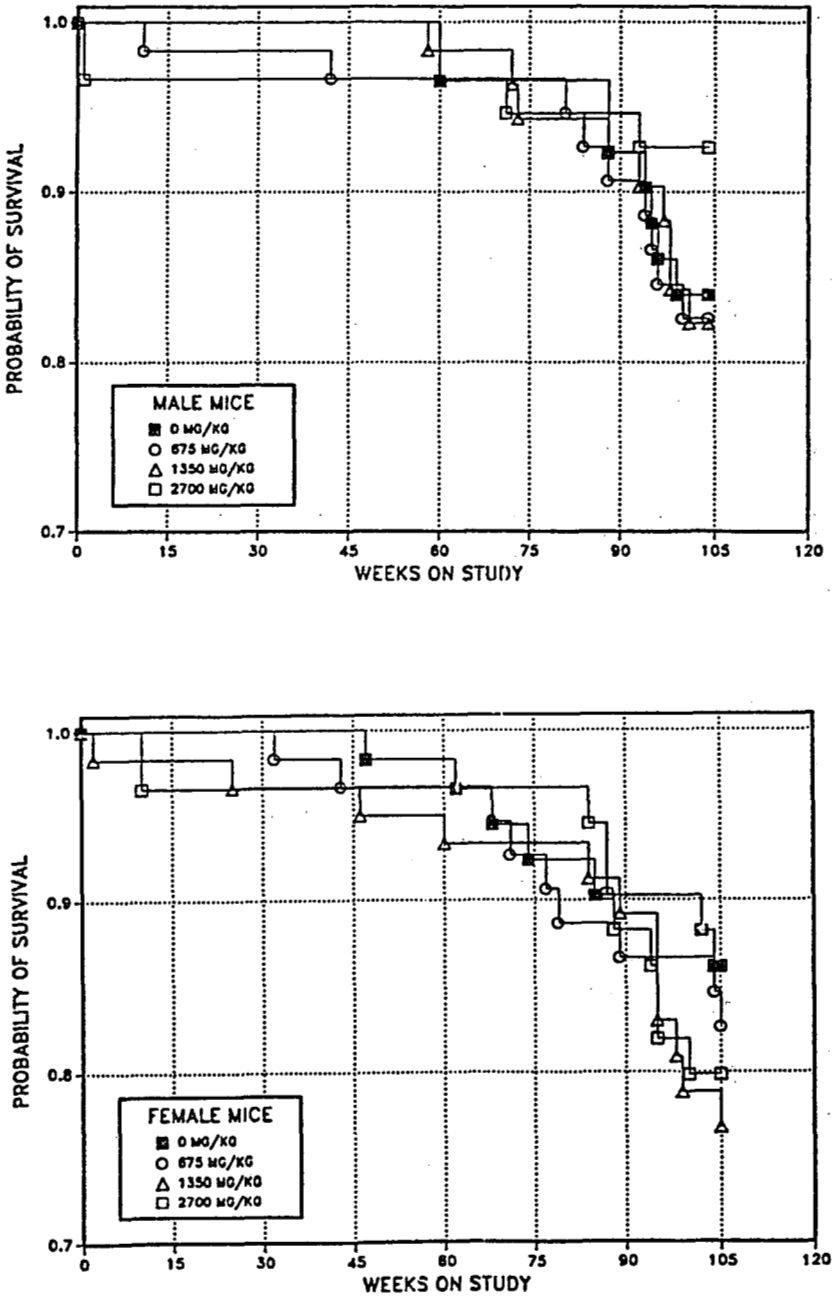


FIGURE 6
Kaplan-Meier Survival Curves for Male and Female Mice Administered Salicylazosulfapyridine by Gavage for 2 Years

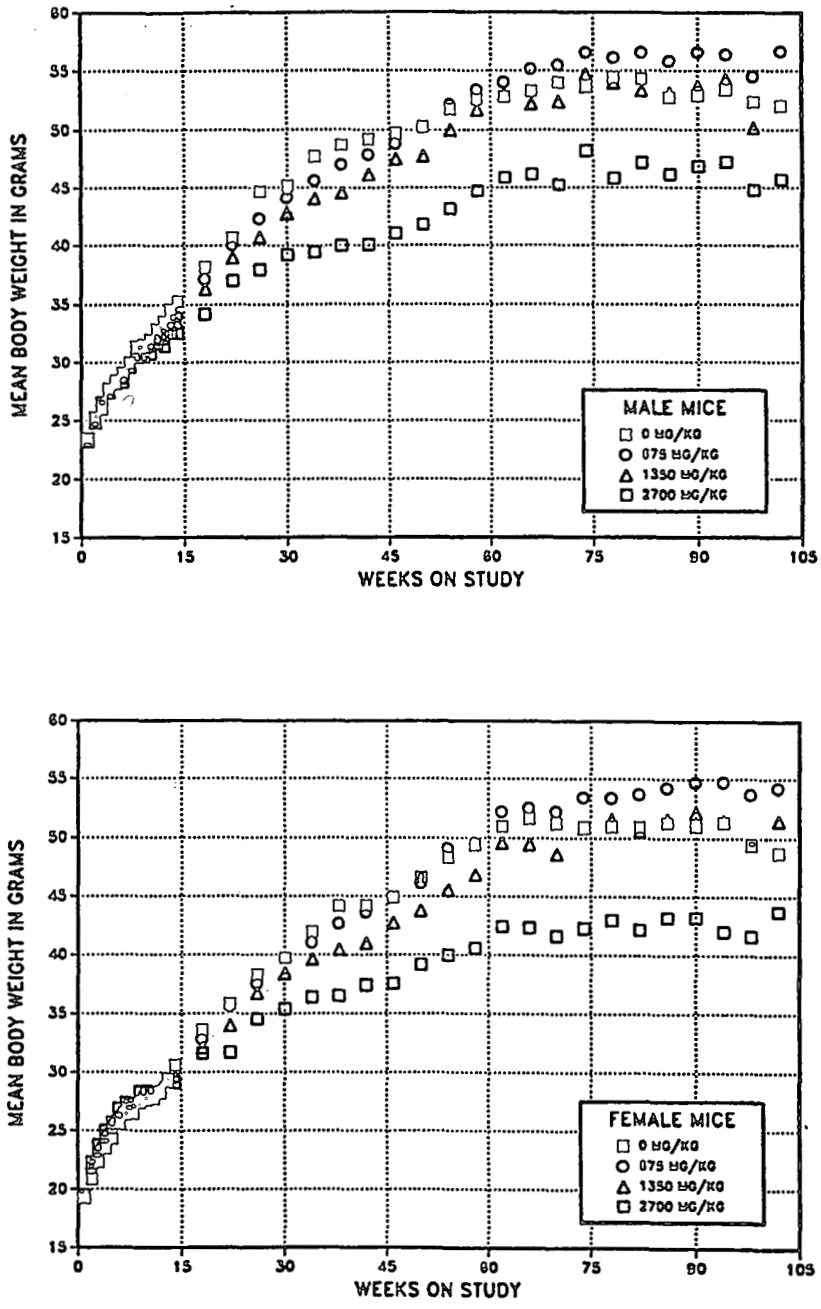


FIGURE 7
Growth Curves for Male and Female Mice
Administered Salicylazosulfapyridine by Gavage for 2 Years

TABLE 12
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	675 mg/kg Av. Wt. (g)	675 mg/kg Wt. (% of controls)	675 mg/kg No. of Survivors	1,350 mg/kg Av. Wt. (g)	1,350 mg/kg Wt. (% of controls)	1,350 mg/kg No. of Survivors	2,700 mg/kg Av. Wt. (g)	2,700 mg/kg Wt. (% of controls)	2,700 mg/kg No. of Survivors
1	23.5	60	23.2	99	60	23.3	99	60	23.2	99	60
2	25.3	60	25.0	99	60	24.8	98	60	25.0	99	58
3	25.9	60	26.3	102	60	26.4	102	60	26.6	103	58
4	27.7	60	27.6	100	60	27.4	99	60	27.7	100	58
5	28.4	60	28.5	100	60	28.1	99	60	28.1	99	58
6	29.1	60	28.7	99	60	28.7	99	60	28.3	97	58
7	30.0	60	29.9	100	60	30.0	100	60	29.5	98	58
8	31.4	60	30.6	98	60	30.5	97	60	30.4	97	58
9	31.6	60	31.2	99	60	30.5	97	60	30.7	97	58
10	32.0	60	31.3	98	60	31.5	98	60	30.8	96	58
11	32.9	60	32.0	97	60	32.2	98	60	31.7	96	58
12	33.5	60	32.5	97	59	32.1	96	60	31.4	94	58
13	34.6	60	33.8	98	59	33.3	96	60	32.5	94	58
14	35.2	60	34.0	97	59	33.4	95	60	32.5	92	58
18	38.2	60	37.1	97	59	36.3	95	60	34.2	90	58
22	40.7	60	40.1	99	59	38.9	96	60	37.0	91	58
26	44.7	59	42.3	95	59	40.7	91	60	37.9	85	58
30	45.2	59	44.1	98	59	42.7	95	60	39.2	87	58
34	47.7	59	45.6	96	59	44.0	92	60	39.4	83	58
38	48.7	59	47.0	97	59	44.6	92	60	40.0	82	58
42	49.2	59	47.9	97	59	46.2	94	60	40.1	82	58
46	49.7	59	48.8	98	58	47.5	96	60	41.0	83	58
50	50.2	59	50.3	100	58	47.8	95	60	41.8	83	58
54	51.7	58	52.1	101	58	50.0	97	60	43.1	83	58
58	52.6	58	53.4	102	58	51.7	98	59	44.7	85	58
62	52.8	56	54.0	102	58	53.0	100	59	45.9	87	58
66[a]	53.3	46	55.2	104	48	52.2	98	49	46.2	87	48
70	54.0	46	55.5	103	48	52.4	97	49	45.2	84	48
74	53.6	46	56.6	106	48	54.7	102	47	48.2	90	47
78	54.4	46	56.1	103	48	54.0	99	47	45.8	84	47
82	54.3	46	56.5	104	47	53.3	98	47	47.2	87	47
86	52.7	46	55.8	106	46	53.1	101	47	46.2	88	47
90	52.9	44	56.6	107	45	53.7	102	46	46.8	89	47
94	53.4	44	56.4	106	45	54.3	102	45	47.2	88	46
98	52.3	41	54.5	104	42	50.1	96	44	44.8	86	46
102	52.0	40	56.7	109	41	52.1	100	41	45.7	88	46
Mean for weeks											
1-13	29.7		29.3	99		29.1	98		28.9	97	
14-52	45.0		43.7	97		42.2	94		38.3	85	
53-102	53.1		55.3	104		52.7	99		45.9	86	

[a] Interim evaluation occurred during week 66.

TABLE 13
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	675 mg/kg Av. Wt. (g)	675 mg/kg Wt. (% of controls)	675 mg/kg No. of Survivors	1,350 mg/kg Av. Wt. (g)	1,350 mg/kg Wt. (% of controls)	1,350 mg/kg No. of Survivors	2,700 mg/kg Av. Wt. (g)	2,700 mg/kg Wt. (% of controls)	2,700 mg/kg No. of Survivors
1	19.2	60	19.2	100	60	19.6	102	60	19.5	102	60
2	20.8	60	21.6	104	60	22.2	107	59	22.3	107	59
3	22.3	59	22.8	102	60	23.5	105	59	23.8	107	59
4	23.5	59	24.0	102	60	24.8	106	59	25.0	106	59
5	24.3	59	24.9	103	60	25.8	106	59	25.6	105	59
6	25.6	59	26.1	102	60	26.5	104	59	26.9	105	59
7	26.3	59	26.8	102	60	27.5	105	59	27.4	104	59
8	26.5	59	26.8	101	60	27.1	102	59	27.3	103	59
9	27.4	59	27.6	101	60	27.9	102	59	28.4	104	59
10	27.6	59	27.7	100	60	28.1	102	59	28.4	103	58
11	27.7	58	27.8	100	60	28.0	101	59	28.3	102	56
12	28.2	58	28.5	101	60	28.7	102	59	28.4	101	56
13	29.4	58	29.3	100	60	29.2	99	59	29.4	100	56
14	30.6	58	29.5	96	60	29.7	97	59	29.1	95	56
18	33.6	58	32.8	98	60	32.1	96	59	31.6	94	56
22	35.8	58	35.6	99	60	34.0	95	59	31.7	89	56
26	38.3	58	37.5	98	60	36.7	96	58	34.5	90	56
30	39.7	58	39.7	100	60	38.4	97	58	35.4	89	56
34	42.0	58	41.0	98	59	39.6	94	58	36.4	87	56
38	44.2	58	42.7	97	59	40.4	91	58	36.5	83	56
42	44.2	58	43.6	99	59	41.0	93	58	37.4	85	56
46	44.9	58	44.8	100	58	42.7	95	57	37.5	84	56
50	46.6	57	46.1	99	58	43.8	94	57	39.1	84	56
54	48.3	57	49.1	102	58	45.6	94	57	40.0	83	56
58	49.4	57	49.6	100	58	46.8	95	57	40.6	82	56
62	51.0	56	52.2	102	58	49.6	97	56	42.5	83	56
66[a]	51.6	46	52.5	102	48	49.5	96	46	42.3	82	46
70	51.2	45	52.2	102	47	48.6	95	45	41.6	81	46
74	51.0	45	53.4	105	46	50.8	100	45	42.3	83	46
78	51.0	44	53.4	105	45	51.6	101	45	43.0	84	46
82	50.9	44	53.7	106	44	50.6	99	45	42.2	83	46
86	51.3	43	54.3	106	44	51.6	101	44	43.2	84	45
90	51.0	43	54.7	107	43	52.2	102	43	43.2	85	42
94	51.3	43	54.8	107	43	51.5	100	43	42.0	82	41
98	49.5	43	53.7	109	43	49.4	100	40	41.6	84	39
102	48.7	42	54.2	111	43	51.5	106	38	43.7	90	38
Mean for weeks											
1-13	25.3		25.6	101		26.1	103		26.2	104	
14-52	40.0		39.3	98		37.8	95		34.9	87	
53-102	50.5		52.9	105		49.9	99		42.2	84	

[a] Interim evaluation occurred during week 66.

Pathology and Statistical Analysis

This section describes the statistically significant and biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the liver, spleen, forestomach, and other organs. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one dose group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: The absolute and relative liver weights of 1,350 mg/kg male mice were significantly greater than those of controls at the 15-month interim evaluation (Table F7). Incidences of hepatocellular adenoma (single and multiple or multiple) in all dosed groups of male and female mice were significantly greater than those in controls at 2 years (Tables 14, C3, and D3) and occurred with a positive trend. Furthermore, the incidences of hepatocellular adenoma (single and multiple) in 675 and 2,700 mg/kg male mice and all dosed groups of female mice exceeded the ranges in historical controls from NTP 2-year corn oil gavage studies (Tables 14, C4a, and D4a). The incidences of hepatocellular carcinoma (single and multiple) in 1,350 mg/kg male mice and all dosed groups of female mice were significantly greater than those in controls. The incidences of hepatocellular carcinoma (single and multiple) in vehicle control, 675, and 1,350 mg/kg male mice and all dosed groups of female mice exceeded the ranges in historical controls from NTP 2-year corn oil gavage studies (Tables 14, C4a, and D4a). Additionally, the combined incidences of hepatocellular adenoma or carcinoma were greater in dosed mice than those in controls, and in males, the incidences increased with increasing dose.

The incidences of nonneoplastic cytologic alterations of the liver in 1,350 and 2,700 mg/kg male and female mice at the 15-month interim evaluation were significantly greater than those in controls (Tables 14, C5, and D5). At the end of the 2-year study, the incidences of eosinophilic foci in all dosed groups of male and female mice were significantly greater than those in controls. The incidences of clear cell foci in 675 and 2,700 mg/kg male mice were significantly greater than that in controls.

Hepatocellular adenomas were nodular and occasionally multinodular masses of hepatocyte proliferation that varied in their tinctorial properties. Characteristic features included well-defined borders, variable compression of the surrounding parenchyma, alteration of the hepatic architecture with the absence of portal areas and central veins, and hepatic cords intersecting at an angle to the surrounding hepatic parenchyma. Carcinomas were generally larger and more irregular than adenomas. Compression and invasion of the surrounding parenchyma were typical, as were abnormal growth patterns with normal appearing and/or atypical hepatocytes arranged in solid sheets and trabeculae three or more cells thick. Eosinophilic foci were typically nodular lesions with generally discrete borders and normal lobular architecture with hepatic cords that blended with those of the surrounding normal parenchyma. The hepatocytes of eosinophilic foci were often larger and more eosinophilic than histologically normal hepatocytes of the adjacent parenchyma. Clear cell foci were discrete nodular lesions that consisted of enlarged vacuolated hepatocytes.

Cytologic alteration was observed at the 15-month interim evaluation and was most prominent in male mice receiving 2,700 mg/kg. It was characterized primarily by loss of cytoplasmic vacuolization, presumably due to the loss of glycogen from centrilobular hepatocytes with concomitant accentuation of the lobular hepatic architecture and an apparent increase in the size of the hepatocytes. Lesions of minimal severity involved hepatocytes immediately surrounding the central veins. With increasing severity, more hepatocytes were involved and cytoplasmic vacuolization was essentially absent from centrilobular hepatocytes and decreased in hepatocytes located more peripherally in the hepatic lobules. The loss of cytoplasmic vacuolization was most likely physiologic in nature. Mean body weights of 2,700 mg/kg males and females at 15 months and the end of the 2-year study were lower than those of the control groups. The degree of hepatocellular vacuolization is known to change with the nutritional status of the animal; it is often decreased or absent in early death or moribund animals and in animals fasted prior to sacrifice.

Hepatocellular cytoplasmic vacuolization may also vary with the time of day depending upon whether the animal is in a pre- or postprandial status. The significance of the apparent absence of this change at the 2-year evaluation is not clear. The severity of the lesion was essentially minimal at 15 months, and at 2 years it may have been masked by spontaneous changes that occur in the liver with advancing age.

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Cytologic Alterations[a]	0	2	8**	10**
Hepatocellular Adenoma	2	2	0	2
Hepatocellular Carcinoma	0	0	1	0
2-Year Study				
Number Examined Microscopically	50	50	50	50
Clear Cell Foci	2	14**	5	11*
Eosinophilic Foci	6	19**	20**	22**
Hepatocellular Adenoma (Multiple)				
Overall rate	1/50 (2%)	21/50 (42%)**	15/50 (30%)**	27/50 (54%)**
Hepatocellular Adenoma (Single and Multiple)[b]				
Overall rate[c]	13/50 (26%)	32/50 (64%)	28/50 (56%)	42/50 (84%)
Adjusted rate[d]	32.5%	76.2%	66.6%	87.5%
Terminal rate[e]	13/40 (33%)	31/41 (76%)	27/41 (66%)	40/46 (87%)
First incidence (days)	728 (T)	666	678	497
Logistic regression test[f]	P<0.001	P<0.001	P=0.002	P<0.001
Hepatocellular Carcinoma (Multiple)				
Overall rate	1/50 (2%)	4/50 (8%)	5/50 (10%)	0/50 (0%)
Hepatocellular Carcinoma (Single and Multiple)[g]				
Overall rate	13/50 (26%)	15/50 (30%)	23/50 (46%)	8/50 (16%)
Adjusted rate	29.2%	33.8%	51.0%	17.4%
Terminal rate	9/40 (23%)	12/41 (29%)	19/41 (46%)	8/46 (17%)
First incidence (days)	420	567	611	728 (T)
Logistic regression test	P=0.154N	P=0.415	P=0.035	P=0.159N
Hepatocellular Adenoma or Carcinoma[h]				
Overall rate	24/50 (48%)	38/50 (76%)	38/50 (76%)	44/50 (88%)
Adjusted rate	54.3%	84.4%	82.6%	91.7%
Terminal rate	20/40 (50%)	34/41 (83%)	33/41 (80%)	42/46 (91%)
First incidence (days)	420	567	611	497
Logistic regression test	P<0.001	P=0.004	P=0.005	P<0.001

(continued)

* Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test (interim evaluation) or the logistic regression test (2-year study)
** P≤0.01
(T)Terminal sacrifice

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Female				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Cytologic Alterations	0	3	6**	8**
Hepatocellular Adenoma	1	0	1	2
2-Year Study				
Number Examined Microscopically	50	50	50	49
Eosinophilic Foci	5	17**	15*	19**
Hepatocellular Adenoma (Multiple)				
Overall rate	3/50 (6%)	12/50 (24%)**	12/50 (24%)**	13/49 (27%)**
Hepatocellular Adenoma (Single and Multiple)[i]				
Overall rate	12/50 (24%)	28/50 (56%)	25/50 (50%)	28/49 (57%)
Adjusted rate	29.3%	63.6%	65.7%	71.7%
Terminal rate	12/41 (29%)	25/41 (61%)	24/37 (65%)	27/38 (71%)
First incidence (days)	735 (T)	539	618	655
Logistic regression test	P=0.002	P=0.001	P=0.002	P<0.001
Hepatocellular Carcinoma (Multiple)				
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	1/49 (2%)
Hepatocellular Carcinoma (Single and Multiple)[j]				
Overall rate	2/50 (4%)	10/50 (20%)	10/50 (20%)	9/49 (18%)
Adjusted rate	4.9%	23.7%	27.0%	23.7%
Terminal rate	2/41 (5%)	9/41 (22%)	10/37 (27%)	9/38 (24%)
First incidence (days)	735 (T)	551	735 (T)	735 (T)
Logistic regression test	P=0.059	P=0.017	P=0.009	P=0.019
Hepatocellular Adenoma or Carcinoma[k]				
Overall rate	14/50 (28%)	32/50 (64%)	28/50 (56%)	29/49 (59%)
Adjusted rate	34.1%	71.1%	73.6%	74.3%
Terminal rate	14/41 (34%)	28/41 (68%)	27/37 (73%)	28/38 (74%)
First incidence (days)	735 (T)	539	618	655
Logistic regression test	P=0.005	P<0.001	P=0.001	P<0.001

[a] Number of animals with lesion
[b] Historical incidence for 2-year NTP corn oil gavage studies with vehicle control groups (mean ± standard deviation): 254/763 (33.3% ± 13.4%), range 14%-58%
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in a dose group is indicated by N.
[g] Historical incidence: 127/763 (16.6% ± 4.5%), range 8%-24%
[h] Historical incidence: 340/763 (44.6% ± 14.6%), range 25%-72%
[i] Historical incidence: 99/759 (13.0% ± 8.4%), range 2%-28%
[j] Historical incidence: 38/759 (5.0% ± 3.7%), range 0%-14%
[k] Historical incidence: 131/759 (17.3% ± 9.8%), range 4%-37%

Spleen: The absolute and relative spleen weights of females receiving 1,350 and 2,700 mg/kg were significantly greater than those of controls at the 15-month interim evaluation (Table F7). The incidences of hematopoietic cell proliferation and hemosiderin pigment in all dosed groups of male and female mice were significantly greater than those in controls at the 15-month interim evaluation (Tables 15, C5, and D5). The incidences of hemosiderin pigment in dosed groups of male and female mice at the end of the 2-year study were significantly greater than those in controls. At the end of the 2-year study, the incidences of hematopoietic cell proliferation in dosed groups of female mice were significantly greater than that in controls.

Hematopoietic cell proliferation was a minimal to moderate change consisting of a diffuse increase in the number of hematopoietic cells within the splenic red pulp. Hemosiderin pigment was generally a minimal to mild change characterized by increased numbers of macrophages containing numerous prominent, irregular, brown-black, intracytoplasmic granules scattered within the red pulp. Increased splenic hemosiderin pigment is suggestive of increased erythrocyte destruction (hemolysis).

TABLE 15
Incidences of Nonneoplastic Lesions of the Spleen in Mice in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control		675 mg/kg		1,350 mg/kg		2,700 mg/kg	
Male								
15-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Hematopoietic Cell Proliferation[a]	2	(1.5)[b]	8*	(1.5)	10**	(1.6)	10**	(2.6)
Hemosiderin Pigment	0		4*	(1.0)	10**	(1.5)	10**	(2.0)
2-Year Study								
Number Examined Microscopically	50		50		49		50	
Hematopoietic Cell Proliferation	11	(2.0)	16	(2.4)	20*	(2.5)	13	(1.9)
Hemosiderin Pigment	2	(2.0)	25**	(1.2)	32**	(1.4)	47**	(1.6)
Female								
15-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Hematopoietic Cell Proliferation	2	(2.5)	7*	(1.6)	10**	(2.4)	10**	(2.0)
Hemosiderin Pigment	0		10**	(1.7)	10**	(2.0)	10**	(2.3)
2-Year Study								
Number Examined Microscopically	50		50		50		49	
Hematopoietic Cell Proliferation	7	(2.4)	21**	(2.5)	19**	(2.5)	23**	(2.2)
Hemosiderin Pigment	14	(1.3)	37**	(1.6)	39**	(1.5)	46**	(1.8)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test (interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Forestomach: The incidence of squamous cell papilloma was significantly lower in 2,700 mg/kg females than in controls (vehicle control, 5/50; 675 mg/kg, 1/50; 1,350 mg/kg, 1/50; 2,700 mg/kg, 0/50; Table D3). The incidences of hyperplasia were significantly lower in 2,700 mg/kg males (18/50, 11/50, 11/49, 10/50; Table C5) and in 1,350 and 2,700 mg/kg females (12/50, 6/49, 4/50, 4/49; Table D5). Epithelial (squamous) hyperplasia and hyperkeratosis with or without the occurrence of squamous cell neoplasms are sometimes encountered in gavage studies. Such lesions may be associated with irritation or trauma inflicted during the gavage procedure. The biological significance of the chemical-related lower incidences of forestomach lesions in dosed male and female mice is not certain, but may be related to the antiinflammatory properties of salicylazosulfapyridine.

Other Organs: The incidences of hemangiosarcoma (0/50, 2/50, 4/50, 1/49; Table D3) were marginally greater in the spleen of dosed female mice than in controls. The incidences of mineralization of the glandular stomach (1/50, 11/50, 9/48, 7/50; Table C5) were greater in dosed males than in controls. The incidences of thyroid gland follicle degeneration (1/50, 5/50, 6/50, 10/50) and dilatation in the uterus (4/50, 17/50, 11/50, 11/49) in dosed groups of females were greater than in controls (Table D5).

The incidences of dilatation in the seminal vesicle (14/50, 2/50, 4/50, 0/50) and thyroid gland follicular cell hyperplasia (9/50, 4/50, 3/50, 2/50) were lower in dosed males than in controls (Table C5). The incidences of renal tubule casts (13/50, 11/50, 12/50, 3/50) and regeneration (38/50, 40/50, 40/50, 24/50) were lower in males administered 2,700 mg/kg than in controls (Table C5). The incidence of ductal cysts in the preputial gland (45/49, 40/49, 31/49, 38/50; Table C5) was lower in males administered 1,350 mg/kg than in controls. The incidences of thyroid gland follicular cell hyperplasia (20/50, 5/50, 2/50, 1/50; Table D5) were lower in dosed females than in controls. The incidence of cysts within thyroid gland follicles (6/50, 4/50, 3/50, 0/50; Table D5), was lower in females administered 2,700 mg/kg than in controls.

The biological significance of these incidences is uncertain. In general, 1) the lesions represent typical age-related changes encountered in chronic studies, 2) the increased or decreased incidences were marginal and did not have a clear dose-related trend, or 3) there was usually no similar effect in animals of the other sex.

GENETIC TOXICOLOGY

Salicylazosulfapyridine (33-6,666 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 when tested in a preincubation protocol with and without induced rat or hamster liver S9 metabolic activation enzymes (Table E1). It did not induce sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3) in cultured Chinese hamster ovary cells, with or without induced rat liver S9 (Bishop *et al.*, 1990). In contrast to the negative results obtained *in vitro*, results from *in vivo* genotoxicity tests with salicylazosulfapyridine yielded generally positive results.

Salicylazosulfapyridine gave a strongly positive response in a micronucleus assay conducted with peripheral blood smears obtained from mice used in the 13-week toxicity study (Table E4; Bishop *et al.*, 1990). Significant increases in the frequencies of micronucleated polychromatic erythrocytes were observed in male and female mice administered 2,700 mg salicylazosulfapyridine/kg body weight. Significantly elevated micronucleus frequencies were also observed in normochromatic erythrocytes in male and female mice administered 675, 1,350, or 2,700 mg/kg. A dose-related increase in the percentage of polychromatic erythrocytes was also observed in all dosed groups of males and females, indicating that erythropoiesis was stimulated in animals dosed with salicylazosulfapyridine.

Salicylazosulfapyridine was subsequently tested for induction of chromosomal aberrations in bone marrow cells of male mice following single gavage administrations of 250 to 1,000 mg/kg (Table E5; Bishop *et al.*, 1990). These doses, selected on the basis of results from a preliminary range-finding study, were less than all but the lowest dose tested in the 13-week study. No significant increases in chromosomal aberrations were noted in either of the two trials conducted.

Subsequent micronucleus tests with salicylazosulfapyridine confirmed the positive response observed in the initial 13-week peripheral blood test. A small but significant increase in polychromatic erythrocytes was observed in the bone marrow of male mice administered 250 to 2,000 mg salicylazosulfapyridine/kg body weight in corn oil by gavage, twice at 24-hour intervals; sampling was performed 24 hours after administration of the second dose (Table E6; Bishop *et al.*, 1990).

A specialized micronucleus test was performed with salicylazosulfapyridine to investigate the aneuploidy-inducing potential of the compound, implied by the positive results from micronuclei assays (which detect both numerical and structural chromosomal aberrations) and the negative results from the *in vitro* and *in vivo* chromosomal aberrations assays (which detect only structural damage). In this micronucleus/kinetochore-staining assay (Table E7; Witt *et al.*, 1992b), salicylazosulfapyridine induced dose-related increases in the number of total micronucleated polychromatic erythrocytes; in addition, the micronuclei that were induced were predominantly kinetochore-positive (contained a fluorescent signal indicating the presence of a kinetochore and presumably, therefore, an entire chromosome rather than a fragment). Salicylazosulfapyridine also induced a significant increase in kinetochore-negative micronuclei, but only at the highest dose tested in the second trial; the majority of induced micronuclei stained positive for the presence of a kinetochore. These results imply that salicylazosulfapyridine produces aneuploidogenic rather than clastogenic chromosomal effects.

Because positive results were observed in micronucleus experiments that employed multiple dosing protocols (standard for a micronucleus assay), and because the single-dose chromosomal aberrations protocol was negative, salicylazosulfapyridine was tested for induction of micronuclei and chromosomal aberrations in nonstandard protocols that were designed to measure the influence of treatment schedules. Table E8 presents results from a series of bone marrow micronucleus tests performed with male and female mice. Significant increases in micronucleated polychromatic erythrocytes were observed in each of two trials in which female mice were dosed with salicylazosulfapyridine three times by gavage. Male mice were administered salicylazosulfapyridine either by single (Trial 1) or triple (Trial 2) gavage protocols. Results of the first experiment were negative, whereas results obtained in the second trial using the triple-treatment protocol were positive, thus underscoring the relationship between dosing schedule and detection of a genotoxic response.

Salicylazosulfapyridine was further tested for induction of chromosomal aberrations in a nonstandard, triple-treatment protocol that used three gavage administrations separated by 24-hour intervals in an attempt to mimic the same exposure environment that produced the positive micronucleus test results. The highest dose used in this experiment was 4,000 mg/kg. Again, no induction of chromosomal aberrations by salicylazosulfapyridine was noted in mouse bone marrow cells (Table E9). These results further support the hypothesis that salicylazosulfapyridine is aneuploidogenic.

Because the carcinogenicity of salicylazosulfapyridine was being evaluated by the NTP in both rats and mice, a micronucleus test was also performed in male rats using the triple-treatment protocol (Table E10). The overall results were considered to be equivocal because the weakly positive response obtained in the first trial with doses as great as 2,700 mg/kg did not repeat in the second trial when doses as great as 3,000 mg/kg were tested. Thus, there appears to be a species difference in response to bone marrow erythrocyte micronucleus induction by salicylazosulfapyridine.

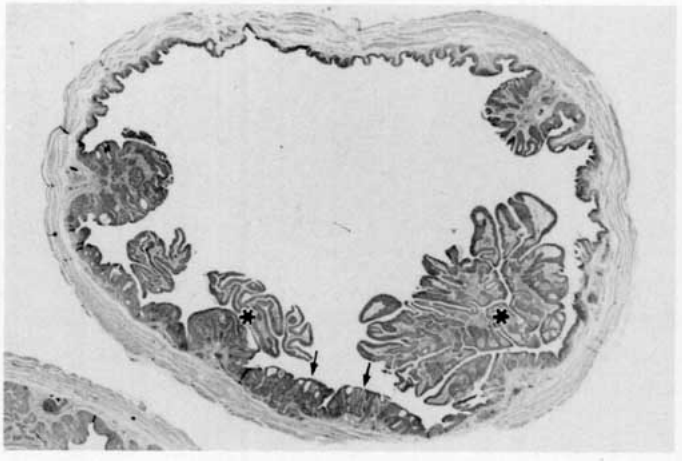


PLATE 1
Urinary bladder from a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. Multiple papillomas (*) and variable mucosal (transitional) epithelial hyperplasia (arrows). H&E; 6.5×

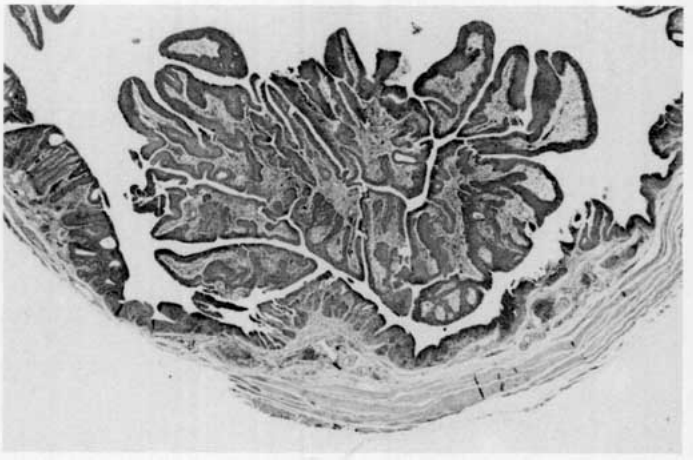


PLATE 2
Higher magnification of Plate 1. Papillomas consist of hyperplastic mucosal epithelium forming papillary fronds supported by fibrous stroma. H&E; 13×

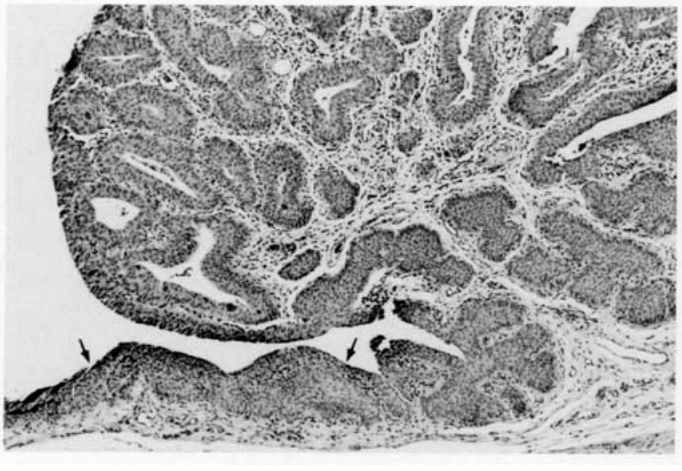


PLATE 3
Urinary bladder from a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. Details of a papilloma showing hyperplastic epithelium within the neoplasm supported by fibrovascular stroma. Note hyperplastic mucosal epithelium adjacent to the base of the papilloma (arrows). H&E; 52×

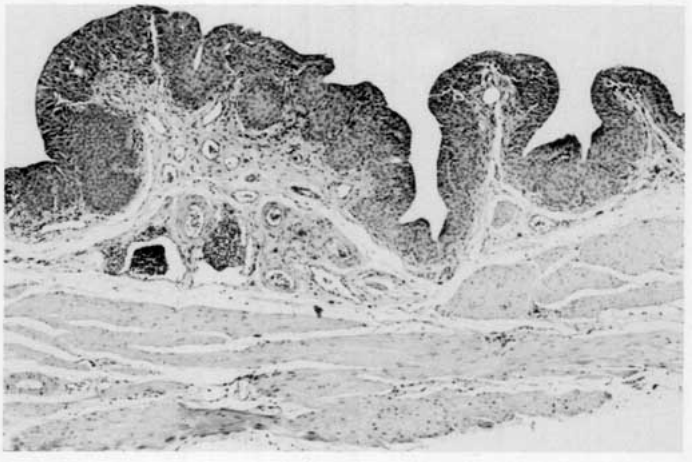


PLATE 4
Urinary bladder from a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. Moderate mucosal hyperplasia; note folding of the mucosa. H&E; 52×

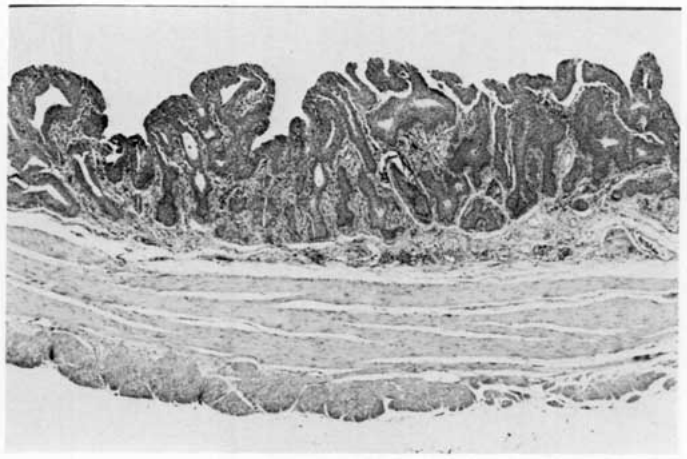


PLATE 5
Urinary bladder from a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. Marked mucosal hyperplasia; the hyperplastic epithelium forms thick complex folds that project into the lumen. H&E; 25×

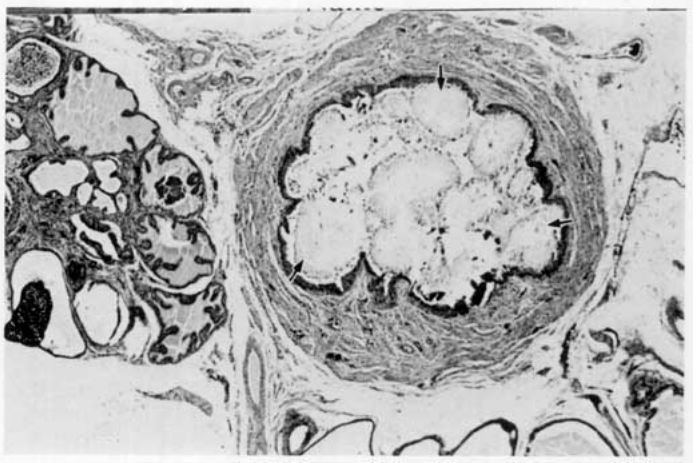


PLATE 6
Example of concretions observed in the urinary bladder, ureter and urethra. Multiple concretions (arrows) occlude the lumen of the urethra of a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. H&E; 26×

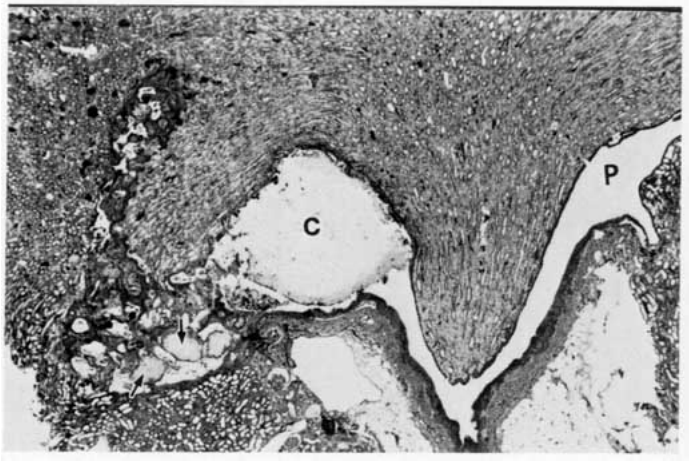


PLATE 7
Kidney from a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. Renal pelvis (P) with concretions (C) in the lumen and incorporated within hyperplastic transitional epithelium (arrows). H&E; 13×

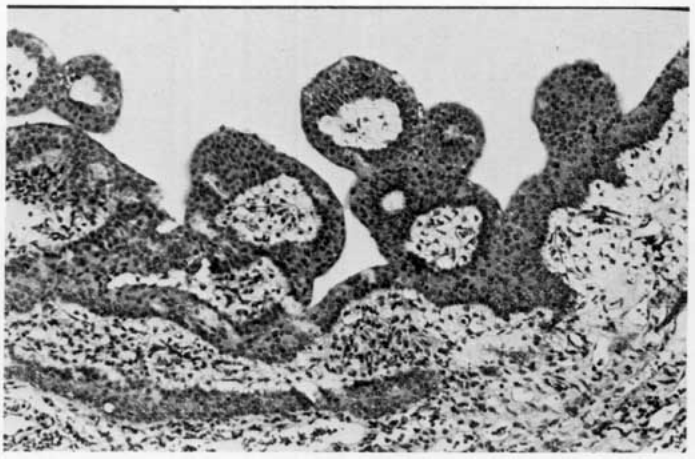


PLATE 8
Kidney from a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. Nodular and papillary thickening of the transitional epithelium of the renal pelvis. H&E; 104×

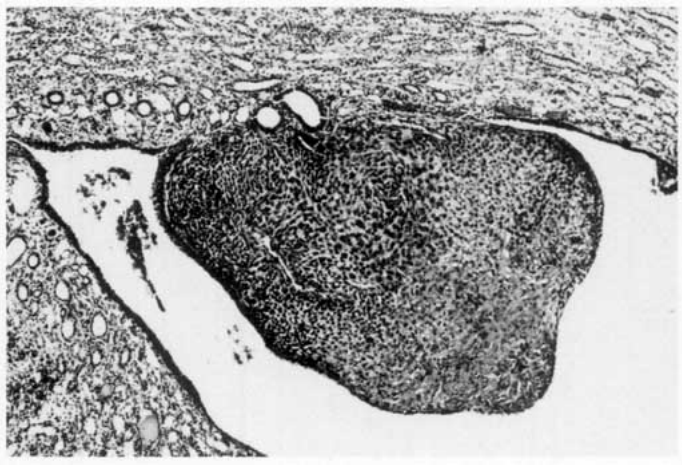


PLATE 9
Kidney from a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. Focal atypical transitional hyperplasia consist of a nodule of polyhedral to spindle cells projecting into the renal pelvis. H&E; 52×

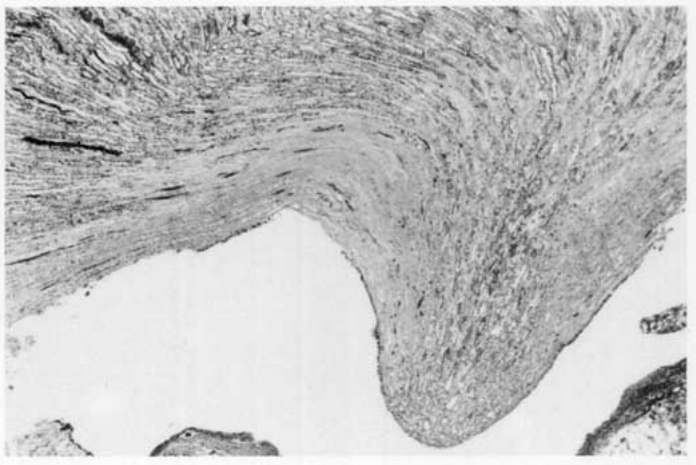


PLATE 10
Kidney from a male F344/N rat administered 337.5 mg/kg salicylazosulfapyridine in corn oil by gavage for 2 years. Renal papillary necrosis; note lack of cellular detail, pyknotic nuclei and cellular debris. H&E; 20×

DISCUSSION AND CONCLUSIONS

Salicylazosulfapyridine, a drug widely used in the treatment of ulcerative colitis, has complex biological activities when it is cleaved into 5-aminosalicylic acid (anti-inflammatory) and sulfapyridine (antimicrobial). Salicylazosulfapyridine was nominated for toxicity and carcinogenicity study by the National Cancer Institute based on its widespread use and because it is a representative of the aryl sulfonamide class.

The 16-day and 13-week studies were conducted to characterize the toxic effects of salicylazosulfapyridine in F344/N rats and B6C3F$_1$ mice, to identify potential target organs, and to estimate dose ranges that would be compatible with growth and survival in longer term studies. In the 16-day studies, salicylazosulfapyridine was administered (0, 675, 1,350, and 2,700 mg salicylazosulfapyridine/kg) in corn oil by gavage to groups of five male and five female F344/N rats and B6C3F$_1$ mice. Final mean body weights of dosed rats ranged from 5% to 32% less than those of controls while final mean body weights and weight gains of dosed mice were generally similar to those of controls. Chemical-related gross lesions included enlarged, discolored thyroid glands in male and female rats and enlarged cecae/large intestines in male and female rats and in male mice. Microscopic lesions were present in the thymus in male and female rats given 2,700 mg/kg and in the thyroid and pituitary glands in male and female rats receiving 1,350 or 2,700 mg/kg. Rat serum triiodothyronine and thyroxine concentrations were decreased in a dose-dependent manner and this was most pronounced in males. Considered together, the clinical chemistry and microscopic evaluations revealed evidence indicative of chemical-induced increased activity of the thyroid gland.

Subsequent investigations were conducted to characterize the toxic effects of repeated exposures of salicylazosulfapyridine in rats and mice with emphasis on morphologic and functional alterations of the pituitary-thyroid axis. In rats, the decreased concentrations of triiodothyronine and thyroxine evident in 2,700 mg/kg male and female rats in the 16-day study were also evident in 337.5 mg/kg male rats in the 13-week study. There were minor decreases in thyroxine concentration in all groups of dosed male and female mice in the 13-week study. However, there were no differences in triiodothyronine and thyroid-stimulating hormone concentrations between dosed and control animals, suggesting the thyroxine changes were not biologically relevant. Sulfonamides are known goitrogens which act by inhibiting thyroid peroxidase, an enzyme required for the iodination of thyroglobulin during thyroid hormone biosynthesis (Capen *et al.*, 1991). Rats appear to be especially susceptible to this effect but the mouse also is sensitive to the goitrogenic effects of sulfonamides (Capen *et al.*, 1991). Thyroid sensitivity in F344 rats but not B6C3F$_1$ mice fed sulfamethazine, an analogue of salicylazosulfapyridine, has been reported (Heath and Littlefield, 1984).

In the 13-week mouse study, there was marginal evidence of a responsive anemia. The anemia was probably related to a methemoglobinemia as exhibited in female mice given 1,350 or 2,700 mg/kg. Increased erythrocyte methemoglobin concentrations cause increased red cell turnover. The anemia that results then stimulates an erythropoietic response resulting in reticulocytosis. Sulfonamides probably cause methemoglobinemia indirectly, through metabolites, since they do not cause increased methemoglobin formation *in vitro* (Nelson, 1979). Activation of salicylazosulfapyridine to the sulfapyridine metabolite by liver microsomes has been shown to cause methemoglobinemia *in vitro* (Pirmohamed *et al.*, 1991). Interestingly, pharmacokinetic studies indicated much higher maximum plasma concentrations of sulfapyridine in mice than in rats following oral administration of salicylazosulfapyridine (NTP, 1994a; Appendix L). The maximum plasma concentrations of sulfapyridine in female mice were equal to, or greater than, those for male mice at the same dose. The area under the concentration-time curve was greater for female mice compared to males for all doses. Thus, female mice were exposed to higher concentrations of sulfapyridine for a longer period of time than male mice,

possibly explaining the observed gender difference in methemoglobin.

There were minimal increases in alanine aminotransferase and alkaline phosphatase activities in 1,350 and 2,700 mg/kg male mice, and these changes may be consistent with the centrilobular hypertrophy observed microscopically in the liver.

The significance of the chemical-related decreases in sperm motility in all dosed groups of male rats in the 13-week study is unclear. Nevertheless, these results are consistent with those of Pholpramool and Srikhao (1983) who noted slightly decreased sperm motility in Fischer rats receiving up to 600 mg salicylazosulfapyridine/kg body weight by gavage. Other investigators have shown that when male Sprague-Dawley rats were fed salicylazosulfapyridine at doses up to 617 mg/kg per day for 8 weeks and then mated to virgin females, there were dose-dependent declines in fertility accompanied by significant reductions in litter sizes. Male rats fed the metabolite sulfapyridine also had reduced litter sizes when mated to untreated virgins, while those fed the metabolite 5-aminosalicylic acid sired litters of comparable size to those of control rats (Ó'Moráin *et al.*, 1984). Similarly, NTP-sponsored reproductive assessment of salicylazosulfapyridine using continuous breeding protocols found decreased male fertility in the absence of changes in sperm motility at doses up to 400 mg/kg (corn oil gavage) in Sprague-Dawley rats (EHRT, 1992). The different outcomes in these studies may be the result of strain differences. An evaluation of sperm quality (density, motility, and morphology) in time-course studies indicated that the metabolite sulfapyridine may be directly toxic to developing spermatozoa in humans (Toovey *et al.*, 1981).

Doses selected for the 2-year study in male and female rats (0, 84, 168, and 337.5 mg/kg by corn oil gavage) were based on the results of the 13-week study. It was anticipated that the high dose (337.5 mg/kg) would cause marginal toxicity as suggested by the lower body weight gains and the thyroid gland effects observed in the 16-day and 13-week studies, and that 84 and 168 mg/kg would probably encompass no-adverse-effect-levels with respect to toxicity.

There were several reasons thyroid gland neoplasms were expected to occur in the 2-year rat study. These included: 1) the perturbation of serum hormone concentrations indicative of pituitary gland disturbances (thyroid-stimulating hormone, triiodothyronine, and thyroxine); 2) histologic evidence of thyroid gland follicular cell hyperplasia; and 3) the reported goitrogenic and carcinogenic activities of sulfonamides in general, and of the structural analogues of salicylazosulfapyridine in particular. Consequently, male rats that appeared to be the most sensitive in the 13-week study were given 337.5 mg salicylazosulfapyridine/kg body weight for 6 months, after which animals received only the corn oil vehicle for the remainder of the 2-year study. In this way the progression or regression of thyroid gland lesions in the absence of a sustained exposure could be evaluated.

The thyroid gland hyperplasia seen in the 13-week study was not observed in the 2-year study, and there was no evidence of chemical-related thyroid gland follicular cell adenomas or carcinomas. While follicular cell neoplasms of the thyroid gland are rare in untreated F344 rats, they are readily induced by chemicals with goitrogenic activity; this is seen as a secondary result of an increase in thyroid-stimulating hormone by goitrogens (Capen, 1997). In the present studies, hypothyroidism (decreased triiodothyronine and thyroxine concentrations) was evident in the male and female rats receiving 2,700 mg/kg in the 16-day study but was only evident in the 337.5 mg/kg male rats in the 13-week study. At the 15-month evaluation, there was no biochemical evidence of hypothyroidism indicating that the thyroid gland effects in rats were transient; the rats may have adapted to the mildly goitrogenic doses used in this study. Carcinogenic activities of structurally related compounds have proved to be inconsistent. A related para-amino aryl sulfonamide, sulfamethoxazole, produced thyroid gland tumors in rats (Swarm *et al.*, 1973). In contrast, another structural analogue, sulfisoxazole, was not carcinogenic in F344/N rats or in B6C3F$_1$ mice (NCI, 1979). When sulfamethoxazole was fed to rats for 52 or 60 weeks, it induced thyroid gland adenomas with evidence of lung metastasis. However, withdrawal of the drug from the diet after 6 or 13 weeks yielded normal thyroid gland follicle structure (Swarm *et al.*, 1973).

The principal adverse effect of salicylazosulfapyridine in rats in the 2-year study was transitional epithelial papilloma of the urinary tract, which was accompanied by increased incidences of concretions (diagnosed as calculi at necropsy). There was a significant ($P < 0.01$) positive association between the presence of grossly diagnosed concretions (calculi) and the development of transitional epithelial papillomas of the urinary bladder in male rats. The observed concretions were considered to be precipitated salicylazosulfapyridine or a metabolite, and they were present in all animals with urinary tract papillomas as well as in some rats that did not develop papillomas. However, the animals without papillomas invariably had mild to moderate mucosa (transitional) hyperplasia, which may be a precursor to epithelial neoplasms of the urinary tract. The association between calculi and papillomas of the urinary bladder has been observed in other studies (Okumura *et al.*, 1992; NTP, 1983b, 1986) and supports the contention that urinary calculi/concretions observed in the present studies may have influenced the development of papillomas. The mechanical irritation caused by calculi/concretions may have stimulated epithelial cell proliferation and subsequent neoplasm development.

Core-study male rats showed a significant, dose-related increase in the incidence of urinary bladder transitional epithelial papillomas as well as a corresponding increase in the incidence of mucosa hyperplasia. The increased neoplasm incidence was considered to be chemical related. The stop-exposure male rats had no urinary bladder neoplasms or concretions/calculi, which further suggests that these lesions may be correlated. Transitional epithelial papillomas of the kidney were not observed in male rats, but there were increased incidences of transitional epithelial hyperplasia and atypical transitional epithelial hyperplasia that were dose related.

In female rats, two 168 mg/kg animals had urinary bladder transitional epithelial papillomas, and the increased incidence of mucosa hyperplasia was significant and dose related. Two 337.5 mg/kg female rats had transitional cell papillomas of the kidney, and the increased incidences of transitional epithelial hyperplasia were significant and increased with increasing dose. Transitional epithelial papillomas of the kidney are rare in control female rats and had not been observed in 920 corn oil gavage controls in previous NTP studies. Moreover, these neoplasms were not found in 1,977 untreated or in 1,944 corn oil gavage control female F344/N rats (Haseman *et al.*, 1990). Because of the rarity of these neoplasms, these two neoplasms (and the two urinary bladder papillomas with a similar morphology) were considered to be chemical related.

The incidence of mononuclear cell leukemia in male rats receiving 337.5 mg/kg was significantly lower than that in controls. There were also concurrent increases in the incidences of splenic hematopoietic cell proliferation and hemosiderin pigmentation in 337.5 mg/kg male rats. The biological significance of these effects is uncertain. However, in a number of NTP studies, chemicals that have resulted in a significant reduction in the incidence of mononuclear cell leukemia have frequently been associated with changes suggestive of hematopoietic toxicity at 13 weeks, including increased incidences of splenic hematopoietic cell proliferation, hemosiderin pigmentation, and fibrosis (NTP, 1982, 1989, 1994b, 1996). This association has not been observed in all studies in which the incidence of mononuclear cell leukemia in treated groups is lower than in controls (NTP, 1987, 1992).

The doses selected for the 2-year study in male and female mice were 0, 675, 1,350, or 2,700 mg/kg salicylazosulfapyridine, based on the absence of chemical-related mortality, body weight effects, and lesions in the 13-week study. In the 2-year study, salicylazosulfapyridine induced liver neoplasms in mice. The incidences of hepatocellular adenoma in all dosed groups of male and female mice were at least double those in controls, significantly greater than those in controls by logistic regression analysis, and occurred with positive trends. Multiple hepatocellular adenomas occurred in dosed males and females more frequently than in controls. The incidences of hepatocellular adenoma in male mice receiving 675 and 2,700 mg/kg and in all groups of dosed female mice exceeded the historical control ranges from NTP 2-year corn oil gavage studies. The incidences of hepatocellular carcinoma in 1,350 mg/kg male mice and all dosed groups of female mice were significantly greater than those in controls, and multiple hepatocellular carcinomas were also evident in dosed male and female mice. The incidences of hepatocellular carcinoma in 675 and 1,350 mg/kg male mice and all

dosed groups of female mice exceeded the ranges in historical controls from NTP 2-year corn oil gavage studies. Collectively, the combined incidences of adenoma or carcinoma in both male and female dosed groups were statistically greater than those in controls. Considered together, these data provide clear evidence that the increased incidences of liver neoplasms were related to the administration of salicylazosulfapyridine. At the end of the 2-year study, incidences of eosinophilic foci in dosed groups of males and females were greater than those in controls.

The incidences of hemosiderin pigment and hematopoietic cell proliferation in all dosed groups of male and female mice were greater than those in the controls at the 15-month interim evaluation and at the end of the 2-year study, and the increases were generally significant.

In 2,700 mg/kg female mice, the incidence of squamous cell papilloma of the forestomach was significantly lower than that in controls. The incidences of forestomach hyperplasia were significantly lower than those in controls in 2,700 mg/kg males and in 1,350 and 2,700 mg/kg females. The biological significance of the lower incidences of the forestomach lesions in dosed male and female mice is not certain, but may be related to the anti-inflammatory properties of salicylazosulfapyridine.

Results from the toxicokinetic studies in F344/N rats and B6C3F$_1$ mice allow a comparison of the plasma concentrations of salicylazosulfapyridine and its metabolites with those attained in humans at therapeutic dose concentrations. Following a 4 g dose of salicylazosulfapyridine to human male volunteers (approximately 50 mg/kg), the median maximum serum concentration of salicylazosulfapyridine was 21 μg/mL (53 μM) and the maximum mean serum concentration of sulfapyridine plus its metabolites was 33 $\pm$ 9 μg/mL (Schröder and Campbell, 1972). In a B6C3F$_1$ mouse toxicokinetic study (NTP, 1994a; Appendix L), maximum plasma concentrations of salicylazosulfapyridine ranged from 16 to 42 μM in males and 40 to 212 μM in females given doses ranging from 67.5 to 2,700 mg/kg. Thus, except for the highest doses in females, plasma concentrations of salicylazosulfapyridine were comparable to those observed in humans. The maximum plasma concentration of sulfapyridine in the mouse toxicokinetic study ranged from 90 to 260 μM (23 to 65 μg/mL) in males and 110 to 484 μM (28 to 120 μg/mL) in females. Again, the plasma concentrations attained in the mouse study are similar to human therapeutic plasma concentrations.

Toxicokinetic studies in male F344/N rats indicated that salicylazosulfapyridine was less well absorbed by rats than by mice. At an equivalent dose (675 mg/kg) the highest plasma concentrations of salicylazosulfapyridine and sulfapyridine in rats were approximately 20% and 30% of those in mice, respectively (NTP, 1994a). Pharmacokinetic measurements following intravenous administration indicated that rats would clear salicylazosulfapyridine more slowly than mice (Appendix L). Thus, peak exposure may be less in rats, but the duration of exposure may be longer than in mice. This observation may explain in part why mice did not accumulate salicylazosulfapyridine precipitate in the urinary tract even though mice were given an 8-fold greater dose than rats.

There have been a limited number of *in vitro* studies conducted with salicylazosulfapyridine and/or its metabolites, and in general, the results have indicated that none of these compounds are mutagenic *in vitro* (Voogd *et al.*, 1980; Zeiger *et al.*, 1988; Bishop *et al.*, 1990; Witt *et al.*, 1992b). The exception was an *in vitro* study with human lymphocytes that showed increased frequencies of micronuclei, an indication of chromosomal damage, after treatment with salicylazosulfapyridine (Mackay *et al.*, 1989). Results from *in vivo* studies further suggest that salicylazosulfapyridine can induce chromosomal damage, perhaps in the form of aneuploidy, in mammalian cells. Chronic exposure to therapeutic concentrations of salicylazosulfapyridine was associated with increases in micronuclei and sister chromatid exchanges in peripheral blood lymphocytes of ulcerative colitis patients (Fox *et al.*, 1987). Several studies have shown induction of micronuclei in mouse bone marrow following multiple treatments with high doses of salicylazosulfapyridine (Bishop *et al.*, 1990; Witt *et al.*, 1992a). A bone marrow micronucleus test using the same protocol in rats and mice gave negative results in both cases (Appendix E). The plasma concentrations of salicylazosulfapyridine and sulfapyridine in F344 rats were shown to be 20% to 30% of that attained in mice following administration of comparable doses of salicylazosulfapyridine (NTP, 1994a). Although multiple

dosing with salicylazosulfapyridine, compared with a single dose administration, did not lead to increased plasma concentrations of salicylazosulfapyridine in B6C3F$_1$ mice, the peak (C_{max}) and total (AUC) concentrations of sulfapyridine were increased by multiple dosing (Zheng *et al.*, 1993). *In vivo* and *in vitro* test results indicated that the genotoxic moiety of the salicylazosulfapyridine molecule is primarily the sulfapyridine subunit; 5-aminosalicylic acid has been shown not to induce genetic damage. Therefore, the data from mouse and rat *in vivo* studies show that the mouse is more susceptible to salicylazosulfapyridine-induced genetic damage, and the results are consistent with the observation that mice have greater systemic exposures to sulfapyridine.

The evidence from clinical studies indicates that the increases in the frequency of sister chromatid exchanges and micronuclei in patients maintained on salicylazosulfapyridine therapy for treatment of inflammatory bowel disease are caused by the drug *per se* and not by the disease (Fox *et al.*, 1987; Mackay *et al.*, 1989). In these clinical studies, the dose of salicylazosulfapyridine and the length of treatment to a large extent determined the magnitude of the observed genetic damage. The high sulfapyridine plasma concentrations resulting from salicylazosulfapyridine administration in mice supports the assumption that sulfapyridine and/or its metabolites(s) may be related to the mutagenicity observed in mice and humans (Zheng *et al.*, 1993).

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of salicylazosulfapyridine in male and female F344/N rats based on increased incidences of neoplasms in the urinary tract. There was an increased incidence of transitional epithelial papilloma of the urinary bladder in males and a low incidence of rare transitional epithelial papillomas of the kidney and of the urinary bladder in females. There was *clear evidence of carcinogenic activity* of salicylazosulfapyridine in male and female B6C3F$_1$ mice based on increased incidences of hepatocellular neoplasms.

Increased incidences of nonneoplastic lesions of the urinary bladder and kidney in male and female rats and of the spleen in male rats were observed. Increased incidences of nonneoplastic lesions of the liver and spleen in male and female mice were observed.

Decreased incidences of mononuclear cell leukemia in male and female rats were related to salicylazosulfapyridine administration. Decreased incidences of forestomach squamous cell papilloma in female mice and forestomach hyperplasia in male and female mice were related to salicylazosulfapyridine administration.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF SALICYLAZOSULFAPYRIDINE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
Disposition Summary					
Animals initially in study	70	60	60	60	70
6-Month interim evaluation	10				10
15-Month interim evaluation	10	10	10	10	10
Early deaths					
Accidental deaths	1	4	1	2	3
Moribund	13	11	16	15	13
Natural deaths	1	2	2	10	4
Survivors					
Died last week of study			1		
Terminal sacrifice	35	33	30	23	30
Animals examined microscopically	70	60	60	60	70
Systems Examined at 6 Months With No Neoplasms Observed					
Alimentary System					
Cardiovascular System					
Endocrine System					
General Body System					
Genital System					
Hematopoietic System					
Integumentary System					
Musculoskeletal System					
Nervous System					
Respiratory System					
Special Senses System					
Urinary System					
15-Month Interim Evaluation					
Alimentary System					
Intestine large, colon	(10)	(9)	(10)	(10)	(8)
Carcinoma	1 (10%)				
Liver	(10)	(10)	(10)	(10)	
Hepatocellular adenoma		1 (10%)			
Endocrine System					
Adrenal medulla	(10)				(10)
Pheochromocytoma benign					1 (10%)
Islets, pancreatic	(10)				(10)
Adenoma					1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)	(9)
Pars distalis, adenoma	1 (10%)	3 (30%)			2 (22%)
Genital System					
Preputial gland	(10)	(10)	(10)	(10)	
Adenoma			1 (10%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
15-Month Interim Evaluation (continued)					
Genital System (continued)					
Testes	(10)	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	6 (60%)	6 (60%)	6 (60%)	9 (90%)	3 (30%)
Interstitial cell, adenoma	3 (30%)	1 (10%)	4 (40%)	1 (10%)	6 (60%)
Respiratory System					
Lung	(10)	(10)	(10)	(10)	(10)
Alveolar/bronchiolar carcinoma	1 (10%)				
Systems Examined With No Neoplasms Observed					
Cardiovascular System					
General Body System					
Hematopoietic System					
Integumentary System					
Musculoskeletal System					
Nervous System					
Special Senses System					
Urinary System					
2-Year Study					
Alimentary System					
Intestine large, cecum	(50)	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)				(49)
Carcinoma					1 (2%)
Intestine small, jejunum	(50)	(49)	(50)	(49)	
Intestine small, ileum	(49)	(49)	(50)	(50)	(49)
Leiomyosarcoma	1 (2%)				
Liver	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)	
Hepatocellular carcinoma		1 (2%)	1 (2%)		
Hepatocellular adenoma	2 (4%)				
Histiocytic sarcoma		1 (2%)			
Leiomyosarcoma, metastatic, stomach, forestomach	1 (2%)				
Osteosarcoma, metastatic, bone				1 (2%)	
Osteosarcoma, metastatic, tissue NOS			1 (2%)		
Mesentery	(17)	(14)	(18)	(12)	(16)
Fibrous histiocytoma	1 (6%)				
Leiomyosarcoma, metastatic, stomach, forestomach	1 (6%)				
Osteosarcoma, metastatic, tissue NOS			1 (6%)		
Pancreas	(50)	(50)	(50)	(50)	(48)
Fibrous histiocytoma	1 (2%)				
Leiomyosarcoma, metastatic, stomach, forestomach	1 (2%)				
Mixed tumor benign		1 (2%)		1 (2%)	
Acinar cell, adenoma	9 (18%)	6 (12%)	5 (10%)	10 (20%)	2 (4%)
Acinar cell, adenoma, multiple	3 (6%)		2 (4%)		2 (4%)
Acinar cell, carcinoma, multiple	1 (2%)				

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
Alimentary System (continued)					
Pharynx			(2)		(1)
Squamous cell carcinoma			1 (50%)		
Squamous cell papilloma			1 (50%)		1 (100%)
Salivary glands	(50)	(50)	(50)	(50)	(50)
Adenoma				1 (2%)	
Schwannoma malignant, metastatic, skin					1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)				
Squamous cell carcinoma				1 (2%)	
Squamous cell papilloma	1 (2%)				
Stomach, glandular	(49)				(50)
Tongue				(1)	
Squamous cell carcinoma				1 (100%)	
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	
Vena cava, chordoma, metastatic, spinal cord			1 (2%)		
Heart	(50)	(50)	(50)	(50)	(50)
Schwannoma benign				2 (4%)	1 (2%)
Schwannoma malignant		1 (2%)	1 (2%)		
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Adenoma			1 (2%)		2 (4%)
Histiocytic sarcoma		1 (2%)			
Adrenal medulla	(50)	(49)	(50)	(49)	(50)
Pheochromocytoma malignant			1 (2%)		2 (4%)
Pheochromocytoma complex	1 (2%)				
Pheochromocytoma benign	12 (24%)	6 (12%)	5 (10%)	7 (14%)	3 (6%)
Bilateral, pheochromocytoma benign	3 (6%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)	(49)
Adenoma	2 (4%)	3 (6%)	6 (12%)	5 (10%)	
Carcinoma	1 (2%)	1 (2%)			
Pituitary gland	(50)	(50)	(49)	(49)	(49)
Ganglioneuroma	1 (2%)				
Pars distalis, adenoma	14 (28%)	16 (32%)	18 (37%)	18 (37%)	18 (37%)
Pars intermedia, adenoma			1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Bilateral, C-cell, carcinoma		1 (2%)			
C-cell, adenoma	3 (6%)	9 (18%)	5 (10%)	6 (12%)	4 (8%)
C-cell, carcinoma	2 (4%)	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Follicular cell, adenoma	4 (8%)		3 (6%)	1 (2%)	
Follicular cell, carcinoma	1 (2%)		1 (2%)		2 (4%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
General Body System					
Tissue NOS	(1)		(1)		
Osteosarcoma			1 (100%)		
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	2 (4%)		5 (10%)
Carcinoma	2 (4%)	1 (2%)	3 (6%)		2 (4%)
Prostate	(50)	(50)	(50)	(50)	(50)
Adenoma		1 (2%)			
Seminal vesicle	(50)	(50)	(50)	(49)	(50)
Testes	(50)	(49)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	44 (88%)	37 (76%)	39 (78%)	43 (86%)	34 (68%)
Interstitial cell, adenoma	1 (2%)	4 (8%)	7 (14%)	2 (4%)	3 (6%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)			
Lymph node	(9)	(15)	(14)	(10)	(6)
Inguinal, fibrous histiocytoma, metastatic, skin				1 (10%)	
Mediastinal, osteosarcoma, metastatic, tissue NOS			1 (7%)		
Pancreatic, histiocytic sarcoma		1 (7%)			
Lymph node, mandibular	(50)	(50)	(50)	(49)	(50)
Histiocytic sarcoma		1 (2%)			
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(49)
Spleen	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)			
Histiocytic sarcoma		1 (2%)			
Leiomyosarcoma, metastatic, stomach, forestomach	1 (2%)				
Osteosarcoma, metastatic, tissue NOS			1 (2%)		
Thymus	(47)	(50)	(49)	(49)	(49)
Thymoma benign	1 (2%)				
Integumentary System					
Mammary gland	(48)	(49)	(47)	(49)	(49)
Carcinoma			1 (2%)		
Fibroadenoma	3 (6%)	4 (8%)	4 (9%)	3 (6%)	4 (8%)
Fibroadenoma, multiple			1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
Integumentary System (continued)					
Skin	(50)	(50)	(50)	(50)	(50)
Basal cell adenoma	2 (4%)	3 (6%)			
Basal cell carcinoma		1 (2%)			
Keratoacanthoma	3 (6%)	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Squamous cell papilloma	1 (2%)	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Trichoepithelioma			1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)	5 (10%)	1 (2%)	3 (6%)	6 (12%)
Subcutaneous tissue, fibrosarcoma				1 (2%)	
Subcutaneous tissue, fibrous histiocytoma				1 (2%)	
Subcutaneous tissue, lipoma					1 (2%)
Subcutaneous tissue, liposarcoma		1 (2%)			
Subcutaneous tissue, schwannoma benign					1 (2%)
Subcutaneous tissue, schwannoma malignant			1 (2%)		2 (4%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Hamartoma		1 (2%)			
Osteosarcoma				1 (2%)	1 (2%)
Skeletal muscle	(1)	(1)	(1)	(1)	(1)
Fibrous histiocytoma	1 (100%)				
Hemangiosarcoma					1 (100%)
Histiocytic sarcoma		1 (100%)			
Osteosarcoma, metastatic, tissue NOS			1 (100%)		
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)				
Glioma malignant			1 (2%)		
Meningioma benign					1 (2%)
Spinal cord		(1)	(1)		
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)				
Alveolar/bronchiolar carcinoma					2 (4%)
Chordoma, metastatic, spinal cord			1 (2%)		
Histiocytic sarcoma		1 (2%)			
Osteosarcoma, metastatic, bone				1 (2%)	1 (2%)
Osteosarcoma, metastatic, tissue NOS			1 (2%)		
Nose	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)				
Special Senses System					
Zymbal's gland	(1)				
Carcinoma	1 (100%)				

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Lipoma			1 (2%)		
Osteosarcoma, metastatic, bone					1 (2%)
Renal tubule, adenoma			1 (2%)		
Urinary bladder	(50)	(49)	(50)	(50)	(47)
Papilloma			2 (4%)	4 (8%)	
Papilloma, multiple				2 (4%)	
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)			
Leukemia mononuclear	13 (26%)	18 (36%)	12 (24%)	3 (6%)	10 (20%)
Mesothelioma malignant	1 (2%)	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Neoplasm Summary					
Total animals with primary neoplasms[c]					
15-Month interim evaluation	9	10	10	10	10
2-Year study	49	46	49	48	46
Total primary neoplasms					
15-Month interim evaluation	12	11	11	10	13
2-Year study	144	132	141	124	120
Total animals with benign neoplasms					
15-Month interim evaluation	9	10	10	10	10
2-Year study	49	44	48	47	42
Total benign neoplasms					
15-Month interim evaluation	10	11	11	10	13
2-Year study	114	103	113	112	93
Total animals with malignant neoplasms					
15-Month interim evaluation	2				
2-Year study	23	24	23	9	21
Total malignant neoplasms					
15-Month interim evaluation	2				
2-Year study	30	29	28	12	27
Total animals with metastatic neoplasms					
2-Year study	2		4	5	4
Total metastatic neoplasms					
2-Year study	5		12	13	7

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control

Number of Days on Study	1 5 0	4 7 3	4 7 7	5 0 0	5 2 3	5 5 1	6 0 5	6 3 2	6 5 3	6 7 6	6 8 4	7 0 8	7 1 7	7 1 7	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 1 1	0 4 2	0 5 7	0 3 2	0 2 9	0 5 1	0 3 6	0 0 9	0 4 7	0 5 0	0 4 8	0 4 1	0 0 5	0 5 8	0 2 8	0 0 2	0 0 6	0 1 5	0 2 1	0 2 5	0 3 0	0 3 4	0 3 9	0 4 6	0 5 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																			X						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X										
Leiomyosarcoma, metastatic, stomach, forestomach									X																
Mesentery		+		+		+			+						+	+					+			+
Fibrous histiocytoma				X																					
Leiomyosarcoma, metastatic, stomach, forestomach									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma				X																					
Leiomyosarcoma, metastatic, stomach, forestomach									X																
Acinar cell, adenoma											X			X	X		X							X	
Acinar cell, adenoma, multiple																							X		
Acinar cell, carcinoma, multiple																X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma									X																
Squamous cell papilloma				X																					
Stomach, glandular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex												X													
Pheochromocytoma benign										X									X			X			
Bilateral, pheochromocytoma benign									X				X		X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma																									
Pars distalis, adenoma		X				X					X		X		X							X	X		X

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 0 0 1	0 0 1 3	0 0 0 4	0 0 0 8	0 1 1 0	0 1 1 2	0 1 1 4	0 1 1 6	0 1 1 7	0 1 1 9	0 2 2 0	0 2 2 2	0 2 2 3	0 2 2 4	0 2 2 7	0 3 3 1	0 3 3 3	0 3 3 5	0 3 3 8	0 4 4 0	0 4 4 3	0 4 4 5	0 5 5 2	0 5 5 3	0 5 5 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X																					2
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Mesentery	+									+		+		+		+					+		+	+	+	17
Fibrous histiocytoma																										1
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Acinar cell, adenoma					X					X										X					X	9
Acinar cell, adenoma, multiple															X								X			3
Acinar cell, carcinoma, multiple																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																										1
Pheochromocytoma benign			X			X					X	X	X	X			X			X			X			12
Bilateral, pheochromocytoma benign																										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						2
Carcinoma							X																			1
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma																							X			1
Pars distalis, adenoma					X	X	X						X								X				X	14

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	1 5 0	4 7 3	4 7 7	5 0 0	5 2 3	5 5 1	6 0 5	6 3 2	6 5 3	6 7 6	6 8 4	7 0 8	7 1 7	7 1 7	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 1 1	0 4 2	0 5 7	0 3 2	0 2 9	0 5 1	0 3 6	0 0 9	0 4 7	0 5 0	0 4 8	0 4 1	0 5 5	0 5 8	0 2 8	0 2 2	0 0 6	0 1 5	0 2 1	0 2 5	0 3 0	0 3 4	0 3 9	0 4 6	0 5 4
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
C-cell, carcinoma																			X						
Follicular cell, adenoma																									
Follicular cell, carcinoma																		X							
General Body System																									
Tissue NOS													+												
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Carcinoma												X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X		X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+									+	+	+					+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, stomach, forestomach									X																
Thymus	+	I	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																							X		X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma													X												
Keratoacanthoma																				X					
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																					
Fibrous histiocytoma				X																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant											X														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 0 1	0 0 3	0 0 4	0 0 8	0 1 0	0 1 2	0 1 4	0 1 6	0 1 7	0 1 9	0 2 0	0 2 2	0 2 3	0 2 4	0 2 7	0 3 1	0 3 3	0 3 5	0 3 8	0 4 0	0 4 3	0 4 5	0 5 2	0 5 3	0 5 5	Total Tissues/ Tumors
Endocrine System (continued)																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X					X														3
C-cell, carcinoma																				X						2
Follicular cell, adenoma			X			X	X																	X		4
Follicular cell, carcinoma																										1
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery										X																1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma												X														2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+							+				+														9
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Thymoma benign							X																			1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma					X																					3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																		X								2
Keratoacanthoma					X			X																		3
Squamous cell papilloma														X												1
Subcutaneous tissue, fibroma																X										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibrous histiocytoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	1 5 0	4 7 3	4 7 7	5 0 0	5 2 3	5 5 1	6 0 5	6 3 2	6 5 3	6 7 6	6 8 4	7 0 8	7 1 7	7 1 7	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 1 1	0 4 2	0 5 7	0 3 2	0 2 9	0 5 1	0 3 6	0 0 9	0 4 7	0 5 0	0 4 8	0 4 1	0 0 5	0 5 8	0 2 8	0 0 2	0 0 6	0 1 5	0 2 1	0 2 5	0 3 0	0 3 4	0 3 9	0 4 6	0 5 4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma										X															
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland							+																		
Carcinoma							X																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X					X	X	X			X	X	X					
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 0 1	0 0 3	0 0 4	0 0 8	0 1 0	0 1 2	0 1 4	0 1 6	0 1 7	0 1 9	0 2 0	0 2 2	0 2 3	0 2 4	0 2 7	0 3 1	0 3 3	0 3 5	0 3 8	0 4 0	0 4 3	0 4 5	0 5 2	0 5 3	0 5 6	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X									X	X											X	X	13
Mesothelioma malignant										X																1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg

Number of Days on Study	0 8 5	2 3 4	2 4 3	4 1 4	4 2 4	4 6 0	5 1 5	6 0 5	6 2 5	6 5 4	6 5 9	6 6 2	6 8 0	6 9 1	6 9 2	7 0 9	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 8 1	0 7 8	0 8 8	1 0 6	0 9 4	0 9 9	1 0 5	1 0 9	0 9 8	0 8 6	0 7 3	1 0 3	1 0 8	1 0 0	1 0 2	1 1 5	0 9 7	0 7 2	0 7 9	0 8 5	0 9 0	0 9 3	1 0 1	1 0 4	1 0 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																							X		
Histiocytic sarcoma									X																
Mesentery				+		+	+		+					+								+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor benign																									
Acinar cell, adenoma											X									X				X	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Adrenal medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X		X					
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X	X	X		X								X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, carcinoma																									
C-cell, adenoma													X		X			X							X
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg
(continued)

Number of Days on Study	729	729	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	11112	11127	10071	10074	10075	10076	10077	10080	10082	10083	10084	10087	10089	10091	10092	10095	10096	11010	11011	11013	11014	11016	11018	11019	11020	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Histiocytic sarcoma																										1
Mesentery		+		+	+					+							+	+			+					14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor benign								X																		1
Acinar cell, adenoma																	X	X					X			6
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant										X																1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign		X			X	X	X		X														X			6
Bilateral, pheochromocytoma benign	X																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						3
Carcinoma											X															1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X		X		X	X	X	X		X		X	X			X							16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, carcinoma					X																					1
C-cell, adenoma				X							X						X	X							X	9
C-cell, carcinoma			X																							1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg
(continued)

Number of Days on Study	0 8 5	2 3 4	2 4 3	4 1 4	4 2 4	4 6 0	5 1 5	6 0 5	6 2 5	6 5 4	6 5 9	6 6 2	6 8 0	6 9 1	6 9 2	7 0 9	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 8 1	0 7 8	0 8 8	1 0 6	0 9 4	0 9 9	1 0 5	1 0 9	0 9 8	0 8 6	0 7 3	1 0 3	1 0 8	1 0 0	1 0 2	1 1 5	0 9 7	0 7 2	0 7 9	0 8 5	0 9 0	0 9 3	1 0 1	1 0 4	1 0 7
Genital System (continued)																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X
Interstitial cell, adenoma															X									
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															
Lymph node									+		+	+			+						+	+		
Pancreatic, histiocytic sarcoma									X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X				
Histiocytic sarcoma									X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma														X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																X					X			
Basal cell carcinoma														X										
Keratoacanthoma																	X							
Squamous cell papilloma																				X				
Subcutaneous tissue, fibroma										X	X					X								
Subcutaneous tissue, liposarcoma								X																
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hamartoma							X																	
Skeletal muscle									+															
Histiocytic sarcoma									X															
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+																	
Spinal cord							+																	
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg
(continued)

Number of Days on Study	729	729	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	11012	11017	10071	10074	10075	10076	10077	10080	10082	10083	10084	10087	10089	10091	10092	10095	10096	11010	11011	11013	11014	11016	11018	11019	11020	Total Tissues/ Tumors
Genital System (continued)																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X			X	X		X		X	X	X	X	X	X	X	X	X	X	37
Interstitial cell, adenoma									X				X		X											4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node	+	+		+	+										+	+	+	+						+		15
Pancreatic, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma			X										X					X								4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma											X															3
Basal cell carcinoma																										1
Keratoacanthoma	X									X																3
Squamous cell papilloma															X											2
Subcutaneous tissue, fibroma																	X							X		5
Subcutaneous tissue, liposarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hamartoma																										1
Skeletal muscle																										1
Histiocytic sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg
(continued)

Number of Days on Study	0	2	2	4	4	4	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	8	3	4	1	2	6	1	0	2	5	5	6	8	9	9	0	2	2	2	2	2	2	2	2	2
	5	4	3	4	4	0	5	5	5	4	9	2	0	1	2	9	6	9	9	9	9	9	9	9	9
Carcass ID Number	0	0	0	1	0	0	1	1	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	1	1
	8	7	8	0	9	9	0	0	9	8	7	0	0	0	0	1	9	7	7	8	9	9	0	0	0
	1	8	8	6	4	9	5	9	8	6	3	3	8	0	2	5	7	2	9	5	0	3	1	4	7
Special Senses System																									
Eye											+														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Leukemia mononuclear				X						X	X	X	X	X	X					X		X		X	
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg
(continued)

Number of Days on Study	729	729	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	112	117	071	074	075	076	077	080	082	083	084	087	089	091	092	095	096	110	111	113	114	116	118	119	120	Total Tissues/ Tumors
Special Senses System																										
Eye																				+						2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear	X			X	X		X	X	X														X	X		18
Mesothelioma malignant									X																	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg

Number of Days on Study	2 3 3	3 9 6	4 1 4	4 3 5	4 3 7	5 0 2	5 1 5	5 3 6	5 4 9	5 7 8	6 1 1	6 1 1	6 3 9	6 8 0	6 9 5	6 9 6	7 0 2	7 0 4	7 0 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 3 9	1 3 6	1 4 4	1 8 4	1 4 7	1 7 1	1 7 8	1 5 3	1 4 8	1 3 3	1 3 7	1 7 5	1 5 5	1 4 0	1 6 9	1 4 6	1 6 2	1 5 1	1 5 8	1 3 4	1 3 8	1 4 3	1 4 9	1 5 4	1 6 0
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																								
Osteosarcoma, metastatic, tissue NOS					X																			
Mesentery				+	+					+				+	+			+		+	+		+	
Osteosarcoma, metastatic, tissue NOS					X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma												X										X		
Acinar cell, adenoma, multiple																		X						
Pharynx							+						+											
Squamous cell carcinoma													X											
Squamous cell papilloma							X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vena cava, chordoma, metastatic, spinal cord																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								
Pheochromocytoma benign																								
Bilateral, pheochromocytoma benign																			X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X								X										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X							X		X		X	X	X			X	X			X		
Pars intermedia, adenoma																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X		X							X	
C-cell, carcinoma																								
Follicular cell, adenoma						X																		
Follicular cell, carcinoma																	X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg
(continued)

Number of Days on Study	729	729	729	729	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	16 1	16 8	17 4	17 9	13 1	13 2	13 5	14 1	14 2	14 5	15 0	15 2	15 6	15 7	15 9	16 3	16 4	16 5	16 6	16 7	17 0	17 2	17 3	17 6	17 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X																	1
Osteosarcoma, metastatic, tissue NOS																										1
Mesentery		+			+						+		+		+		+				+		+	+		18
Osteosarcoma, metastatic, tissue NOS																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell, adenoma	X													X			X									5
Acinar cell, adenoma, multiple																								X		2
Pharynx																										2
Squamous cell carcinoma																										1
Squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vena cava, chordoma, metastatic, spinal cord																						X				1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant											X															1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																									X	1
Pheochromocytoma benign					X										X	X	X							X		5
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X							X			X				X										6
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma							X	X	X		X	X	X			X		X						X		18
Pars intermedia, adenoma			X																							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X												X										5
C-cell, carcinoma								X													X					2
Follicular cell, adenoma										X	X															3
Follicular cell, carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg
(continued)

Number of Days on Study	2 3 3	3 9 6	4 1 4	4 3 5	4 3 7	5 0 2	5 1 5	5 3 6	5 4 9	5 7 8	6 1 1	6 1 1	6 3 9	6 8 0	6 9 5	6 9 6	7 0 2	7 0 4	7 0 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 3 9	1 3 6	1 4 4	1 8 4	1 4 7	1 7 1	1 7 8	1 5 3	1 4 8	1 3 3	1 3 7	1 7 5	1 5 5	1 4 0	1 6 9	1 4 6	1 6 2	1 5 1	1 5 8	1 3 4	1 3 8	1 4 3	1 4 9	1 5 4	1 6 0
General Body System																								
Tissue NOS					+																			
Osteosarcoma					X																			
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery															X									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma						X					X					X								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																								
Bilateral, interstitial cell, adenoma						X		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X
Interstitial cell, adenoma			X		X		X						X									X		
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+	+	+	+		+					+				+	+		+		
Mediastinal, osteosarcoma, metastatic, tissue NOS					X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery															X									
Osteosarcoma, metastatic, tissue NOS					X																			
Thymus	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+
Carcinoma																		X						
Fibroadenoma																X								
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma													X		X	X								
Squamous cell papilloma																								
Trichoepithelioma													X											
Subcutaneous tissue, fibroma												X												
Subcutaneous tissue, schwannoma malignant																				X				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																			
Osteosarcoma, metastatic, tissue NOS					X																			
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant			X																					
Spinal cord														+										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg
(continued)

Number of Days on Study	729	729	729	729	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	16 1	16 8	17 4	17 9	13 1	13 2	13 5	14 1	14 2	14 5	15 0	15 2	15 6	15 7	15 9	16 3	16 4	16 5	16 6	16 7	17 0	17 2	17 3	17 6	17 7	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Osteosarcoma																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery																								X		2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X		X		2
Carcinoma																										3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery																								X		1
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	39
Interstitial cell, adenoma																X								X		7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+	+														+					+		14
Mediastinal, osteosarcoma, metastatic, tissue NOS																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery																										1
Osteosarcoma, metastatic, tissue NOS																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Fibroadenoma	X		X																				X			4
Fibroadenoma, multiple									X																	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										3
Squamous cell papilloma								X									X								X	3
Trichoepithelioma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Osteosarcoma, metastatic, tissue NOS																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg
(continued)

Number of Days on Study	2 3 3	3 9 6	4 1 4	4 3 5	4 3 7	5 0 2	5 1 5	5 3 6	5 4 9	5 7 8	6 1 1	6 1 1	6 3 9	6 8 0	6 9 5	6 9 6	7 0 2	7 0 4	7 0 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 3 9	1 3 6	1 4 4	1 8 4	1 4 7	1 7 1	1 7 8	1 5 3	1 4 8	1 3 3	1 3 7	1 7 5	1 5 5	1 4 0	1 6 9	1 4 6	1 6 2	1 5 1	1 5 8	1 3 4	1 3 8	1 4 3	1 4 9	1 5 4	1 6 0
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma, metastatic, spinal cord																								
Osteosarcoma, metastatic, tissue NOS					X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye													+									+		
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																								
Renal tubule, adenoma																								
Ureter											+													
Urethra											+				+									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X				X	X	X				X		X	X		X		X			
Mesothelioma malignant															X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg
(continued)

Number of Days on Study	729	729	729	729	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	16101	16108	16744	16799	17331	17332	17335	17341	17342	17345	17350	17352	17356	17357	17359	17363	17364	17365	17366	17367	17370	17372	17373	17376	17377	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma, metastatic, spinal cord																						X				1
Osteosarcoma, metastatic, tissue NOS																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																									+	3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																	X									1
Renal tubule, adenoma																	X									1
Ureter																										1
Urethra																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma								X																X		2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X																				X	X	12
Mesothelioma malignant																								X		2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg

Number of Days on Study	1 2 2 0	2 4 0 8	4 2 0 4	4 3 0 6	4 7 0 3	5 6 0 5	5 8 0 1	5 8 0 5	6 1 0 3	6 3 0 5	6 4 0 5	6 5 0 3	6 5 0 8	6 5 0 9	6 5 0 9	6 7 0 2	6 8 0 4	6 8 0 7	6 9 0 6	7 0 0 4	7 0 0 4	7 0 0 4	7 0 0 5	7 0 0 8	7 1 0 8
Carcass ID Number	2 2 3 7	2 3 0 4	2 0 0 3	2 0 0 6	2 2 0 6	2 0 0 0	2 0 0 1	1 9 0 7	2 3 0 7	2 2 0 4	2 0 0 9	2 3 0 4	2 2 0 2	2 2 0 8	2 3 0 5	2 1 0 4	2 1 0 8	2 2 0 5	2 0 0 2	1 9 0 2	1 9 0 3	1 9 0 5	2 3 0 0	2 0 0 5	2 0 0 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X														
Osteosarcoma, metastatic, bone				X																					
Mesentery							+	+				+				+				+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery								X																	
Mixed tumor benign																									
Acinar cell, adenoma																				X		X	X		X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									X
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X				X			
Bilateral, pheochromocytoma benign										X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X															X	
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X					X	X	X	X		X		X				X				X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X					X	
C-cell, carcinoma												X													
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg
(continued)

Number of Days on Study	723	726	729	729	729	729	729	729	729	729	729	729	731	731	731	731	732	732	732	732	732	732	732	732	732	
Carcass ID Number	21 1	21 9	19 6	19 9	20 8	21 5	22 0	22 3	23 9	23 2	23 6	23 9	19 1	19 4	19 8	20 7	21 0	21 2	21 3	21 6	21 7	22 1	23 1	23 8	24 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Osteosarcoma, metastatic, bone																										1
Mesentery	+		+		+				+				+	+								+				12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery																										1
Mixed tumor benign	X																									1
Acinar cell, adenoma				X	X	X								X					X		X					10
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma													X													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+																									1
Squamous cell carcinoma	X																									1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign																								X		2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign		X				X				X		X												X		7
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X						X			X		5
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Pars distalis, adenoma	X				X	X			X									X	X	X			X			18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																						X	X	X	X	6
C-cell, carcinoma																										1
Follicular cell, adenoma																						X				1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg (continued)

Number of Days on Study	1	2	4	4	4	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	2	4	2	3	7	6	8	8	1	3	4	5	5	5	5	7	8	8	9	0	0	0	0	0	1
	2	0	8	6	3	5	1	5	3	5	5	3	8	9	9	2	4	7	6	4	4	4	5	8	8
Carcass ID Number	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2
	2	3	0	0	2	0	0	9	3	2	0	3	2	2	3	1	1	2	0	9	9	9	3	0	0
	7	3	4	3	6	0	1	7	7	4	9	4	2	8	5	4	8	5	2	2	3	5	0	5	6
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery								X																	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Mesothelioma malignant, metastatic, mesentery								X																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery								X																	
Bilateral, interstitial cell, adenoma					X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X		X	X
Interstitial cell, adenoma										X													X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+			+	+		+											
Inguinal, fibrous histiocytoma, metastatic, skin											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																		X							X
Squamous cell papilloma																			X						
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																						X			
Subcutaneous tissue, fibrous histiocytoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma				X																					
Skeletal muscle								+																	
Mesothelioma malignant, metastatic, mesentery								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg (continued)

Number of Days on Study	723	726	729	729	729	729	729	729	729	729	729	729	731	731	731	731	732	732	732	732	732	732	732	732	732	
Carcass ID Number	211	219	196	199	208	215	220	223	229	232	236	239	191	194	198	207	210	212	213	216	217	221	231	238	240	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery	X																									2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, mesentery																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery	X												X													3
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Interstitial cell, adenoma																										2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+		+		+																			10
Inguinal, fibrous histiocytoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma										X														X		3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										2
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma		X														X	X									3
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Mesothelioma malignant, metastatic, mesentery																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg
(continued)

Number of Days on Study	1 2 4 4 4 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 2 4 2 3 7 6 8 8 1 3 4 5 5 5 5 7 8 8 9 0 0 0 0 0 1 2 0 8 6 3 5 1 5 3 5 5 3 8 9 9 2 4 7 6 4 4 4 5 8 8
Carcass ID Number	2 2 2 2 2 2 2 1 2 2 2 2 2 2 2 2 2 2 2 1 1 1 2 2 2 2 3 0 0 2 0 0 9 3 2 0 3 2 2 3 1 1 2 0 9 9 9 3 0 0 7 3 4 3 6 0 1 7 7 4 9 4 2 8 5 4 8 5 2 2 3 5 0 5 6
Urinary System	
Kidney	+ +
Ureter	+ + + M +
Urethra	+
Urinary bladder	+ +
Mesothelioma malignant, metastatic, mesentery	X
Papilloma	
Papilloma, multiple	X
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X
Mesothelioma malignant	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg
(continued)

Number of Days on Study	7 2 3	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 1 1	2 1 9	1 9 6	1 9 9	2 0 8	2 1 5	2 2 0	2 2 3	2 2 9	2 3 2	2 3 6	2 3 9	1 9 1	1 9 4	1 9 8	2 0 7	2 1 0	2 1 2	2 1 3	2 1 6	2 1 7	2 2 1	2 3 1	2 3 8	2 4 0	Total Tissues/ Tumors
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter	+	+		+		+					+				+			+					+	+	+	13
Urethra		+	+													+				+						5
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery																										1
Papilloma	X									X					X						X				4
Papilloma, multiple		X																								2
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Mesothelioma malignant	X												X													3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg (Stop-Exposure)

Number of Days on Study	0 8 5	1 2 0	1 3 0	2 4 0	3 6 1	3 8 3	4 2 3	4 3 0	4 6 6	5 0 6	5 4 2	5 4 7	5 6 8	5 8 5	6 4 4	6 4 8	6 6 2	6 8 4	6 9 6	7 0 4	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 6 8	2 9 6	2 7 0	2 5 1	2 9 3	2 9 9	2 8 4	2 9 7	3 0 4	2 9 8	2 7 4	3 0 5	2 8 5	2 2 5 3	2 6 9	3 0 1	2 5 7	2 9 0	2 8 8	2 7 9	2 5 4	2 5 8	2 6 2	2 6 6	2 6 7	2 7 5
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																										
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery						+				+					+		+	+								
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																			X							
Acinar cell, adenoma, multiple																										
Pharynx																		+								
Squamous cell papilloma																		X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin																										
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																										
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																				X						
Pheochromocytoma benign																						X				
Bilateral, pheochromocytoma benign																										
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X			X		X	X		X	X	X		X		X		X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X				X						
C-cell, carcinoma																										
Follicular cell, carcinoma																										
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg (Stop-Exposure) (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 8 1	2 8 6	2 9 1	3 0 0	3 0 7	2 5 6	2 5 9	2 6 0	2 6 1	2 6 3	2 6 4	2 6 5	2 6 7	2 7 2	2 7 3	2 7 7	2 7 8	2 8 3	2 8 7	2 9 2	2 9 5	2 9 9	3 0 3	3 0 6	3 0 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+		49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Carcinoma		X																								1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Mesentery	+											+			+	+	+		+	+	+		+	+		16
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Acinar cell, adenoma											X															2
Acinar cell, adenoma, multiple		X											X													2
Pharynx																										1
Squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Schwannoma malignant, metastatic, skin													X													1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Schwannoma benign							X																			1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma					X												X									2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pheochromocytoma malignant																		X								2
Pheochromocytoma benign										X														X		3
Bilateral, pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pars distalis, adenoma		X	X		X		X					X						X	X			X				18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
C-cell, adenoma		X												X												4
C-cell, carcinoma			X																				X			2
Follicular cell, carcinoma			X											X												2
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg (Stop-Exposure) (continued)

Number of Days on Study	0 8 5	1 2 0	1 3 0	2 4 0	3 6 1	3 8 3	4 2 3	4 3 0	4 6 6	5 0 6	5 4 2	5 4 7	5 6 8	5 8 5	6 4 4	6 4 8	6 6 2	6 8 4	6 9 6	7 0 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 6 8	2 9 6	2 7 0	2 5 1	2 9 3	2 8 9	2 8 4	2 9 7	3 0 4	2 9 8	2 7 4	3 0 5	2 8 5	2 5 3	2 6 9	3 0 1	2 5 7	2 9 0	2 8 8	2 8 9	2 5 4	2 5 8	2 6 2	2 6 6	2 7 5
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma						X																			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																									
Bilateral, interstitial cell, adenoma							X		X					X				X	X	X	X	X		X	X
Interstitial cell, adenoma															X	X									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node											+		+	+				+						+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma															X				X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, schwannoma benign							X																		
Subcutaneous tissue, schwannoma malignant											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma					X																				
Skeletal muscle								+																	
Hemangiosarcoma								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma benign																				X					
Peripheral nerve									+					+											
Spinal cord														+											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg (Stop-Exposure) (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 8 1	2 8 6	2 9 1	3 0 0	3 0 7	2 5 6	2 5 9	2 6 0	2 6 1	2 6 3	2 6 4	2 6 5	2 6 7	2 7 2	2 7 3	2 7 7	2 7 8	2 8 3	2 8 7	2 9 2	2 9 5	2 9 9	3 0 3	3 0 6	3 0 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery	X																						X			2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X												X		X	X								5
Carcinoma						X																				2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery	X																						X			2
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	34
Interstitial cell, adenoma																			X							3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+																					6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma																X				X						4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																			X				X			3
Squamous cell papilloma									X																	1
Subcutaneous tissue, fibroma		X		X						X			X						X							6
Subcutaneous tissue, lipoma		X																								1
Subcutaneous tissue, schwannoma benign																										1
Subcutaneous tissue, schwannoma malignant													X													2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma benign																										1
Peripheral nerve																										2
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg (Stop-Exposure) (continued)

Number of Days on Study	0 8 5	1 2 0	1 3 0	2 4 0	3 6 1	3 8 3	4 2 3	4 3 0	4 6 6	5 0 6	5 4 2	5 4 7	5 6 8	6 8 5	6 4 4	6 4 8	6 6 2	6 8 4	6 9 6	7 0 4	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 6 8	2 9 6	2 7 0	2 5 1	2 9 3	2 8 9	2 8 4	2 9 7	3 0 4	2 9 8	2 7 4	3 0 5	2 8 5	2 5 3	2 6 9	3 0 1	2 5 7	2 9 0	2 8 8	2 7 9	2 5 4	2 5 8	2 6 2	2 6 6	2 7 5
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								
Osteosarcoma, metastatic, bone					X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																						+		
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone					X																			
Urinary bladder	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X		X						X
Mesothelioma malignant																								

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg (Stop-Exposure) (continued)

Number of Days on Study	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	281	286	291	300	307	256	259	260	261	263	264	265	267	272	273	277	278	283	287	292	295	299	303	306	309	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma													X						X							2
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X			X	X	X		X						X										10
Mesothelioma malignant	X																							X		2

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	15/50 (30%)	7/49 (14%)	6/50 (12%)	8/49 (16%)
Adjusted rate[b]	38.2%	21.2%	18.7%	27.5%
Terminal rate[c]	11/35 (31%)	7/33 (21%)	5/31 (16%)	4/23 (17%)
First incidence (days)	653	729 (T)	704	635
Life table test[d]	P=0.303N	P=0.064N	P=0.054N	P=0.324N
Logistic regression test[d]	P=0.147N	P=0.057N	P=0.041N	P=0.127N
Cochran-Armitage test[d]	P=0.091N			
Fisher exact test[d]		P=0.050N	P=0.024N	P=0.084N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	16/50 (32%)	7/49 (14%)	7/50 (14%)	8/49 (16%)
Adjusted rate	39.8%	21.2%	21.8%	27.5%
Terminal rate	11/35 (31%)	7/33 (21%)	6/31 (19%)	4/23 (17%)
First incidence (days)	653	729 (T)	704	635
Life table test	P=0.262N	P=0.045N	P=0.067N	P=0.265N
Logistic regression test	P=0.114N	P=0.036N	P=0.048N	P=0.087N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.031N	P=0.028N	P=0.056N
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	4/50 (8%)	5/50 (10%)	3/50 (6%)
Adjusted rate	8.6%	11.5%	15.4%	11.4%
Terminal rate	3/35 (9%)	3/33 (9%)	4/31 (13%)	2/23 (9%)
First incidence (days)	729 (T)	691	696	684
Life table test	P=0.378	P=0.468	P=0.292	P=0.480
Logistic regression test	P=0.493	P=0.466	P=0.286	P=0.577
Cochran-Armitage test	P=0.554N			
Fisher exact test		P=0.500	P=0.357	P=0.661N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	6/50 (12%)	3/50 (6%)
Adjusted rate	8.6%	11.5%	18.0%	11.4%
Terminal rate	3/35 (9%)	3/33 (9%)	4/31 (13%)	2/23 (9%)
First incidence (days)	729 (T)	691	696	684
Life table test	P=0.357	P=0.468	P=0.187	P=0.480
Logistic regression test	P=0.477	P=0.466	P=0.185	P=0.577
Cochran-Armitage test	P=0.569N			
Fisher exact test		P=0.500	P=0.243	P=0.661N
Pancreas: Adenoma				
Overall rate	12/50 (24%)	6/50 (12%)	7/50 (14%)	10/50 (20%)
Adjusted rate	31.4%	17.3%	20.7%	35.9%
Terminal rate	9/35 (26%)	5/33 (15%)	5/31 (16%)	6/23 (26%)
First incidence (days)	684	659	611	704
Life table test	P=0.282	P=0.127N	P=0.243N	P=0.394
Logistic regression test	P=0.482	P=0.116N	P=0.214N	P=0.590
Cochran-Armitage test	P=0.488N			
Fisher exact test		P=0.096N	P=0.154N	P=0.405N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Pancreas: Adenoma or Carcinoma				
Overall rate	13/50 (26%)	6/50 (12%)	7/50 (14%)	10/50 (20%)
Adjusted rate	34.1%	17.3%	20.7%	35.9%
Terminal rate	10/35 (29%)	5/33 (15%)	5/31 (16%)	6/23 (26%)
First incidence (days)	684	659	611	704
Life table test	P=0.353	P=0.087N	P=0.180N	P=0.469
Logistic regression test	P=0.537N	P=0.077N	P=0.154N	P=0.526N
Cochran-Armitage test	P=0.403N			
Fisher exact test		P=0.062N	P=0.105N	P=0.318N
Pancreatic Islets: Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	6/50 (12%)	5/50 (10%)
Adjusted rate	5.3%	9.1%	17.1%	18.3%
Terminal rate	1/35 (3%)	3/33 (9%)	4/31 (13%)	3/23 (13%)
First incidence (days)	684	729 (T)	502	613
Life table test	P=0.056	P=0.472	P=0.109	P=0.113
Logistic regression test	P=0.127	P=0.474	P=0.125	P=0.190
Cochran-Armitage test	P=0.146			
Fisher exact test		P=0.500	P=0.134	P=0.218
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	6/50 (12%)	5/50 (10%)
Adjusted rate	8.1%	12.1%	17.1%	18.3%
Terminal rate	2/35 (6%)	4/33 (12%)	4/31 (13%)	3/23 (13%)
First incidence (days)	684	729 (T)	502	613
Life table test	P=0.124	P=0.466	P=0.199	P=0.198
Logistic regression test	P=0.245	P=0.467	P=0.224	P=0.314
Cochran-Armitage test	P=0.280			
Fisher exact test		P=0.500	P=0.243	P=0.357
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	14/50 (28%)	16/50 (32%)	18/49 (37%)	18/49 (37%)
Adjusted rate	34.3%	43.1%	45.4%	50.5%
Terminal rate	9/35 (26%)	12/33 (36%)	10/31 (32%)	7/22 (32%)
First incidence (days)	473	680	396	428
Life table test	P=0.037	P=0.345	P=0.174	P=0.064
Logistic regression test	P=0.162	P=0.355	P=0.216	P=0.216
Cochran-Armitage test	P=0.198			
Fisher exact test		P=0.414	P=0.238	P=0.238
Preputial Gland: Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	5.3%	2.2%	7.4%	0.0%
Terminal rate	1/35 (3%)	0/33 (0%)	0/31 (0%)	0/23 (0%)
First incidence (days)	708	424	502	—[e]
Life table test	P=0.291N	P=0.527N	P=0.451	P=0.330N
Logistic regression test	P=0.226N	P=0.470N	P=0.518	P=0.269N
Cochran-Armitage test	P=0.241N			
Fisher exact test		P=0.500N	P=0.500	P=0.247N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	5/50 (10%)	0/50 (0%)
Adjusted rate	7.7%	5.1%	13.4%	0.0%
Terminal rate	1/35 (3%)	1/33 (3%)	2/31 (6%)	0/23 (0%)
First incidence (days)	684	424	502	—
Life table test	P=0.238N	P=0.533N	P=0.303	P=0.185N
Logistic regression test	P=0.156N	P=0.486N	P=0.357	P=0.133N
Cochran-Armitage test	P=0.161N			
Fisher exact test		P=0.500N	P=0.357	P=0.121N
Skin: Squamous Cell Papilloma				
Overall rate	1/50 (2%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.9%	6.1%	9.7%	3.1%
Terminal rate	1/35 (3%)	2/33 (6%)	3/31 (10%)	0/23 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	696
Life table test	P=0.485	P=0.479	P=0.262	P=0.691
Logistic regression test	P=0.547	P=0.479	P=0.262	P=0.741
Cochran-Armitage test	P=0.577N			
Fisher exact test		P=0.500	P=0.309	P=0.753N
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	8.6%	8.8%	8.0%	6.8%
Terminal rate	3/35 (9%)	2/33 (6%)	0/31 (0%)	0/23 (0%)
First incidence (days)	729 (T)	726	639	687
Life table test	P=0.545N	P=0.635	P=0.609	P=0.655N
Logistic regression test	P=0.438N	P=0.629	P=0.637	P=0.569N
Cochran-Armitage test	P=0.397N			
Fisher exact test		P=0.661N	P=0.661N	P=0.500N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	4/50 (8%)	5/50 (10%)	6/50 (12%)	3/50 (6%)
Adjusted rate	11.4%	14.7%	16.9%	9.7%
Terminal rate	4/35 (11%)	4/33 (12%)	3/31 (10%)	0/23 (0%)
First incidence (days)	729 (T)	726	639	687
Life table test	P=0.522	P=0.463	P=0.304	P=0.627
Logistic regression test	P=0.473N	P=0.453	P=0.314	P=0.574N
Cochran-Armitage test	P=0.401N			
Fisher exact test		P=0.500	P=0.370	P=0.500N
Skin: Basal Cell Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	5.4%	8.7%	0.0%	0.0%
Terminal rate	1/35 (3%)	2/33 (6%)	0/31 (0%)	0/23 (0%)
First incidence (days)	717	709	—	—
Life table test	P=0.120N	P=0.467	P=0.276N	P=0.331N
Logistic regression test	P=0.092N	P=0.473	P=0.263N	P=0.282N
Cochran-Armitage test	P=0.073N			
Fisher exact test		P=0.500	P=0.247N	P=0.247N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Skin: Trichoepithelioma or Basal Cell Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	5.4%	8.7%	2.6%	0.0%
Terminal rate	1/35 (3%)	2/33 (6%)	0/31 (0%)	0/23 (0%)
First incidence (days)	717	709	639	—
Life table test	P=0.163N	P=0.467	P=0.549N	P=0.331N
Logistic regression test	P=0.117N	P=0.473	P=0.514N	P=0.282N
Cochran-Armitage test	P=0.104N			
Fisher exact test		P=0.500	P=0.500N	P=0.247N
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	2/50 (4%)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted rate	5.4%	11.2%	2.6%	0.0%
Terminal rate	1/35 (3%)	2/33 (6%)	0/31 (0%)	0/23 (0%)
First incidence (days)	717	691	639	—
Life table test	P=0.140N	P=0.309	P=0.549N	P=0.331N
Logistic regression test	P=0.097N	P=0.271	P=0.514N	P=0.282N
Cochran-Armitage test	P=0.086N			
Fisher exact test		P=0.339	P=0.500N	P=0.247N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	6/50 (12%)	9/50 (18%)	6/50 (12%)	3/50 (6%)
Adjusted rate	16.5%	24.9%	16.9%	9.7%
Terminal rate	5/35 (14%)	6/33 (18%)	3/31 (10%)	0/23 (0%)
First incidence (days)	717	691	639	687
Life table test	P=0.293N	P=0.249	P=0.532	P=0.440N
Logistic regression test	P=0.165N	P=0.240	P=0.556	P=0.315N
Cochran-Armitage test	P=0.119N			
Fisher exact test		P=0.288	P=0.620N	P=0.243N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	3/50 (6%)
Adjusted rate	5.7%	13.2%	2.5%	12.5%
Terminal rate	2/35 (6%)	2/33 (6%)	0/31 (0%)	2/23 (9%)
First incidence (days)	729 (T)	654	611	726
Life table test	P=0.449	P=0.203	P=0.536N	P=0.316
Logistic regression test	P=0.574	P=0.199	P=0.510N	P=0.332
Cochran-Armitage test	P=0.563N			
Fisher exact test		P=0.218	P=0.500N	P=0.500
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Fibrous Histiocytoma				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	5/50 (10%)
Adjusted rate	5.7%	13.2%	2.5%	17.4%
Terminal rate	2/35 (6%)	2/33 (6%)	0/31 (0%)	2/23 (9%)
First incidence (days)	729 (T)	654	611	645
Life table test	P=0.153	P=0.203	P=0.536N	P=0.108
Logistic regression test	P=0.242	P=0.199	P=0.510N	P=0.172
Cochran-Armitage test	P=0.264			
Fisher exact test		P=0.218	P=0.500N	P=0.218

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Testes: Adenoma				
Overall rate	45/50 (90%)	41/49 (84%)	46/50 (92%)	45/50 (90%)
Adjusted rate	97.8%	93.2%	100.0%	100.0%
Terminal rate	34/35 (97%)	30/33 (91%)	31/31 (100%)	23/23 (100%)
First incidence (days)	477	515	414	473
Life table test	P=0.003	P=0.462N	P=0.157	P=0.009
Logistic regression test	P=0.208	P=0.434N	P=0.253	P=0.405
Cochran-Armitage test	P=0.405			
Fisher exact test		P=0.264N	P=0.500	P=0.630N
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	9/50 (18%)	5/50 (10%)	6/50 (12%)
Adjusted rate	8.6%	25.4%	14.6%	22.9%
Terminal rate	3/35 (9%)	7/33 (21%)	3/31 (10%)	4/23 (17%)
First incidence (days)	729 (T)	680	680	696
Life table test	P=0.172	P=0.050	P=0.298	P=0.093
Logistic regression test	P=0.293	P=0.048	P=0.299	P=0.145
Cochran-Armitage test	P=0.397			
Fisher exact test		P=0.061	P=0.357	P=0.243
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	11/50 (22%)	7/50 (14%)	7/50 (14%)
Adjusted rate	14.3%	31.2%	20.7%	24.9%
Terminal rate	5/35 (14%)	9/33 (27%)	5/31 (16%)	4/23 (17%)
First incidence (days)	729 (T)	680	680	653
Life table test	P=0.235	P=0.066	P=0.301	P=0.162
Logistic regression test	P=0.404	P=0.063	P=0.298	P=0.278
Cochran-Armitage test	P=0.527			
Fisher exact test		P=0.086	P=0.380	P=0.380
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	4/50 (8%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	11.4%	0.0%	8.5%	4.3%
Terminal rate	4/35 (11%)	0/33 (0%)	2/31 (6%)	1/23 (4%)
First incidence (days)	729 (T)	—	502	729 (T)
Life table test	P=0.353N	P=0.070N	P=0.558N	P=0.324N
Logistic regression test	P=0.250N	P=0.070N	P=0.524N	P=0.324N
Cochran-Armitage test	P=0.232N			
Fisher exact test		P=0.059N	P=0.500N	P=0.181N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate	14.3%	0.0%	11.2%	4.3%
Terminal rate	5/35 (14%)	0/33 (0%)	2/31 (6%)	1/23 (4%)
First incidence (days)	729 (T)	—	502	729 (T)
Life table test	P=0.273N	P=0.038N	P=0.569N	P=0.221N
Logistic regression test	P=0.180N	P=0.038N	P=0.534N	P=0.221N
Cochran-Armitage test	P=0.162N			
Fisher exact test		P=0.028N	P=0.500N	P=0.102N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Urinary Bladder: Papilloma				
Overall rate	0/50 (0%)	0/49 (0%)	2/50 (4%)	6/50 (12%)
Adjusted rate	0.0%	0.0%	6.5%	22.1%
Terminal rate	0/35 (0%)	0/33 (0%)	2/31 (6%)	3/23 (13%)
First incidence (days)	—	—	729 (T)	653
Life table test	P<0.001	—	P=0.212	P=0.006
Logistic regression test	P<0.001	—	P=0.212	P=0.011
Cochran-Armitage test	P<0.001			
Fisher exact test		—	P=0.247	P=0.013
All Organs: Malignant Mesothelioma				
Overall rate	1/50 (2%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.9%	3.0%	5.9%	10.3%
Terminal rate	1/35 (3%)	1/33 (3%)	1/31 (3%)	1/23 (4%)
First incidence (days)	729 (T)	729 (T)	695	585
Life table test	P=0.094	P=0.749	P=0.463	P=0.207
Logistic regression test	P=0.149	P=0.749	P=0.465	P=0.292
Cochran-Armitage test	P=0.165			
Fisher exact test		P=0.753N	P=0.500	P=0.309
All Organs: Mononuclear Cell Leukemia				
Overall rate	13/50 (26%)	18/50 (36%)	12/50 (24%)	3/50 (6%)
Adjusted rate	32.0%	44.3%	29.5%	6.8%
Terminal rate	8/35 (23%)	11/33 (33%)	4/31 (13%)	0/23 (0%)
First incidence (days)	477	414	435	428
Life table test	P=0.021N	P=0.167	P=0.545	P=0.040N
Logistic regression test	P=0.002N	P=0.165	P=0.501N	P=0.007N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.194	P=0.500N	P=0.006N
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	44/50 (88%)	48/50 (96%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	35/35 (100%)	33/33 (100%)	31/31 (100%)	23/23 (100%)
First incidence (days)	473	515	396	428
Life table test	P=0.007	P=0.401N	P=0.264	P=0.025
Logistic regression test	P=0.518	P=0.086N	P=0.886N	P=0.998N
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.056N	P=0.500N	P=0.309N
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	24/50 (48%)	24/50 (48%)	9/50 (18%)
Adjusted rate	49.9%	55.1%	51.9%	22.8%
Terminal rate	12/35 (34%)	14/33 (42%)	9/31 (29%)	1/23 (4%)
First incidence (days)	477	414	414	428
Life table test	P=0.045N	P=0.412	P=0.340	P=0.049N
Logistic regression test	P<0.001N	P=0.385	P=0.580	P=0.002N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.500	P=0.500	P=0.002N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	46/50 (92%)	49/50 (98%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	35/35 (100%)	33/33 (100%)	31/31 (100%)	23/23 (100%)
First incidence (days)	473	414	396	428
Life table test	P=0.007	P=0.561N	P=0.211	P=0.018
Logistic regression test	P=0.512	P=0.722N	—[f]	—
Cochran-Armitage test	P=0.597			
Fisher exact test		P=0.181N	P=0.753N	P=0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of Salicylazosulfapyridine

	Vehicle Control	337.5 mg/kg
Adrenal Medulla: Benign Pheochromocytoma		
Overall rate[a]	15/50 (30%)	4/50 (8%)
Adjusted rate[b]	38.2%	13.3%
Terminal rate[c]	11/35 (31%)	4/30 (13%)
First incidence (days)	653	729 (T)
Life table test[d]		P=0.016N
Logistic regression test[d]		P=0.015N
Fisher exact test[d]		P=0.005N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma		
Overall rate	16/50 (32%)	6/50 (12%)
Adjusted rate	39.8%	19.4%
Terminal rate	11/35 (31%)	5/30 (17%)
First incidence (days)	653	704
Life table test		P=0.048N
Logistic regression test		P=0.039N
Fisher exact test		P=0.014N
Mammary Gland: Fibroadenoma		
Overall rate	3/50 (6%)	4/50 (8%)
Adjusted rate	8.6%	12.1%
Terminal rate	3/35 (9%)	2/30 (7%)
First incidence (days)	729 (T)	644
Life table test		P=0.414
Logistic regression test		P=0.412
Fisher exact test		P=0.500
Pancreas: Adenoma		
Overall rate	12/50 (24%)	4/48 (8%)
Adjusted rate	31.4%	12.8%
Terminal rate	9/35 (26%)	3/30 (10%)
First incidence (days)	684	696
Life table test		P=0.064N
Logistic regression test		P=0.062N
Fisher exact test		P=0.033N
Pancreas: Adenoma or Carcinoma		
Overall rate	13/50 (26%)	4/48 (8%)
Adjusted rate	34.1%	12.8%
Terminal rate	10/35 (29%)	3/30 (10%)
First incidence (days)	684	696
Life table test		P=0.041N
Logistic regression test		P=0.040N
Fisher exact test		P=0.019N
Pancreatic Islets: Adenoma or Carcinoma		
Overall rate	3/50 (6%)	0/49 (0%)
Adjusted rate	8.1%	0.0%
Terminal rate	2/35 (6%)	0/30 (0%)
First incidence (days)	684	—[e]
Life table test		P=0.154N
Logistic regression test		P=0.150N
Fisher exact test		P=0.125N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of Salicylazosulfapyridine
(continued)

	Vehicle Control	337.5 mg/kg
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	14/50 (28%)	18/49 (37%)
Adjusted rate	34.3%	46.4%
Terminal rate	9/35 (26%)	10/30 (33%)
First incidence (days)	473	423
Life table test		P=0.140
Logistic regression test		P=0.177
Fisher exact test		P=0.238
Preputial Gland: Adenoma		
Overall rate	1/50 (2%)	5/50 (10%)
Adjusted rate	2.5%	16.7%
Terminal rate	0/35 (0%)	5/30 (17%)
First incidence (days)	684	729 (T)
Life table test		P=0.072
Logistic regression test		P=0.064
Fisher exact test		P=0.102
Preputial Gland: Adenoma or Carcinoma		
Overall rate	3/50 (6%)	7/50 (14%)
Adjusted rate	7.7%	21.8%
Terminal rate	1/35 (3%)	6/30 (20%)
First incidence (days)	684	383
Life table test		P=0.106
Logistic regression test		P=0.122
Fisher exact test		P=0.159
Skin: Keratoacanthoma		
Overall rate	3/50 (6%)	3/50 (6%)
Adjusted rate	8.6%	10.0%
Terminal rate	3/35 (9%)	3/30 (10%)
First incidence (days)	729 (T)	729 (T)
Life table test		P=0.591
Logistic regression test		P=0.591
Fisher exact test		P=0.661N
Skin: Squamous Cell Papilloma or Keratoacanthoma		
Overall rate	4/50 (8%)	4/50 (8%)
Adjusted rate	11.4%	13.3%
Terminal rate	4/35 (11%)	4/30 (13%)
First incidence (days)	729 (T)	729 (T)
Life table test		P=0.557
Logistic regression test		P=0.557
Fisher exact test		P=0.643N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Basal Cell Adenoma		
Overall rate	6/50 (12%)	4/50 (8%)
Adjusted rate	16.5%	13.3%
Terminal rate	5/35 (14%)	4/30 (13%)
First incidence (days)	717	729 (T)
Life table test		P=0.474N
Logistic regression test		P=0.502N
Fisher exact test		P=0.370N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of Salicylazosulfapyridine
(continued)

	Vehicle Control	337.5 mg/kg
Skin (Subcutaneous Tissue): Fibroma		
Overall rate	2/50 (4%)	6/50 (12%)
Adjusted rate	5.7%	19.3%
Terminal rate	2/35 (6%)	5/30 (17%)
First incidence (days)	729 (T)	696
Life table test		P=0.089
Logistic regression test		P=0.077
Fisher exact test		P=0.134
Skin (Subcutaneous Tissue): Benign or Malignant Schwannoma		
Overall rate	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	7.9%
Terminal rate	0/35 (0%)	1/30 (3%)
First incidence (days)	—	423
Life table test		P=0.103
Logistic regression test		P=0.156
Fisher exact test		P=0.121
Testes: Adenoma		
Overall rate	45/50 (90%)	37/50 (74%)
Adjusted rate	97.8%	97.3%
Terminal rate	34/35 (97%)	29/30 (97%)
First incidence (days)	477	423
Life table test		P=0.466N
Logistic regression test		P=0.308N
Fisher exact test		P=0.033N
Thyroid Gland (C-cell): Adenoma		
Overall rate	3/50 (6%)	4/50 (8%)
Adjusted rate	8.6%	12.3%
Terminal rate	3/35 (9%)	2/30 (7%)
First incidence (days)	729 (T)	648
Life table test		P=0.409
Logistic regression test		P=0.410
Fisher exact test		P=0.500
Thyroid Gland (C-cell): Adenoma or Carcinoma		
Overall rate	5/50 (10%)	6/50 (12%)
Adjusted rate	14.3%	18.5%
Terminal rate	5/35 (14%)	4/30 (13%)
First incidence (days)	729 (T)	648
Life table test		P=0.387
Logistic regression test		P=0.373
Fisher exact test		P=0.500
Thyroid Gland (Follicular Cell): Adenoma		
Overall rate	4/50 (8%)	0/50 (0%)
Adjusted rate	11.4%	0.0%
Terminal rate	4/35 (11%)	0/30 (0%)
First incidence (days)	729 (T)	—
Life table test		P=0.083N
Logistic regression test		P=0.083N
Fisher exact test		P=0.059N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of Salicylazosulfapyridine
(continued)

	Vehicle Control	337.5 mg/kg
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma		
Overall rate	5/50 (10%)	2/50 (4%)
Adjusted rate	14.3%	6.7%
Terminal rate	5/35 (14%)	2/30 (7%)
First incidence (days)	729 (T)	729 (T)
Life table test		P=0.280N
Logistic regression test		P=0.280N
Fisher exact test		P=0.218N
All Organs: Mononuclear Cell Leukemia		
Overall rate	13/50 (26%)	10/50 (20%)
Adjusted rate	32.0%	30.9%
Terminal rate	8/35 (23%)	8/30 (27%)
First incidence (days)	477	648
Life table test		P=0.492N
Logistic regression test		P=0.468N
Fisher exact test		P=0.318N
All Organs: Benign Neoplasms		
Overall rate	49/50 (98%)	42/50 (84%)
Adjusted rate	100.0%	100.0%
Terminal rate	35/35 (100%)	30/30 (100%)
First incidence (days)	473	423
Life table test		P=0.552
Logistic regression test		P=0.329N
Fisher exact test		P=0.015N
All Organs: Malignant Neoplasms		
Overall rate	23/50 (46%)	21/50 (42%)
Adjusted rate	49.9%	55.7%
Terminal rate	12/35 (34%)	14/30 (47%)
First incidence (days)	477	361
Life table test		P=0.459
Logistic regression test		P=0.525N
Fisher exact test		P=0.420N
All Organs: Benign or Malignant Neoplasms		
Overall rate	49/50 (98%)	46/50 (92%)
Adjusted rate	100.0%	100.0%
Terminal rate	35/35 (100%)	30/30 (100%)
First incidence (days)	473	361
Life table test		P=0.259
Logistic regression test		P=0.814
Fisher exact test		P=0.181N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the dosed group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE A4
Historical Incidence of Urinary Bladder Papilloma in Male F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	1/904 (0.1%)
Standard deviation	0.5%
Range	0%-2%

[a] Data as of 17 June 1994

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
Disposition Summary					
Animals initially in study	70	60	60	60	70
6-Month interim evaluation	10				10
15-Month interim evaluation	10	10	10	10	10
Early deaths					
Accidental deaths	1	4	1	2	3
Moribund	13	11	16	15	13
Natural deaths	1	2	2	10	4
Survivors					
Died last week of study			1		
Terminal sacrifice	35	33	30	23	30
Animals examined microscopically	70	60	60	60	70
6-Month Interim Evaluation					
Alimentary System					
Intestine large, colon	(10)				(10)
Parasite metazoan	3 (30%)				1 (10%)
Intestine large, rectum	(9)				(10)
Parasite metazoan					1 (10%)
Liver	(10)				(10)
Clear cell focus	1 (10%)				
Granuloma	1 (10%)				
Inflammation, chronic					1 (10%)
Metaplasia, osseous					1 (10%)
Pancreas	(10)				(10)
Atrophy					1 (10%)
Tongue	(1)				
Hemorrhage	1 (100%)				
Cardiovascular System					
Heart	(10)				(10)
Cardiomyopathy	7 (70%)				2 (20%)
Endocrine System					
Adrenal cortex	(10)				(10)
Accessory adrenal cortical nodule	1 (10%)				2 (20%)
Pituitary gland	(10)				(10)
Pars distalis, cyst	2 (20%)				1 (10%)
Pars distalis, hyperplasia, focal					1 (10%)
Pars intermedia, cyst	1 (10%)				
Thyroid gland	(10)				(10)
Follicular cell, hypertrophy	2 (20%)				3 (30%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
6-Month Interim Evaluation (continued)					
Genital System					
Preputial gland	(10)				(10)
Inflammation, chronic	7 (70%)				7 (70%)
Inflammation, suppurative	2 (20%)				1 (10%)
Prostate	(10)				(10)
Corpora amylacea	1 (10%)				1 (10%)
Inflammation, suppurative					1 (10%)
Hematopoietic System					
Lymph node, mandibular	(10)				(10)
Hyperplasia, lymphoid	1 (10%)				
Pigmentation					1 (10%)
Lymph node, mesenteric	(10)				(10)
Hemorrhage					1 (10%)
Spleen	(10)				(10)
Hematopoietic cell proliferation	1 (10%)				
Pigmentation, hemosiderin	6 (60%)				3 (30%)
Thymus	(10)				(10)
Hemorrhage	6 (60%)				1 (10%)
Integumentary System					
Skin	(10)				(10)
Cyst epithelial inclusion					1 (10%)
Respiratory System					
Lung	(10)				(10)
Hemorrhage	1 (10%)				
Inflammation, subacute	2 (20%)				
Alveolar epithelium, hyperplasia	1 (10%)				
Nose	(10)				(10)
Exudate					1 (10%)
Foreign body					1 (10%)
Fungus					1 (10%)
Mucosa, hyperplasia					1 (10%)
Mucosa, metaplasia, squamous					1 (10%)
Urinary System					
Kidney	(10)				(10)
Mineralization	1 (10%)				1 (10%)
Nephropathy	8 (80%)				9 (90%)
Renal tubule, dilatation					1 (10%)
Systems Examined With No Lesions Observed					
General Body System					
Musculoskeletal System					
Nervous System					
Special Senses System					

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
15-Month Interim Evaluation					
Alimentary System					
Intestine large, colon	(10)	(9)	(10)	(10)	
Parasite metazoan				1 (10%)	
Intestine large, rectum	(10)	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)	1 (10%)	2 (20%)		
Intestine small, ileum	(10)	(10)	(10)	(10)	
Hyperplasia, lymphoid			1 (10%)		
Liver	(10)	(10)	(10)	(10)	(10)
Basophilic focus	2 (20%)	4 (40%)	3 (30%)		2 (20%)
Clear cell focus	5 (50%)	4 (40%)	6 (60%)	3 (30%)	4 (40%)
Granuloma	2 (20%)				4 (40%)
Hepatodiaphragmatic nodule		1 (10%)		1 (10%)	
Inflammation, chronic	1 (10%)	2 (20%)		1 (10%)	1 (10%)
Mixed cell focus	2 (20%)	3 (30%)	6 (60%)	3 (30%)	2 (20%)
Bile duct, hyperplasia	8 (80%)	5 (50%)	6 (60%)	3 (30%)	4 (40%)
Hepatocyte, vacuolization cytoplasmic	8 (80%)	6 (60%)	2 (20%)		6 (60%)
Lobules, necrosis			1 (10%)	1 (10%)	
Mesentery	(2)	(3)	(1)	(2)	(2)
Fat, hemorrhage	1 (50%)				
Fat, necrosis	1 (50%)	3 (100%)	1 (100%)	2 (100%)	2 (100%)
Pancreas	(10)	(10)	(10)	(10)	(10)
Atrophy	3 (30%)	7 (70%)	5 (50%)	5 (50%)	3 (30%)
Acinar cell, basophilic focus			1 (10%)		2 (20%)
Acinar cell, hyperplasia, focal	2 (20%)	3 (30%)	3 (30%)	3 (30%)	2 (20%)
Stomach, forestomach	(10)	(10)	(10)	(10)	(10)
Edema					1 (10%)
Mineralization			1 (10%)		
Cardiovascular System					
Heart	(10)	(10)	(10)	(10)	(10)
Cardiomyopathy	6 (60%)	4 (40%)	6 (60%)	3 (30%)	5 (50%)
Inflammation, subacute		1 (10%)			
Pericardium, fibrosis				1 (10%)	
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)	3 (30%)	3 (30%)	5 (50%)	2 (20%)
Degeneration, fatty				1 (10%)	
Hyperplasia, focal	1 (10%)		1 (10%)		1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)	(9)
Pars distalis, angiectasis	1 (10%)				
Pars distalis, cyst	1 (10%)			4 (40%)	
Pars distalis, hyperplasia, focal	3 (30%)	1 (10%)	3 (30%)	1 (10%)	2 (22%)
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst		1 (10%)	2 (20%)		1 (10%)
C-cell, hyperplasia		1 (10%)	1 (10%)	1 (10%)	
Follicle, cyst	1 (10%)			1 (10%)	
Follicular cell, hypertrophy		1 (10%)	4 (40%)	2 (20%)	1 (10%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
15-Month Interim Evaluation (continued)					
Genital System					
Epididymis	(10)	(10)	(10)	(10)	(10)
Atypia cellular		3 (30%)	4 (40%)	3 (30%)	2 (20%)
Hypospermia			1 (10%)		2 (20%)
Preputial gland	(10)	(10)	(10)	(10)	(10)
Inflammation, chronic	8 (80%)	8 (80%)	7 (70%)	6 (60%)	8 (80%)
Inflammation, suppurative	2 (20%)	2 (20%)			2 (20%)
Prostate	(10)	(10)	(10)	(10)	(10)
Corpora amylacea	2 (20%)	2 (20%)		2 (20%)	
Edema				1 (10%)	
Inflammation, suppurative	6 (60%)	3 (30%)	2 (20%)	3 (30%)	7 (70%)
Testes	(10)	(10)	(10)	(10)	(10)
Interstitial cell, hyperplasia	4 (40%)	4 (40%)	3 (30%)	1 (10%)	5 (50%)
Seminiferous tubule, atrophy			1 (10%)		1 (10%)
Hematopoietic System					
Lymph node					(1)
Mediastinal, hemorrhage					1 (100%)
Lymph node, mandibular	(10)	(10)	(10)	(10)	(10)
Ectasia					1 (10%)
Hemorrhage	3 (30%)	2 (20%)	1 (10%)	2 (20%)	3 (30%)
Pigmentation	1 (10%)				
Lymph node, mesenteric	(10)	(10)	(10)	(10)	(10)
Hemorrhage				1 (10%)	
Hyperplasia, lymphoid	1 (10%)				
Spleen	(10)	(10)	(10)	(10)	(10)
Fibrosis			1 (10%)		1 (10%)
Hematopoietic cell proliferation	1 (10%)	3 (30%)		2 (20%)	
Hemorrhage			1 (10%)		
Pigmentation, hemosiderin	2 (20%)			4 (40%)	
Thymus	(9)	(8)	(10)	(10)	(10)
Cyst			1 (10%)		
Hemorrhage	1 (11%)				
Integumentary System					
Mammary gland	(9)	(9)	(10)	(10)	(9)
Hyperplasia, cystic	1 (11%)	1 (11%)	2 (20%)		
Nervous System					
Brain	(10)	(10)	(10)	(10)	
Compression		1 (10%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
15-Month Interim Evaluation (continued)					
Respiratory System					
Lung	(10)	(10)	(10)	(10)	(10)
Hemorrhage		1 (10%)			
Infiltration cellular, histiocyte				2 (20%)	1 (10%)
Inflammation, subacute			3 (30%)	2 (20%)	1 (10%)
Alveolar epithelium, hyperplasia		1 (10%)	3 (30%)	1 (10%)	1 (10%)
Nose	(10)	(10)	(10)	(10)	(10)
Exudate		2 (20%)		1 (10%)	1 (10%)
Foreign body		3 (30%)			1 (10%)
Fungus					1 (10%)
Mucosa, hyperplasia			1 (10%)		1 (10%)
Mucosa, metaplasia, squamous					1 (10%)
Urinary System					
Kidney	(10)	(10)	(10)	(10)	(10)
Mineralization					2 (20%)
Nephropathy	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Renal tubule, dilatation	1 (10%)			2 (20%)	
Transitional epithelium, hyperplasia				1 (10%)	
Urethra					(1)
Bulbourethral gland, ectasia					1 (100%)
Systems Examined With No Lesions Observed					
General Body System					
Musculoskeletal System					
Special Senses System					
2-Year Study					
Alimentary System					
Esophagus	(50)	(50)	(49)	(49)	(50)
Inflammation, suppurative					1 (2%)
Perforation				1 (2%)	
Intestine large, colon	(49)	(50)	(50)	(48)	(50)
Inflammation, subacute				1 (2%)	
Parasite metazoan	7 (14%)	3 (6%)	4 (8%)	5 (10%)	3 (6%)
Intestine large, rectum	(50)	(50)	(50)	(49)	(49)
Parasite metazoan	10 (20%)	4 (8%)	9 (18%)	5 (10%)	7 (14%)
Ulcer				1 (2%)	
Intestine large, cecum	(50)	(50)	(50)	(50)	
Dilatation				1 (2%)	
Inflammation, subacute				1 (2%)	
Parasite metazoan			2 (4%)	1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)	
Erosion				1 (2%)	
Ulcer				1 (2%)	
Intestine small, jejunum	(50)	(49)	(50)	(49)	
Erosion			1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
Alimentary System (continued)					
Intestine small, ileum	(49)	(49)	(50)	(50)	(49)
Inflammation, chronic active	1 (2%)				
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis		2 (4%)			
Basophilic focus	33 (66%)	33 (66%)	26 (52%)	20 (40%)	34 (68%)
Clear cell focus	32 (64%)	23 (46%)	24 (48%)	16 (32%)	18 (36%)
Congestion	1 (2%)				
Degeneration, cystic	4 (8%)	1 (2%)			1 (2%)
Developmental malformation				1 (2%)	
Eosinophilic focus	7 (14%)	10 (20%)	7 (14%)	9 (18%)	6 (12%)
Granuloma					2 (4%)
Hematopoietic cell proliferation		3 (6%)	1 (2%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	5 (10%)	2 (4%)	3 (6%)	2 (4%)	3 (6%)
Inflammation, chronic					1 (2%)
Inflammation, subacute				2 (4%)	1 (2%)
Mixed cell focus	5 (10%)	3 (6%)	7 (14%)	2 (4%)	6 (12%)
Bile duct, hyperplasia	45 (90%)	39 (78%)	38 (76%)	21 (42%)	37 (74%)
Centrilobular, atrophy	3 (6%)	4 (8%)	4 (8%)		3 (6%)
Centrilobular, necrosis		1 (2%)			1 (2%)
Hepatocyte, vacuolization cytoplasmic	2 (4%)	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Lobules, necrosis		2 (4%)	2 (4%)	1 (2%)	2 (4%)
Mesentery	(17)	(14)	(18)	(12)	(16)
Accessory spleen		1 (7%)		1 (8%)	
Fibrosis			1 (6%)		
Fat, hemorrhage		1 (7%)	1 (6%)		
Fat, necrosis	14 (82%)	13 (93%)	14 (78%)	9 (75%)	14 (88%)
Pancreas	(50)	(50)	(50)	(50)	(48)
Atrophy	18 (36%)	26 (52%)	18 (36%)	19 (38%)	21 (44%)
Pigmentation			1 (2%)		
Acinar cell, basophilic focus	1 (2%)	1 (2%)	1 (2%)		3 (6%)
Acinar cell, cytoplasmic alteration	1 (2%)	1 (2%)	3 (6%)	15 (30%)	3 (6%)
Acinar cell, hyperplasia, focal	16 (32%)	11 (22%)	14 (28%)	8 (16%)	14 (29%)
Salivary glands	(50)	(50)	(50)	(50)	(50)
Atrophy			1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Edema	1 (2%)		1 (2%)	4 (8%)	
Erosion			1 (2%)	2 (4%)	
Inflammation, chronic				1 (2%)	
Mineralization				1 (2%)	
Perforation				1 (2%)	
Ulcer	1 (2%)	1 (2%)	1 (2%)	7 (14%)	
Mucosa, hyperplasia				9 (18%)	
Stomach, glandular	(49)	(50)	(50)	(50)	(50)
Cyst				1 (2%)	
Erosion	1 (2%)	1 (2%)	1 (2%)	2 (4%)	
Mineralization			1 (2%)		
Ulcer	1 (2%)			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	(50)
Embolus	1 (2%)				
Hypertrophy			1 (2%)	5 (10%)	
Inflammation, chronic active				2 (4%)	
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	23 (46%)	27 (54%)	27 (54%)	24 (48%)	21 (42%)
Foreign body				1 (2%)	
Inflammation, subacute				1 (2%)	1 (2%)
Mineralization				2 (4%)	
Thrombosis					1 (2%)
Pericardium, fibrosis	1 (2%)				
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	19 (38%)	19 (38%)	13 (26%)	8 (16%)	12 (24%)
Basophilic focus				1 (2%)	
Congestion	1 (2%)	1 (2%)			
Cyst	1 (2%)				1 (2%)
Degeneration, fatty	8 (16%)	6 (12%)	9 (18%)	8 (16%)	6 (12%)
Hematopoietic cell proliferation		1 (2%)		2 (4%)	1 (2%)
Hemorrhage	2 (4%)			1 (2%)	
Hyperplasia, focal	4 (8%)	8 (16%)	6 (12%)	3 (6%)	3 (6%)
Hypertrophy, focal	5 (10%)	2 (4%)	3 (6%)		3 (6%)
Necrosis		1 (2%)			2 (4%)
Adrenal medulla	(50)	(49)	(50)	(49)	(50)
Hyperplasia	15 (30%)	18 (37%)	16 (32%)	14 (29%)	9 (18%)
Islets, pancreatic	(50)	(50)	(50)	(50)	(49)
Hyperplasia		1 (2%)		1 (2%)	1 (2%)
Parathyroid gland	(46)	(49)	(49)	(45)	
Hyperplasia			1 (2%)	1 (2%)	
Pituitary gland	(50)	(50)	(49)	(49)	(49)
Congestion	1 (2%)				
Pars distalis, angiectasis	4 (8%)	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Pars distalis, cyst	5 (10%)	2 (4%)	3 (6%)	5 (10%)	5 (10%)
Pars distalis, hyperplasia, focal	15 (30%)	11 (22%)	13 (27%)	12 (24%)	5 (10%)
Pars intermedia, angiectasis		2 (4%)	1 (2%)	1 (2%)	2 (4%)
Pars intermedia, cyst	2 (4%)	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Pars intermedia, hyperplasia		1 (2%)			
Pars nervosa, gliosis		1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)	4 (8%)	2 (4%)	1 (2%)	4 (8%)
C-cell, hyperplasia	14 (28%)	9 (18%)	10 (20%)	11 (22%)	12 (24%)
Follicle, cyst	1 (2%)	3 (6%)	1 (2%)		3 (6%)
Follicular cell, hyperplasia	1 (2%)			1 (2%)	2 (4%)
Follicular cell, hypertrophy	1 (2%)	2 (4%)		4 (8%)	2 (4%)
General Body System					
None					

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(50)
Atypia cellular	25 (50%)	33 (66%)	36 (72%)	31 (62%)	25 (50%)
Hypospermia	40 (80%)	34 (68%)	37 (74%)	36 (72%)	32 (64%)
Preputial gland	(50)	(50)	(50)	(50)	(50)
Ectasia	20 (40%)	17 (34%)	17 (34%)	14 (28%)	14 (28%)
Hyperplasia	1 (2%)		1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic	24 (48%)	18 (36%)	16 (32%)	9 (18%)	25 (50%)
Inflammation, suppurative	19 (38%)	15 (30%)	10 (20%)	17 (34%)	18 (36%)
Prostate	(50)	(50)	(50)	(50)	(50)
Corpora amylacea	28 (56%)	28 (56%)	19 (38%)	11 (22%)	25 (50%)
Ectasia			1 (2%)		1 (2%)
Edema				2 (4%)	
Hemorrhage			1 (2%)	3 (6%)	
Hyperplasia, lymphoid	1 (2%)				2 (4%)
Inflammation, suppurative	17 (34%)	19 (38%)	21 (42%)	21 (42%)	24 (48%)
Epithelium, hyperplasia	8 (16%)	8 (16%)	13 (26%)	3 (6%)	4 (8%)
Seminal vesicle	(50)	(50)	(50)	(49)	(50)
Dilatation	1 (2%)	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Hemorrhage			1 (2%)	2 (4%)	
Inflammation, suppurative			2 (4%)	4 (8%)	
Testes	(50)	(49)	(50)	(50)	(50)
Interstitial cell, hyperplasia	1 (2%)	5 (10%)	8 (16%)	1 (2%)	5 (10%)
Seminiferous tubule, atrophy		2 (4%)	1 (2%)	2 (4%)	3 (6%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Hypercellularity	3 (6%)		3 (6%)	5 (10%)	2 (4%)
Myelofibrosis		1 (2%)			2 (4%)
Lymph node	(9)	(15)	(14)	(10)	(6)
Inguinal, hyperplasia, lymphoid			1 (7%)		
Mediastinal, congestion					1 (17%)
Mediastinal, ectasia					1 (17%)
Mediastinal, hemorrhage	6 (67%)	8 (53%)	6 (43%)	4 (40%)	3 (50%)
Mediastinal, hyperplasia, lymphoid		1 (7%)		1 (10%)	1 (17%)
Mediastinal, pigmentation	5 (56%)	9 (60%)	7 (50%)	5 (50%)	3 (50%)
Lymph node, mandibular	(50)	(50)	(50)	(49)	(50)
Congestion				1 (2%)	
Ectasia	5 (10%)	3 (6%)	4 (8%)		4 (8%)
Hemorrhage	4 (8%)	8 (16%)		3 (6%)	7 (14%)
Hyperplasia, lymphoid	5 (10%)	4 (8%)		7 (14%)	3 (6%)
Hyperplasia, plasma cell	1 (2%)				2 (4%)
Pigmentation		3 (6%)			1 (2%)
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(49)
Hemorrhage	3 (6%)	2 (4%)		4 (8%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)				1 (2%)
Pigmentation		2 (4%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
Hematopoietic System (continued)					
Spleen	(50)	(50)	(50)	(50)	(50)
Developmental malformation		1 (2%)			
Fibrosis	8 (16%)	8 (16%)	2 (4%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation	14 (28%)	15 (30%)	17 (34%)	23 (46%)	14 (28%)
Hyperplasia, reticulum cell				1 (2%)	
Pigmentation, hemosiderin	14 (28%)	15 (30%)	15 (30%)	30 (60%)	13 (26%)
Lymphoid follicle, atrophy				5 (10%)	
Thymus	(47)	(50)	(49)	(49)	(49)
Cyst					1 (2%)
Hemorrhage				1 (2%)	1 (2%)
Cortex, atrophy				2 (4%)	
Integumentary System					
Mammary gland	(48)	(49)	(47)	(49)	(49)
Hyperplasia, cystic	11 (23%)	8 (16%)	12 (26%)	10 (20%)	10 (20%)
Hyperplasia, lobular	2 (4%)	4 (8%)	3 (6%)	6 (12%)	
Skin	(50)	(50)	(50)	(50)	(50)
Acanthosis				1 (2%)	
Cyst epithelial inclusion	2 (4%)	3 (6%)	2 (4%)	1 (2%)	5 (10%)
Foreign body		1 (2%)			
Hemorrhage	1 (2%)				1 (2%)
Inflammation, chronic	1 (2%)				
Inflammation, suppurative		2 (4%)			
Subcutaneous tissue, edema					1 (2%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	
Calvarium, osteopetrosis				1 (2%)	
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Compression	4 (8%)	4 (8%)	8 (16%)	4 (8%)	4 (8%)
Hemorrhage			1 (2%)		1 (2%)
Hydrocephalus	1 (2%)	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, chronic			1 (2%)		
Mineralization	1 (2%)				
Necrosis	1 (2%)		1 (2%)		
Peripheral nerve					(2)
Atrophy					1 (50%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Congestion	1 (2%)	4 (8%)	1 (2%)	4 (8%)	3 (6%)
Edema		3 (6%)	1 (2%)	4 (8%)	3 (6%)
Fibrosis			1 (2%)	1 (2%)	1 (2%)
Foreign body		5 (10%)	2 (4%)		3 (6%)
Hemorrhage		1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	8 (16%)	8 (16%)	1 (2%)	12 (24%)	4 (8%)
Inflammation, granulomatous			1 (2%)		1 (2%)
Inflammation, subacute	3 (6%)	5 (10%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, suppurative		1 (2%)			
Metaplasia, osseous				1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	10 (20%)	3 (6%)	7 (14%)	6 (12%)	3 (6%)
Fat, mediastinum, necrosis	1 (2%)	1 (2%)			
Nose	(50)	(50)	(50)	(50)	(50)
Exudate	15 (30%)	12 (24%)	12 (24%)	14 (28%)	13 (26%)
Foreign body	4 (8%)	7 (14%)	1 (2%)	2 (4%)	5 (10%)
Fungus	6 (12%)	4 (8%)	3 (6%)	2 (4%)	4 (8%)
Mucosa, hyperplasia	6 (12%)	1 (2%)	5 (10%)	6 (12%)	6 (12%)
Mucosa, metaplasia, squamous	1 (2%)	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Trachea	(50)	(50)	(50)	(50)	
Hemorrhage			1 (2%)		
Special Senses System					
Eye		(2)	(3)		(1)
Cataract		2 (100%)	3 (100%)		
Phthisis bulbi					1 (100%)
Retina, atrophy		2 (100%)	3 (100%)		
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Concretion		1 (2%)	13 (26%)	33 (66%)	
Cyst	1 (2%)	2 (4%)			
Hemorrhage		1 (2%)	1 (2%)	1 (2%)	
Hydronephrosis		1 (2%)	1 (2%)	28 (56%)	
Infarct				1 (2%)	
Inflammation, suppurative	6 (12%)	7 (14%)	8 (16%)	6 (12%)	8 (16%)
Mineralization	3 (6%)	10 (20%)	11 (22%)	13 (26%)	3 (6%)
Nephropathy	48 (96%)	47 (94%)	50 (100%)	48 (96%)	46 (92%)
Papilla, fibrosis			1 (2%)	1 (2%)	
Papilla, necrosis			1 (2%)	4 (8%)	
Renal tubule, cytoplasmic alteration					1 (2%)
Renal tubule, dilatation		1 (2%)	1 (2%)	11 (22%)	3 (6%)
Renal tubule, hyperplasia			1 (2%)		
Renal tubule, hyperplasia, oncocytic		1 (2%)			
Renal tubule, pigmentation	2 (4%)	4 (8%)	2 (4%)	3 (6%)	1 (2%)
Transitional epithelium, hyperplasia	10 (20%)	10 (20%)	20 (40%)	43 (86%)	4 (8%)
Transitional epithelium, hyperplasia, atypical				3 (6%)	
Transitional epithelium, metaplasia				1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
2-Year Study (continued)					
Urinary System (continued)					
Ureter			(1)	(13)	
Concretion				3 (23%)	
Dilatation			1 (100%)	2 (15%)	
Hemorrhage			1 (100%)		
Inflammation, subacute				1 (8%)	
Mucosa, hyperplasia				12 (92%)	
Urethra			(2)	(5)	
Concretion				1 (20%)	
Hemorrhage			1 (50%)		
Inflammation, subacute				1 (20%)	
Bulbourethral gland, ectasia			1 (50%)		
Lumen, concretion			1 (50%)	2 (40%)	
Lumen, dilatation			1 (50%)		
Mucosa, hyperplasia			1 (50%)	1 (20%)	
Mucosa, metaplasia, squamous				2 (40%)	
Urinary bladder	(50)	(49)	(50)	(50)	(47)
Concretion			1 (2%)	10 (20%)	
Congestion				1 (2%)	
Dilatation		1 (2%)	2 (4%)	7 (14%)	
Hemorrhage		1 (2%)	1 (2%)	4 (8%)	
Inflammation, subacute				3 (6%)	
Inflammation, suppurative			1 (2%)		
Mucosa, hyperplasia			14 (28%)	41 (82%)	1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF SALICYLAZOSULFAPYRIDINE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	1	1		9
Moribund	12	13	14	11
Natural deaths	2	2	5	4
Survivors				
Died last week of study	1	1		
Terminal sacrifice	34	33	31	26
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma	1 (10%)			
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Adenoma		1 (10%)		
Uterus	(10)	(10)	(10)	(10)
Polyp stromal		1 (10%)	1 (10%)	1 (10%)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Keratoacanthoma				1 (10%)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear	1 (10%)		1 (10%)	
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Schwannoma malignant	1 (2%)			
Intestine small, duodenum	(50)	(50)	(50)	(50)
Leiomyoma		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, uterus		1 (2%)		
Hepatocellular adenoma			1 (2%)	
Histiocytic sarcoma, metastatic, skin				1 (2%)
Mesentery	(4)	(7)	(4)	(4)
Carcinoma, metastatic, uterus		1 (14%)		
Fibroma		1 (14%)		
Pancreas	(50)	(50)	(50)	(50)
Pharynx	(1)		(1)	
Squamous cell carcinoma			1 (100%)	
Squamous cell papilloma	1 (100%)			
Stomach, forestomach	(50)	(49)	(50)	(50)
Squamous cell papilloma				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Tongue	(1)	(1)	(1)	
Squamous cell papilloma		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma malignant	3 (6%)			3 (6%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(50)
Ganglioneuroma	1 (2%)			
Pheochromocytoma benign			3 (6%)	
Bilateral, pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Carcinoma		1 (2%)		
Pituitary gland	(50)	(49)	(50)	(50)
Pars distalis, adenoma	26 (52%)	20 (41%)	24 (48%)	13 (26%)
Pars distalis, carcinoma		2 (4%)		
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	3 (6%)	5 (10%)	2 (4%)	5 (10%)
C-cell, carcinoma		1 (2%)		
Follicular cell, adenoma			2 (4%)	
Follicular cell, carcinoma				1 (2%)
General Body System				
Tissue NOS		(1)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
2-Year Study (continued)				
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Carcinoma	1 (2%)	2 (4%)	1 (2%)	
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor benign		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Carcinoma		1 (2%)		
Polyp stromal	6 (12%)	7 (14%)	7 (14%)	3 (6%)
Polyp stromal, multiple				1 (2%)
Sarcoma stromal				1 (2%)
Schwannoma malignant			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(12)	(6)	(9)	(7)
Lymph node, mandibular	(50)	(48)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Spleen	(50)	(50)	(50)	(50)
Thymus	(49)	(49)	(50)	(50)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(48)
Adenoma		1 (2%)	2 (4%)	
Carcinoma	2 (4%)		3 (6%)	1 (2%)
Fibroadenoma	18 (36%)	8 (16%)	18 (36%)	5 (10%)
Fibroadenoma, multiple	4 (8%)	1 (2%)	2 (4%)	
Skin	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Keratoacanthoma	1 (2%)		1 (2%)	
Sarcoma				1 (2%)
Squamous cell papilloma	3 (6%)			
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		
Subcutaneous tissue, lipoma			1 (2%)	
Musculoskeletal System				
Skeletal muscle	(2)	(1)		(1)
Carcinoma, metastatic, uterus		1 (100%)		
Rhabdomyosarcoma				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Carcinoma, metastatic, pituitary gland		3 (6%)		
Glioma malignant, mixed		1 (2%)		
Meningioma malignant		1 (2%)		
Spinal cord				(2)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Histiocytic sarcoma, metastatic, skin				1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Nose	(50)	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)		
Special Senses System				
Zymbal's gland		(1)		
Carcinoma		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Renal tubule, carcinoma			1 (2%)	
Transitional epithelium, papilloma				2 (4%)
Urinary bladder	(49)	(50)	(50)	(50)
Papilloma			2 (4%)	
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	14 (28%)	9 (18%)	8 (16%)	3 (6%)
Lymphoma malignant		1 (2%)		1 (2%)
Lymphoma malignant mixed			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2	2	2	2
2-Year study	44	41	47	31
Total primary neoplasms				
15-Month interim evaluation	2	2	2	2
2-Year study	89	70	86	48
Total animals with benign neoplasms				
15-Month interim evaluation	1	2	1	2
2-Year study	41	30	44	25
Total benign neoplasms				
15-Month interim evaluation	1	2	1	2
2-Year study	68	48	69	35
Total animals with malignant neoplasms				
15-Month interim evaluation	1		1	
2-Year study	21	20	16	12
Total malignant neoplasms				
15-Month interim evaluation	1		1	
2-Year study	21	21	17	13

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Neoplasm Summary (continued)				
Total animals with metastatic neoplasms				
2-Year study		5		2
Total metastatic neoplasms				
2-Year study		8		3
Total animals with uncertain neoplasms — benign or malignant				
2-Year study		1		
Total uncertain neoplasms				
2-Year study		1		

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control

Number of Days on Study	2 6 0	3 3 2	5 0 7	5 9 2	5 9 8	6 2 2	6 3 5	6 4 9	6 6 3	6 6 3	6 8 4	6 9 1	6 9 2	7 0 3	7 0 9	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	3 9 3	4 1 2	4 2 8	3 8 9	3 8 1	4 1 3	4 0 7	4 1 6	4 0 3	4 1 1	4 0 1	3 9 8	3 9 2	4 2 6	4 1 7	4 1 9	3 8 3	3 8 7	3 9 1	3 9 6	4 0 0	4 0 4	4 0 8	4 2 0	4 2 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant												X													
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																							+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Squamous cell papilloma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma							X																		
Bilateral, pheochromocytoma benign												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X	X	X	X	X		X	X	X	X	X	X			X	X		X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X			X											
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma										X															
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X											X		X					

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	4 3 0	3 8 2	3 8 4	3 8 5	3 8 6	3 8 8	3 9 0	3 9 4	3 9 5	3 9 7	3 9 9	4 0 2	4 0 5	4 0 6	4 0 9	4 1 0	4 1 4	4 1 5	4 1 8	4 2 1	4 2 2	4 2 3	4 2 5	4 2 7	4 2 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+		+																		+				4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx					+																					1
Squamous cell papilloma				X																						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue									+																	1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant		X					X											X								3
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma																										1
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X			X			X			X			X		X		X		X	X		X	X	26
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																	X									3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X								X														2
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X												X	X						6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	260	332	507	592	598	622	635	649	663	663	684	691	692	703	709	737	738	738	738	738	738	738	738	738	738
Carcass ID Number	393	412	428	389	381	413	407	416	403	411	401	398	392	426	417	419	383	387	391	396	400	404	408	420	424
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+		+	+		+	+			+						+			+			+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X										
Fibroadenoma			X		X				X					X		X	X		X						
Fibroadenoma, multiple								X															X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								X	
Squamous cell papilloma																				X				X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+						+																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+											+										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X	X		X	X			X		X										X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	4 3 0	3 8 2	3 8 4	3 8 5	3 8 6	3 8 8	3 9 0	3 9 4	3 9 5	3 9 7	3 9 9	4 0 2	4 0 5	4 0 6	4 0 9	4 1 0	4 1 4	4 1 5	4 1 8	4 2 1	4 2 2	4 2 3	4 2 5	4 2 7	4 2 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+																						12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma									X																	2
Fibroadenoma	X	X	X				X	X										X	X			X	X	X	X	18
Fibroadenoma, multiple										X		X														4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Squamous cell papilloma																				X						3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																							+			3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X		X		X								X				X						14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg

Number of Days on Study	2 1 8	2 8 0	3 9 5	3 9 6	4 3 2	4 7 2	5 0 1	5 4 4	5 8 3	6 3 2	6 4 8	6 8 4	6 9 3	7 0 3	7 1 7	7 2 4	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	4 4 9	4 8 6	4 8 1	4 5 5	4 5 9	4 6 8	4 7 3	4 7 9	4 5 0	4 7 6	4 4 6	4 7 8	4 6 9	4 6 2	4 7 4	4 8 7	4 4 3	4 8 8	4 4 2	4 4 7	4 5 3	4 5 7	4 6 1	4 6 6	4 7 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																X									
Mesentery	+				+											+	+			+					
Carcinoma, metastatic, uterus																X									
Fibroma																				X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																		X							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pars distalis, adenoma					X			X	X	X	X	X			X	X	X	X							
Pars distalis, carcinoma																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X			X				X										
C-cell, carcinoma																									
General Body System																									
Tissue NOS				+																					
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Polyp stromal													X			X			X						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	4 7 2	4 8 0	4 8 4	4 8 5	4 4 1	4 4 4	4 4 5	4 4 8	4 5 1	4 5 2	4 5 4	4 5 6	4 5 8	4 6 0	4 6 3	4 6 4	4 6 5	4 6 7	4 7 1	4 7 5	4 7 7	4 8 2	4 8 3	4 8 9	4 9 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																X										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uterus																										1
Mesentery																		+		+						7
Carcinoma, metastatic, uterus																										1
Fibroma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+																			1
Squamous cell papilloma							X																			1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																			X							1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X	X		X	X			X					X				X	X					X	20
Pars distalis, carcinoma		X																								2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X														X							5
C-cell, carcinoma							X																			1
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				2
Carcinoma										X	X															2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign						X																				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Polyp stromal										X										X		X			X	7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg
(continued)

Number of Days on Study	2 1 8	2 8 0	3 9 5	3 9 6	4 3 2	4 7 2	5 0 1	5 4 4	5 8 3	6 3 2	6 4 8	6 8 4	6 9 3	7 0 3	7 1 7	7 2 4	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	4 4 9	4 8 6	4 8 1	4 5 5	4 5 9	4 6 8	4 7 3	4 7 9	4 5 0	4 7 6	4 4 6	4 7 8	4 6 9	4 6 2	4 7 4	4 8 7	4 4 3	4 8 8	4 4 2	4 4 7	4 5 3	4 5 7	4 6 1	4 6 6	4 7 0
Genital System (continued)																									
Vagina													M			+									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+															+	+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma																X			X		X	X			
Fibroadenoma, multiple																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+									
Carcinoma, metastatic, uterus																X									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland										X															X
Glioma malignant, mixed						X																			
Meningioma malignant			X																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+	+							+											
Zymbal's gland														+											
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X									X		X				X		X				
Lymphoma malignant	X																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 84 mg/kg
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	4 7 2	4 8 0	4 8 4	4 8 5	4 4 1	4 4 4	4 4 5	4 4 8	4 5 1	4 5 2	4 5 4	4 5 6	4 5 8	4 6 0	4 6 3	4 6 4	4 6 5	4 6 7	4 7 1	4 7 5	4 7 7	4 8 2	4 8 3	4 8 9	4 9 0	Total Tissues/ Tumors
Genital System (continued)																										
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+									+													6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Fibroadenoma							X										X			X					X	8
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Carcinoma, metastatic, uterus																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland		X																								3
Glioma malignant, mixed																										1
Meningioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+		+																							5
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X		X		X							X						9
Lymphoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg

Number of Days on Study	5 4 4	6 1 9	6 2 1	6 2 4	6 2 5	6 6 7	6 8 7	6 9 1	6 9 1	6 9 2	6 9 5	6 9 5	6 9 6	7 0 8	7 0 8	7 2 5	7 3 3	7 3 3	7 3 3	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	5 2 2	5 1 8	5 2 6	5 0 8	5 3 2	5 1 5	5 2 1	5 4 0	5 4 7	5 0 7	5 1 0	5 3 0	5 3 1	5 1 4	5 3 5	5 0 6	5 1 2	5 3 7	5 4 3	5 0 3	5 0 9	5 1 3	5 1 7	5 2 3	5 2 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery													+			+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx					+																				
Squamous cell carcinoma					X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									+																
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X		X	X		X					X	X	X		X	X		X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X														
Follicular cell, adenoma	X																								
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																								X	X
Schwannoma malignant																									
Vagina			M																						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	
Carcass ID Number	5 3 3	5 3 8	5 4 1	5 4 6	5 0 1	5 0 2	5 0 4	5 0 5	5 1 1	5 1 6	5 1 9	5 2 0	5 2 4	5 2 5	5 2 7	5 2 9	5 3 4	5 3 6	5 3 9	5 4 2	5 4 4	5 4 8	5 4 9	5 5 0	5 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X																		1
Mesentery																			+					+		4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X								X							X		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X					X	X	X		X		X				X	X			X		X	24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X																		2
Follicular cell, adenoma											X															2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X														X											2
Carcinoma										X																1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X					X							X					X				X	7
Schwannoma malignant															X											1
Vagina															+											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg
(continued)

Number of Days on Study	5 4 4	6 1 9	6 2 1	6 2 4	6 2 5	6 6 7	6 8 7	6 9 1	6 9 1	6 9 2	6 9 5	6 9 5	6 9 6	7 0 8	7 0 8	7 2 5	7 3 3	7 3 3	7 3 3	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	5 2 2	5 1 8	5 2 6	5 0 8	5 3 2	5 1 5	5 2 1	5 4 0	5 4 7	5 0 7	5 1 0	5 3 0	5 3 1	5 1 4	5 3 5	5 0 6	5 1 2	5 3 7	5 4 3	5 0 3	5 0 9	5 1 3	5 1 7	5 2 3	5 2 8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+	+		+				+	+		+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Carcinoma	X															X									
Fibroadenoma		X		X	X			X	X					X			X			X					
Fibroadenoma, multiple												X				X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																			X						
Subcutaneous tissue, lipoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									X
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																									
Ureter												+													
Urethra												+													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma												X													
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X							X						X	X								
Lymphoma malignant mixed													X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 168 mg/kg
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	
Carcass ID Number	5 3 3	5 3 8	5 4 1	5 4 6	5 0 1	5 0 2	5 0 4	5 0 5	5 1 1	5 1 6	5 1 9	5 2 0	5 2 4	5 2 5	5 2 7	5 2 9	5 3 4	5 3 6	5 3 9	5 4 2	5 4 4	5 4 8	5 4 9	5 5 0	5 5 4	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+		+																	+		9
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									2
Carcinoma			X																							3
Fibroadenoma	X	X				X			X		X	X	X	X		X	X									18
Fibroadenoma, multiple																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+								+								2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma											X															1
Ureter																						+				2
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																						X				2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																		X			8
Lymphoma malignant mixed																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg

Number of Days on Study	1 2 2	2 1 4	3 4 9	3 5 8	3 7 5	3 9 3	3 9 8	4 0 5	4 1 6	4 9 5	4 9 5	5 0 8	5 0 8	5 0 8	5 0 8	5 6 8	6 0 3	6 0 7	6 9 3	6 9 6	7 0 3	7 0 4	7 0 9	7 3 3	7 3 8
Carcass ID Number	6 1 9	5 9 0	6 1 0	5 6 9	6 1 3	6 2 0	5 8 6	5 6 1	5 6 3	6 6 6	5 9 5	5 8 1	5 9 7	6 0 0	6 0 5	6 6 4	5 7 6	5 6 7	6 8 4	5 6 5	5 7 2	5 8 0	5 7 9	5 7 7	5 6 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, skin																		X							
Mesentery																									+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																								X	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																			X		X	X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X														
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Polyp stromal																							X		
Polyp stromal, multiple																									
Sarcoma stromal					X																				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	5 7 0	5 7 8	5 8 2	5 8 7	5 8 9	5 9 2	5 9 6	5 9 9	6 0 2	5 6 8	5 7 1	5 7 3	5 7 4	5 7 5	5 8 3	5 8 5	5 8 8	5 9 1	5 9 3	5 9 4	5 9 8	6 0 1	6 0 3	6 0 4	6 0 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, skin																										1
Mesentery								+					+			+										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant						X														X						3
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X		X		X	X	X	X	X						X						X		13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X					X		X			X														5
Follicular cell, carcinoma																							X			1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X												X							2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Polyp stromal				X																				X		3
Polyp stromal, multiple																				X						1
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg
(continued)

Number of Days on Study	1 2 2	2 1 4	3 4 9	3 5 8	3 7 5	3 9 3	3 9 8	4 0 5	4 1 6	4 9 5	4 9 5	5 0 8	5 0 8	5 0 8	5 0 8	5 6 8	6 0 3	6 0 7	6 9 3	6 9 6	7 0 3	7 0 4	7 0 9	7 3 3	7 3 8
Carcass ID Number	6 1 9	5 9 0	6 1 0	5 6 9	6 1 3	6 2 0	5 8 6	5 6 1	5 6 3	5 6 6	5 9 5	5 8 1	5 9 7	6 0 0	6 0 5	5 6 4	5 7 6	5 6 7	5 8 4	5 6 5	5 7 2	5 8 0	5 7 9	5 7 7	5 6 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+	+								+		+			+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Fibroadenoma																	X			X	X	X		X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Sarcoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																					
Rhabdomyosarcoma				X																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve										+						+									
Spinal cord										+						+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, skin																		X							
Sarcoma, metastatic, skin																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Ureter				+													+			+					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Leukemia mononuclear										X						X					X				
Lymphoma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine: 337.5 mg/kg
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	5 7 0	5 7 8	5 8 2	5 8 7	5 8 9	5 9 2	5 9 6	5 9 9	6 0 2	5 6 8	5 7 1	5 7 3	5 7 4	5 7 5	5 8 3	5 8 5	5 8 8	5 9 1	5 9 3	5 9 4	5 9 8	6 0 1	6 0 3	6 0 4	6 0 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																							+			7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Fibroadenoma																										5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										2
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, skin																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+																								2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma		X											X													2
Ureter																	+									4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear																										3
Lymphoma malignant																								X		1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate[b]	2.6%	0.0%	9.7%	0.0%
Terminal rate[c]	0/35 (0%)	0/34 (0%)	3/31 (10%)	0/26 (0%)
First incidence (days)	691	—[e]	737 (T)	—
Life table test[d]	P=0.581N	P=0.505N	P=0.283	P=0.539N
Logistic regression test[d]	P=0.566N	P=0.502N	P=0.320	P=0.525N
Cochran-Armitage test[d]	P=0.499N			
Fisher exact test[d]		P=0.500N	P=0.309	P=0.500N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rate	8.0%	11.8%	9.7%	7.7%
Terminal rate	2/35 (6%)	4/34 (12%)	3/31 (10%)	2/26 (8%)
First incidence (days)	663	737 (T)	737 (T)	737 (T)
Life table test	P=0.493N	P=0.481	P=0.621	P=0.631N
Logistic regression test	P=0.458N	P=0.472	P=0.644N	P=0.610N
Cochran-Armitage test	P=0.344N			
Fisher exact test		P=0.500	P=0.661N	P=0.500N
Heart: Malignant Schwannoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	8.6%	0.0%	0.0%	11.1%
Terminal rate	3/35 (9%)	0/34 (0%)	0/31 (0%)	2/26 (8%)
First incidence (days)	737 (T)	—	—	733
Life table test	P=0.336	P=0.126N	P=0.143N	P=0.523
Logistic regression test	P=0.347	P=0.126N	P=0.143N	P=0.539
Cochran-Armitage test	P=0.443			
Fisher exact test		P=0.121N	P=0.121N	P=0.661N
Mammary Gland: Fibroadenoma				
Overall rate	22/50 (44%)	9/50 (18%)	20/50 (40%)	5/50 (10%)
Adjusted rate	54.3%	25.7%	48.4%	15.6%
Terminal rate	17/35 (49%)	8/34 (24%)	11/31 (35%)	0/26 (0%)
First incidence (days)	507	724	619	603
Life table test	P=0.020N	P=0.008N	P=0.526N	P=0.004N
Logistic regression test	P=0.005N	P=0.007N	P=0.387N	P<0.001N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.004N	P=0.420N	P<0.001N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	22/50 (44%)	10/50 (20%)	21/50 (42%)	5/50 (10%)
Adjusted rate	54.3%	28.6%	49.6%	15.6%
Terminal rate	17/35 (49%)	9/34 (26%)	11/31 (35%)	0/26 (0%)
First incidence (days)	507	724	619	603
Life table test	P=0.020N	P=0.014N	P=0.550	P=0.004N
Logistic regression test	P=0.005N	P=0.013N	P=0.469N	P<0.001N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.009N	P=0.500N	P<0.001N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Mammary Gland: Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	5.6%	0.0%	7.9%	2.9%
Terminal rate	1/35 (3%)	0/34 (0%)	1/31 (3%)	0/26 (0%)
First incidence (days)	709	—	544	568
Life table test	P=0.574	P=0.243N	P=0.481	P=0.596N
Logistic regression test	P=0.545N	P=0.249N	P=0.474	P=0.515N
Cochran-Armitage test	P=0.556N			
Fisher exact test		P=0.247N	P=0.500	P=0.500N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	5/50 (10%)	1/50 (2%)
Adjusted rate	5.6%	2.9%	13.0%	2.9%
Terminal rate	1/35 (3%)	1/34 (3%)	2/31 (6%)	0/26 (0%)
First incidence (days)	709	737 (T)	544	568
Life table test	P=0.546	P=0.507N	P=0.211	P=0.596N
Logistic regression test	P=0.543N	P=0.517N	P=0.201	P=0.515N
Cochran-Armitage test	P=0.522N			
Fisher exact test		P=0.500N	P=0.218	P=0.500N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	24/50 (48%)	10/50 (20%)	23/50 (46%)	6/50 (12%)
Adjusted rate	58.0%	28.6%	53.0%	18.0%
Terminal rate	18/35 (51%)	9/34 (26%)	12/31 (39%)	0/26 (0%)
First incidence (days)	507	724	544	568
Life table test	P=0.024N	P=0.005N	P=0.541	P=0.005N
Logistic regression test	P=0.007N	P=0.004N	P=0.482N	P<0.001N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.003N	P=0.500N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	26/50 (52%)	20/49 (41%)	24/50 (48%)	13/50 (26%)
Adjusted rate	57.6%	48.0%	57.6%	44.4%
Terminal rate	16/35 (46%)	12/33 (36%)	14/31 (45%)	10/26 (38%)
First incidence (days)	598	432	619	693
Life table test	P=0.136N	P=0.265N	P=0.523N	P=0.105N
Logistic regression test	P=0.051N	P=0.332N	P=0.372N	P=0.116N
Cochran-Armitage test	P=0.009N			
Fisher exact test		P=0.180N	P=0.421N	P=0.007N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	26/50 (52%)	22/49 (45%)	24/50 (48%)	13/50 (26%)
Adjusted rate	57.6%	53.0%	57.6%	44.4%
Terminal rate	16/35 (46%)	14/33 (42%)	14/31 (45%)	10/26 (38%)
First incidence (days)	598	432	619	693
Life table test	P=0.115N	P=0.391N	P=0.523N	P=0.105N
Logistic regression test	P=0.039N	P=0.503N	P=0.372N	P=0.116N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.307N	P=0.421N	P=0.007N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Skin: Squamous Cell Papilloma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	8.6%	0.0%	0.0%	0.0%
Terminal rate	3/35 (9%)	0/34 (0%)	0/31 (0%)	0/26 (0%)
First incidence (days)	737 (T)	—	—	—
Life table test	P=0.063N	P=0.126N	P=0.143N	P=0.178N
Logistic regression test	P=0.063N	P=0.126N	P=0.143N	P=0.178N
Cochran-Armitage test	P=0.048N			
Fisher exact test		P=0.121N	P=0.121N	P=0.121N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate	8.6%	0.0%	2.9%	0.0%
Terminal rate	3/35 (9%)	0/34 (0%)	0/31 (0%)	0/26 (0%)
First incidence (days)	737 (T)	—	733	—
Life table test	P=0.117N	P=0.126N	P=0.342N	P=0.178N
Logistic regression test	P=0.108N	P=0.126N	P=0.311N	P=0.178N
Cochran-Armitage test	P=0.086N			
Fisher exact test		P=0.121N	P=0.309N	P=0.121N
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	5/50 (10%)	2/50 (4%)	5/50 (10%)
Adjusted rate	7.8%	12.9%	5.6%	17.4%
Terminal rate	1/35 (3%)	2/34 (6%)	1/31 (3%)	4/26 (15%)
First incidence (days)	684	544	695	495
Life table test	P=0.240	P=0.345	P=0.506N	P=0.230
Logistic regression test	P=0.334	P=0.352	P=0.491N	P=0.278
Cochran-Armitage test	P=0.375			
Fisher exact test		P=0.357	P=0.500N	P=0.357
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	6/50 (12%)	2/50 (4%)	5/50 (10%)
Adjusted rate	7.8%	15.6%	5.6%	17.4%
Terminal rate	1/35 (3%)	3/34 (9%)	1/31 (3%)	4/26 (15%)
First incidence (days)	684	544	695	495
Life table test	P=0.280	P=0.236	P=0.506N	P=0.230
Logistic regression test	P=0.379	P=0.234	P=0.491N	P=0.278
Cochran-Armitage test	P=0.430			
Fisher exact test		P=0.243	P=0.500N	P=0.357
Uterus: Stromal Polyp				
Overall rate	6/50 (12%)	7/50 (14%)	7/50 (14%)	4/50 (8%)
Adjusted rate	16.2%	19.3%	22.6%	14.7%
Terminal rate	5/35 (14%)	5/34 (15%)	7/31 (23%)	3/26 (12%)
First incidence (days)	635	693	737 (T)	709
Life table test	P=0.484N	P=0.479	P=0.414	P=0.562N
Logistic regression test	P=0.436N	P=0.459	P=0.528	P=0.531N
Cochran-Armitage test	P=0.278N			
Fisher exact test		P=0.500	P=0.500	P=0.370N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	6/50 (12%)	7/50 (14%)	7/50 (14%)	5/50 (10%)
Adjusted rate	16.2%	19.3%	22.6%	16.6%
Terminal rate	5/35 (14%)	5/34 (15%)	7/31 (23%)	3/26 (12%)
First incidence (days)	635	693	737 (T)	375
Life table test	P=0.499	P=0.479	P=0.414	P=0.565
Logistic regression test	P=0.537N	P=0.459	P=0.528	P=0.589N
Cochran-Armitage test	P=0.400N			
Fisher exact test		P=0.500	P=0.500	P=0.500N
All Organs: Mononuclear Cell Leukemia				
Overall rate	14/50 (28%)	9/50 (18%)	8/50 (16%)	3/50 (6%)
Adjusted rate	32.0%	23.7%	19.3%	8.4%
Terminal rate	7/35 (20%)	6/34 (18%)	2/31 (6%)	0/26 (0%)
First incidence (days)	260	396	544	495
Life table test	P=0.018N	P=0.215N	P=0.149N	P=0.026N
Logistic regression test	P=0.001N	P=0.156N	P=0.188N	P=0.002N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.171N	P=0.114N	P=0.003N
All Organs: Benign Neoplasms				
Overall rate	41/50 (82%)	30/50 (60%)	44/50 (88%)	25/50 (50%)
Adjusted rate	87.2%	69.6%	93.5%	73.4%
Terminal rate	29/35 (83%)	21/34 (62%)	28/31 (90%)	17/26 (65%)
First incidence (days)	507	432	544	495
Life table test	P=0.327N	P=0.069N	P=0.213	P=0.146N
Logistic regression test	P=0.069N	P=0.024N	P=0.435	P=0.022N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.013N	P=0.288	P<0.001N
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	21/50 (42%)	16/50 (32%)	12/50 (24%)
Adjusted rate	46.1%	48.2%	38.2%	32.9%
Terminal rate	11/35 (31%)	12/34 (35%)	7/31 (23%)	4/26 (15%)
First incidence (days)	260	218	544	358
Life table test	P=0.158N	P=0.521	P=0.280N	P=0.237N
Logistic regression test	P=0.012N	P=0.535N	P=0.271N	P=0.038N
Cochran-Armitage test	P=0.020N			
Fisher exact test		P=0.580N	P=0.204N	P=0.044N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	44/50 (88%)	41/50 (82%)	47/50 (94%)	31/50 (62%)
Adjusted rate	89.8%	83.7%	94.0%	79.2%
Terminal rate	30/35 (86%)	26/34 (76%)	28/31 (90%)	18/26 (69%)
First incidence (days)	260	218	544	358
Life table test	P=0.434N	P=0.469N	P=0.228	P=0.373N
Logistic regression test	P=0.006N	P=0.293N	P=0.263	P=0.023N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.288N	P=0.243	P=0.002N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, heart, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Urinary Bladder Papilloma in Female F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	3/903 (0.3%)
Standard deviation	0.8%
Range	0%-2%

[a] Data as of 17 June 1994

TABLE B4b
Historical Incidence of Transitional Epithelial Papilloma of the Kidney in Female F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	0/920 (0%)

[a] Data as of 17 June 1994

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	1	1		9
Moribund	12	13	14	11
Natural deaths	2	2	5	4
Survivors				
Died last week of study	1	1		
Terminal sacrifice	34	33	31	26
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(9)
Parasite metazoan				1 (11%)
Intestine large, rectum	(10)	(10)	(10)	(9)
Hyperplasia, lymphoid				1 (11%)
Parasite metazoan	1 (10%)	1 (10%)		
Liver	(10)	(10)	(10)	(10)
Basophilic focus	8 (80%)	8 (80%)	10 (100%)	5 (50%)
Clear cell focus		1 (10%)		
Eosinophilic focus			1 (10%)	2 (20%)
Granuloma	1 (10%)	5 (50%)	3 (30%)	1 (10%)
Hepatodiaphragmatic nodule	3 (30%)		2 (20%)	
Inflammation, chronic	1 (10%)	1 (10%)	2 (20%)	
Mixed cell focus		1 (10%)		
Mesentery		(1)	(1)	(2)
Fat, necrosis		1 (100%)	1 (100%)	2 (100%)
Pancreas	(10)	(10)	(10)	(10)
Atrophy	3 (30%)	3 (30%)	3 (30%)	2 (20%)
Acinar cell, basophilic focus	1 (10%)			
Stomach, forestomach	(10)	(10)	(10)	(10)
Mineralization			1 (10%)	
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	1 (10%)	2 (20%)	1 (10%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)	1 (10%)	
Degeneration, fatty		1 (10%)	1 (10%)	
Hyperplasia, focal	1 (10%)			

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
15-Month Interim Evaluation (continued)				
Endocrine System (continued)				
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, angiectasis	1 (10%)	2 (20%)	1 (10%)	
Pars distalis, cyst	6 (60%)	5 (50%)	5 (50%)	4 (40%)
Pars distalis, hyperplasia, focal	1 (10%)	2 (20%)	1 (10%)	2 (20%)
Pars intermedia, cyst	1 (10%)			1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)
Ultimobranchial cyst		1 (10%)		
C-cell, hyperplasia		2 (20%)	1 (10%)	2 (20%)
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Inflammation, chronic		2 (20%)	2 (20%)	
Inflammation, suppurative				1 (10%)
Ovary	(10)	(10)	(10)	(10)
Cyst			1 (10%)	2 (20%)
Uterus	(10)	(10)	(10)	(10)
Hydrometra	3 (30%)	1 (10%)		
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hypercellularity		1 (10%)		
Myelofibrosis		1 (10%)		
Lymph node		(3)		
Mediastinal, hemorrhage		3 (100%)		
Mediastinal, pigmentation		3 (100%)		
Lymph node, mandibular	(10)	(10)	(10)	(10)
Hemorrhage				2 (20%)
Pigmentation	2 (20%)			
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Hemorrhage	3 (30%)	1 (10%)	1 (10%)	
Pigmentation	2 (20%)		1 (10%)	
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	4 (40%)	6 (60%)	2 (20%)	
Pigmentation, hemosiderin	8 (80%)	9 (90%)	8 (80%)	10 (100%)
Thymus	(10)	(10)	(10)	(10)
Hemorrhage			1 (10%)	
Musculoskeletal System				
Bone	(10)	(10)	(10)	(10)
Calvarium, osteopetrosis	1 (10%)			
Nervous System				
Brain	(10)	(10)	(10)	(10)
Compression		1 (10%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Infiltration cellular, histiocyte	1 (10%)	2 (20%)	2 (20%)	2 (20%)
Inflammation, subacute	4 (40%)		1 (10%)	
Metaplasia, osseous			1 (10%)	
Alveolar epithelium, hyperplasia	3 (30%)		1 (10%)	1 (10%)
Nose	(10)	(10)	(10)	(10)
Exudate				1 (10%)
Foreign body				2 (20%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Concretion			1 (10%)	6 (60%)
Cyst			1 (10%)	
Hydronephrosis				1 (10%)
Inflammation, chronic			1 (10%)	
Mineralization	9 (90%)	10 (100%)	8 (80%)	9 (90%)
Nephropathy	4 (40%)	6 (60%)	6 (60%)	10 (100%)
Transitional epithelium, hyperplasia			2 (20%)	8 (80%)
Urinary bladder	(10)	(10)	(10)	(10)
Mucosa, hyperplasia				2 (20%)
Systems Examined With No Lesions Observed				
General Body System				
Integumentary System				
Special Senses System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Diverticulum			1 (2%)	
Perforation	1 (2%)			
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	8 (16%)	6 (12%)	7 (14%)	4 (8%)
Intestine large, rectum	(50)	(50)	(49)	(50)
Parasite metazoan	2 (4%)	4 (8%)	5 (10%)	7 (14%)
Intestine large, cecum	(49)	(49)	(50)	(50)
Hemorrhage	1 (2%)			
Inflammation, subacute	1 (2%)			
Parasite metazoan	1 (2%)	1 (2%)	2 (4%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	3 (6%)	7 (14%)	1 (2%)
Basophilic focus	45 (90%)	43 (86%)	47 (94%)	40 (80%)
Clear cell focus	9 (18%)	7 (14%)	11 (22%)	8 (16%)
Cyst				1 (2%)
Developmental malformation			1 (2%)	
Eosinophilic focus	13 (26%)	13 (26%)	19 (38%)	13 (26%)
Granuloma	15 (30%)	8 (16%)	5 (10%)	3 (6%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)		2 (4%)
Hepatodiaphragmatic nodule	6 (12%)	9 (18%)	4 (8%)	4 (8%)
Inflammation, chronic				1 (2%)
Mixed cell focus	10 (20%)	7 (14%)	11 (22%)	6 (12%)
Bile duct, hyperplasia	16 (32%)	11 (22%)	9 (18%)	4 (8%)
Centrilobular, atrophy	4 (8%)	2 (4%)		2 (4%)
Hepatocyte, vacuolization cytoplasmic	4 (8%)	1 (2%)		
Kupffer cell, pigmentation	3 (6%)			
Lobules, necrosis	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Mesentery	(4)	(7)	(4)	(4)
Accessory spleen	1 (25%)			
Fat, hemorrhage				1 (25%)
Fat, necrosis	3 (75%)	4 (57%)	4 (100%)	4 (100%)
Pancreas	(50)	(50)	(50)	(50)
Atrophy	17 (34%)	16 (32%)	14 (28%)	15 (30%)
Metaplasia, hepatocyte	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Acinar cell, basophilic focus				3 (6%)
Acinar cell, cytoplasmic alteration	2 (4%)	2 (4%)	4 (8%)	4 (8%)
Acinar cell, hyperplasia, focal	1 (2%)	3 (6%)	4 (8%)	1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)			
Stomach, forestomach	(50)	(49)	(50)	(50)
Edema	1 (2%)			
Erosion		1 (2%)		1 (2%)
Ulcer	1 (2%)		1 (2%)	1 (2%)
Mucosa, hyperplasia	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	2 (4%)			
Ulcer	1 (2%)			
Tongue	(1)	(1)	(1)	
Mucosa, hyperplasia	1 (100%)		1 (100%)	
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Aorta, mineralization				1 (2%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	12 (24%)	11 (22%)	16 (32%)	9 (18%)
Inflammation, subacute	1 (2%)			2 (4%)
Mineralization			2 (4%)	
Necrosis				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	13 (26%)	8 (16%)	10 (20%)	16 (32%)
Angiectasis		5 (10%)	1 (2%)	2 (4%)
Cyst	1 (2%)		1 (2%)	
Degeneration, fatty	5 (10%)	10 (20%)	6 (12%)	7 (14%)
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage	1 (2%)	1 (2%)		
Hyperplasia, diffuse		1 (2%)		
Hyperplasia, focal	6 (12%)	6 (12%)	9 (18%)	5 (10%)
Hypertrophy, focal	6 (12%)	4 (8%)	5 (10%)	4 (8%)
Necrosis	1 (2%)	1 (2%)		1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Necrosis	1 (2%)			
Pituitary gland	(50)	(49)	(50)	(50)
Pars distalis, angiectasis	12 (24%)	5 (10%)	7 (14%)	10 (20%)
Pars distalis, cyst	29 (58%)	26 (53%)	18 (36%)	15 (30%)
Pars distalis, hyperplasia				1 (2%)
Pars distalis, hyperplasia, focal	11 (22%)	13 (27%)	12 (24%)	12 (24%)
Pars intermedia, angiectasis	2 (4%)	3 (6%)	1 (2%)	
Pars intermedia, cyst	4 (8%)	5 (10%)	2 (4%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Ultimobranchial cyst	3 (6%)	1 (2%)	3 (6%)	1 (2%)
C-cell, hyperplasia	7 (14%)	10 (20%)	10 (20%)	6 (12%)
Follicle, cyst	4 (8%)		4 (8%)	
Follicular cell, hyperplasia				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Ectasia	17 (34%)	15 (30%)	17 (34%)	18 (36%)
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic	4 (8%)	15 (30%)	8 (16%)	6 (12%)
Inflammation, suppurative	4 (8%)	2 (4%)	4 (8%)	7 (14%)
Ovary	(50)	(50)	(50)	(50)
Cyst	7 (14%)	4 (8%)	1 (2%)	4 (8%)
Uterus	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Hydrometra	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Hyperplasia, cystic	3 (6%)	2 (4%)	2 (4%)	
Endometrium, hyperplasia, focal		1 (2%)		
Vagina		(1)	(1)	
Hyperplasia			1 (100%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hypercellularity		3 (6%)	2 (4%)	2 (4%)
Myelofibrosis	3 (6%)	1 (2%)	1 (2%)	
Necrosis	1 (2%)			
Lymph node	(12)	(6)	(9)	(7)
Iliac, ectasia				1 (14%)
Iliac, hyperplasia, lymphoid				1 (14%)
Mediastinal, congestion				1 (14%)
Mediastinal, ectasia			1 (11%)	
Mediastinal, hemorrhage	6 (50%)	4 (67%)	3 (33%)	3 (43%)
Mediastinal, pigmentation	7 (58%)	4 (67%)	7 (78%)	3 (43%)
Pancreatic, hemorrhage			1 (11%)	1 (14%)
Pancreatic, hyperplasia, lymphoid				1 (14%)
Pancreatic, pigmentation			1 (11%)	
Renal, hemorrhage				1 (14%)
Renal, hyperplasia, lymphoid				1 (14%)
Renal, pigmentation				1 (14%)
Lymph node, mandibular	(50)	(48)	(50)	(50)
Congestion				1 (2%)
Ectasia	7 (14%)	7 (15%)	3 (6%)	1 (2%)
Hemorrhage	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid	4 (8%)	5 (10%)	4 (8%)	
Hyperplasia, plasma cell		1 (2%)		
Pigmentation	6 (12%)	14 (29%)	6 (12%)	7 (14%)
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Ectasia		1 (2%)		
Hemorrhage	2 (4%)	4 (8%)	2 (4%)	6 (12%)
Hyperplasia, lymphoid		1 (2%)		
Pigmentation	10 (20%)	9 (18%)	11 (22%)	2 (4%)
Spleen	(50)	(50)	(50)	(50)
Developmental malformation			2 (4%)	
Fibrosis	3 (6%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	25 (50%)	27 (54%)	36 (72%)	29 (58%)
Hemorrhage	1 (2%)		1 (2%)	
Necrosis	1 (2%)			1 (2%)
Pigmentation, hemosiderin	38 (76%)	33 (66%)	35 (70%)	37 (74%)
Lymphoid follicle, atrophy	1 (2%)			1 (2%)
Lymphoid follicle, hyperplasia	1 (2%)			
Thymus	(49)	(49)	(50)	(50)
Congestion				1 (2%)
Cyst		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)		6 (12%)
Cortex, atrophy				1 (2%)
Epithelial cell, hyperplasia				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(50)	(50)	(48)
Ectasia	10 (20%)	10 (20%)	20 (40%)	4 (8%)
Hyperplasia, lobular	4 (8%)			
Skin	(50)	(50)	(50)	(50)
Acanthosis	1 (2%)		4 (8%)	
Cyst epithelial inclusion	1 (2%)			
Hyperkeratosis			1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)	
Ulcer			2 (4%)	
Subcutaneous tissue, inflammation, subacute				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Calvarium, osteopetrosis	4 (8%)	1 (2%)	1 (2%)	
Femur, osteopetrosis	5 (10%)	3 (6%)	2 (4%)	
Skeletal muscle	(2)	(1)		(1)
Hemorrhage	1 (50%)			
Inflammation, chronic	1 (50%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Compression	10 (20%)	11 (22%)	10 (20%)	4 (8%)
Hemorrhage	2 (4%)	2 (4%)		1 (2%)
Hydrocephalus	3 (6%)	3 (6%)	4 (8%)	
Mineralization		1 (2%)		1 (2%)
Necrosis	1 (2%)		1 (2%)	1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)	3 (6%)	2 (4%)	7 (14%)
Edema	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Foreign body	1 (2%)	2 (4%)	2 (4%)	8 (16%)
Hemorrhage		2 (4%)		2 (4%)
Infiltration cellular, histiocyte	14 (28%)	13 (26%)	9 (18%)	13 (26%)
Inflammation, subacute	1 (2%)	5 (10%)	1 (2%)	2 (4%)
Thrombosis		1 (2%)		
Alveolar epithelium, hyperplasia	2 (4%)	7 (14%)	4 (8%)	2 (4%)
Nose	(50)	(50)	(50)	(50)
Exudate	9 (18%)	9 (18%)	10 (20%)	5 (10%)
Foreign body	3 (6%)	6 (12%)	4 (8%)	2 (4%)
Fungus	1 (2%)	2 (4%)		
Mucosa, hyperplasia	4 (8%)	2 (4%)	1 (2%)	1 (2%)
Mucosa, metaplasia, squamous	1 (2%)	2 (4%)	1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg
2-Year Study (continued)				
Special Senses System				
Eye	(3)	(5)	(2)	(2)
Cataract	1 (33%)	3 (60%)	1 (50%)	2 (100%)
Inflammation, chronic	1 (33%)			
Inflammation, suppurative	1 (33%)			
Phthisis bulbi		2 (40%)	1 (50%)	
Retina, atrophy	2 (67%)	2 (40%)	1 (50%)	2 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Concretion		9 (18%)	34 (68%)	37 (74%)
Cyst		1 (2%)		1 (2%)
Hemorrhage				1 (2%)
Hydronephrosis			3 (6%)	10 (20%)
Infarct			2 (4%)	3 (6%)
Inflammation, suppurative	1 (2%)		1 (2%)	2 (4%)
Mineralization	44 (88%)	47 (94%)	43 (86%)	41 (82%)
Nephropathy	34 (68%)	36 (72%)	41 (82%)	44 (88%)
Papilla, necrosis				1 (2%)
Renal tubule, cytoplasmic alteration				1 (2%)
Renal tubule, dilatation	2 (4%)	2 (4%)	1 (2%)	6 (12%)
Renal tubule, hyperplasia		1 (2%)	1 (2%)	
Renal tubule, necrosis	1 (2%)			
Renal tubule, pigmentation	8 (16%)	6 (12%)	2 (4%)	
Transitional epithelium, hyperplasia	3 (6%)	7 (14%)	23 (46%)	43 (86%)
Ureter			(2)	(4)
Concretion			1 (50%)	2 (50%)
Mucosa, hyperplasia			2 (100%)	4 (100%)
Urethra			(1)	
Mucosa, hyperplasia			1 (100%)	
Urinary bladder	(49)	(50)	(50)	(50)
Concretion			1 (2%)	
Mucosa, hyperplasia	2 (4%)		4 (8%)	12 (24%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF SALICYLAZOSULFAPYRIDINE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	2			
Moribund	5	4	3	4
Natural deaths	3	5	6	
Survivors				
Terminal sacrifice	40	41	41	46
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma			1 (10%)	
Hepatocellular adenoma	2 (20%)	2 (20%)		2 (20%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Squamous cell papilloma	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)		2 (20%)	
Alveolar/bronchiolar carcinoma			1 (10%)	
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(48)	(47)	(47)	(50)
Leiomyosarcoma		1 (2%)		
Intestine large, cecum	(47)	(46)	(46)	(50)
Adenocarcinoma				1 (2%)
Intestine small, jejunum	(47)	(46)	(47)	(50)
Adenocarcinoma			1 (2%)	
Intestine small, ileum	(47)	(46)	(46)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma	2 (4%)			
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma	12 (24%)	11 (22%)	18 (36%)	8 (16%)
Hepatocellular carcinoma, multiple	1 (2%)	4 (8%)	5 (10%)	
Hepatocellular adenoma	12 (24%)	11 (22%)	13 (26%)	15 (30%)
Hepatocellular adenoma, multiple	1 (2%)	21 (42%)	15 (30%)	27 (54%)
Histiocytic sarcoma			1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)	
Mesentery	(4)	(4)	(1)	(1)
Pancreas	(50)	(50)	(50)	(50)
Carcinoma, metastatic, lung	1 (2%)			
Acinus, adenoma	1 (2%)			
Stomach, forestomach	(50)	(50)	(49)	(50)
Squamous cell papilloma	3 (6%)		1 (2%)	
Stomach, glandular	(50)	(50)	(48)	(50)
Adenoma				1 (2%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Carcinoma, metastatic, lung	1 (2%)			
Capsule, adenoma	1 (2%)		2 (4%)	
Adrenal medulla	(50)	(49)	(49)	(50)
Carcinoma, metastatic, lung	1 (2%)			
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			1 (2%)
Pituitary gland	(44)	(46)	(47)	(47)
Pars distalis, adenoma	1 (2%)			
Pars intermedia, adenoma		1 (2%)		
Pars intermedia, carcinoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)			1 (2%)
Follicular cell, carcinoma				1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Preputial gland	(49)	(49)	(49)	(50)
Adenoma				1 (2%)
Prostate	(50)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lymph node	(3)	(3)	(3)	(4)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (33%)	
Mediastinal, histiocytic sarcoma			1 (33%)	
Pancreatic, histiocytic sarcoma			1 (33%)	
Lymph node, mandibular	(50)	(49)	(49)	(49)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma			1 (2%)	
Spleen	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)			1 (2%)
Histiocytic sarcoma			1 (2%)	
Thymus	(45)	(43)	(46)	(46)
Carcinoma, metastatic, lung	1 (2%)			
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, osteosarcoma, metastatic, bone			1 (2%)	
Subcutaneous tissue, plasma cell tumor, benign				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Vertebra, osteosarcoma			1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	9 (18%)	10 (20%)	11 (22%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)		3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma	3 (6%)	8 (16%)	2 (4%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple				1 (2%)
Carcinoma, metastatic, tissue NOS				1 (2%)
Hepatocellular carcinoma, metastatic, liver	4 (8%)	2 (4%)		
Osteosarcoma, metastatic, bone			1 (2%)	
Alveolar epithelium, alveolar/bronchiolar adenoma		1 (2%)		
Mediastinum, alveolar/bronchiolar carcinoma			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Special Senses System				
Harderian gland	(3)	(5)	(1)	(2)
Adenoma	2 (67%)	4 (80%)	1 (100%)	2 (100%)
Carcinoma	1 (33%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(50)	(50)
Hemangioma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			2 (4%)	
Lymphoma malignant	5 (10%)	3 (6%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic				1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	4	2	3	2
2-Year study	40	45	41	45
Total primary neoplasms				
15-Month interim evaluation	4	2	4	2
2-Year study	62	77	77	75
Total animals with benign neoplasms				
15-Month interim evaluation	4	2	2	2
2-Year study	26	36	32	43
Total benign neoplasms				
15-Month interim evaluation	4	2	2	2
2-Year study	35	48	46	56
Total animals with malignant neoplasms				
15-Month interim evaluation			2	
2-Year study	25	26	28	14
Total malignant neoplasms				
15-Month interim evaluation			2	
2-Year study	27	29	31	19
Total animals with metastatic neoplasms				
2-Year study	5	2	2	1
Total metastatic neoplasms				
2-Year study	8	2	5	1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control

Number of Days on Study	1 5 0	3 5 1	4 2 0	4 2 0	6 1 0	6 1 1	6 5 8	6 6 2	6 6 6	6 8 9	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 1 2	0 3 3	0 0 2	0 0 5	0 1 7	0 3 0	0 4 4	0 4 8	0 1 3	0 2 8	0 0 4	0 0 9	0 1 5	0 1 9	0 2 2	0 2 6	0 3 2	0 3 5	0 4 0	0 4 5	0 0 1	0 0 3	0 0 6	0 0 7	0 1 0
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Hemangiosarcoma													X					X						
Hepatocellular carcinoma				X		X		X			X	X			X								X	
Hepatocellular carcinoma, multiple							X																	
Hepatocellular adenoma													X		X			X			X		X	
Hepatocellular adenoma, multiple																								
Mesentery										+			+								+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																	X							
Acinus, adenoma												X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma											X													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																	X							
Capsule, adenoma																			X					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																	X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																								
Pars intermedia, carcinoma					X																			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
None																								

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 1 1	0 1 4	0 1 6	0 1 8	0 2 0	0 2 1	0 2 3	0 2 4	0 2 5	0 2 7	0 2 9	0 3 1	0 3 4	0 3 6	0 3 7	0 3 8	0 3 9	0 4 1	0 4 2	0 4 3	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma		X																								1
Hemangiosarcoma																										2
Hepatocellular carcinoma	X		X					X			X		X													12
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma		X		X			X					X						X				X			X	12
Hepatocellular adenoma, multiple					X																					1
Mesentery				+																						4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, lung																										1
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma													X	X												3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, lung																										1
Capsule, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, lung																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	44
Pars distalis, adenoma									X																	1
Pars intermedia, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																				X						1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	1 5 0	3 5 1	4 2 0	4 2 0	6 1 0	6 1 1	6 5 8	6 6 2	6 6 6	6 8 9	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 1 2	0 3 3	0 0 2	0 0 5	0 1 7	0 3 0	0 4 4	0 4 8	0 1 3	0 2 8	0 0 4	0 0 9	0 1 5	1 1 9	2 2 2	2 2 6	3 2 2	3 3 5	4 4 0	4 4 5	0 0 1	0 0 3	0 0 6	0 1 7	1 1 0
Genital System																									
Coagulating gland																					+				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Thymus	+	+	M	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Carcinoma, metastatic, lung																	X								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X										X				
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma										X							X						X		
Hepatocellular carcinoma, metastatic, liver																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland																			M						
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X												X				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 1 1	0 1 4	0 1 6	0 1 8	0 2 0	0 2 1	0 2 3	0 2 4	0 2 5	0 2 7	0 2 9	0 3 1	0 3 4	0 3 6	0 3 7	0 3 8	0 3 9	0 4 1	0 4 2	0 4 3	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	Total Tissues/ Tumors
Genital System																										
Coagulating gland		+		+														+		+						5
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+					+																			3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X	X	X			X	X					X		X									9
Alveolar/bronchiolar adenoma, multiple	X										X															2
Alveolar/bronchiolar carcinoma																										3
Hepatocellular carcinoma, metastatic, liver	X		X					X																		4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																									+	1
Harderian gland						+													+	+						3
Adenoma						X														X						2
Carcinoma																			X							1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant							X	X																X		5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 675 mg/kg

Number of Days on Study	0 7 5	2 8 8	5 6 7	5 8 8	6 1 1	6 5 2	6 6 5	6 6 6	7 0 0	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 7 8	0 8 3	1 0 5	0 8 9	0 9 0	0 6 4	0 8 2	0 6 1	0 7 6	0 6 5	0 7 1	0 7 4	0 7 9	0 8 4	0 8 8	0 9 1	0 9 5	1 0 0	1 0 6	0 6 2	0 6 3	0 6 6	0 6 7	0 6 8	0 6 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma						X																			
Intestine large, rectum	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatocellular carcinoma			X		X																	X			X
Hepatocellular carcinoma, multiple							X								X		X								
Hepatocellular adenoma								X								X				X	X				
Hepatocellular adenoma, multiple										X		X	X	X	X		X	X	X			X	X	X	X
Mesentery			+			+						+										+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma																		X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 675 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 0	0 7 2	0 7 3	0 7 5	0 7 7	0 8 0	0 8 1	0 8 5	0 8 6	0 8 7	0 9 2	0 9 3	0 9 4	0 9 6	0 9 7	0 9 8	0 9 9	1 0 1	1 0 2	1 0 3	1 0 4	1 0 7	1 0 8	1 0 9	1 1 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyosarcoma																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma										X																1
Hepatocellular carcinoma									X	X								X		X		X	X		X	11
Hepatocellular carcinoma, multiple																								X		4
Hepatocellular adenoma	X		X	X						X		X	X		X											11
Hepatocellular adenoma, multiple							X	X	X		X			X				X	X			X			X	21
Mesentery																										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Coagulating gland														+												1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 675 mg/kg (continued)

Number of Days on Study	0 7 5	2 8 8	5 6 7	5 8 8	6 1 1	6 5 2	6 6 5	6 6 6	7 0 0	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 7 8	0 8 3	1 0 5	0 8 9	0 9 0	0 6 4	0 8 2	0 6 1	0 7 6	0 6 5	0 7 1	0 7 4	0 7 9	0 8 4	0 8 8	0 9 1	0 9 5	1 0 0	1 0 6	0 6 2	0 6 3	0 6 6	0 6 7	0 6 8	0 6 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+								+											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X						X	X			X		
Alveolar/bronchiolar carcinoma				X					X				X		X							X			
Hepatocellular carcinoma, metastatic, liver					X																				
Alveolar epithelium, alveolar/bronchiolar adenoma											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland		+																+						+	
Adenoma																		X						X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant														X				X							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 675 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 0	0 7 2	0 7 3	0 7 5	0 7 7	0 8 0	0 8 1	0 8 5	0 8 6	0 8 7	0 9 2	0 9 3	0 9 4	0 9 6	0 9 7	0 9 8	0 9 9	1 0 1	1 0 2	1 0 3	1 0 4	1 0 7	1 0 8	1 0 9	1 1 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X	X					X			X				X								X			10
Alveolar/bronchiolar carcinoma													X	X							X					8
Hepatocellular carcinoma, metastatic, liver										X																2
Alveolar epithelium, alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+																1
Harderian gland										+						+										5
Adenoma										X						X										4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant				X																						3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg

Number of Days on Study	4 0 2	5 0 4	5 0 5	6 1 1	6 4 8	6 7 8	6 8 1	6 8 1	7 0 2	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 6 8	1 2 7	1 4 9	1 5 7	1 3 9	1 2 4	1 3 2	1 5 5	1 2 8	1 2 3	1 2 9	1 3 3	1 3 6	1 4 0	1 4 4	1 4 8	1 5 3	1 5 6	1 6 6	1 2 1	1 2 2	1 2 5	1 2 6	1 3 0	1 3 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X		X		X						X	X	X	X	X		X	X	X		X
Hepatocellular carcinoma, multiple				X																					
Hepatocellular adenoma												X		X	X			X	X			X	X	X	
Hepatocellular adenoma, multiple						X					X						X				X				
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone								X																	
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aorta, alveolar/bronchiolar carcinoma, metastatic, lung												X													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																			X						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 3 4	1 3 5	1 3 7	1 3 8	1 4 1	1 4 2	1 4 3	1 4 5	1 4 6	1 4 7	1 5 0	1 5 1	1 5 2	1 5 4	1 5 6	1 5 8	1 5 9	1 6 0	1 6 2	1 6 3	1 6 4	1 6 5	1 6 7	1 6 9	1 7 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																X										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X	X		X										X			X						X			18
Hepatocellular carcinoma, multiple			X															X		X				X		5
Hepatocellular adenoma		X				X				X											X			X		13
Hepatocellular adenoma, multiple			X		X				X			X	X			X	X	X		X		X			X	15
Histiocytic sarcoma																									X	1
Osteosarcoma, metastatic, bone																										1
Mesentery							+																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma												X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Aorta, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma										X																2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma					X																					1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg (continued)

	4	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	0	0	1	4	7	8	8	0	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3
	2	4	5	1	8	8	1	1	2	8	8	8	8	8	8	8	8	8	8	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	6	2	4	5	3	2	3	5	2	2	2	3	3	4	4	4	5	6	6	2	2	2	2	3	3
	8	7	9	7	9	4	2	5	8	3	9	3	6	0	4	8	3	1	6	1	2	5	6	0	1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node												+										+			
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung												X													
Mediastinal, histiocytic sarcoma																									
Pancreatic, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, osteosarcoma, metastatic, bone								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X					X	X						X			X		X	X		
Alveolar/bronchiolar adenoma, multiple														X	X										
Alveolar/bronchiolar carcinoma												X										X			
Osteosarcoma, metastatic, bone								X																	
Mediastinum, alveolar/bronchiolar carcinoma												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra					+																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 3 4	1 3 5	1 3 7	1 3 8	1 4 1	1 4 2	1 4 3	1 4 5	1 4 6	1 4 7	1 5 0	1 5 1	1 5 2	1 5 4	1 5 6	1 5 8	1 5 9	1 6 0	1 6 2	1 6 3	1 6 4	1 6 5	1 6 7	1 6 9	1 7 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									X	1
Lymph node																									+	3
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, histiocytic sarcoma																									X	1
Pancreatic, histiocytic sarcoma																									X	1
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									X	1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																									X	1
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, osteosarcoma, metastatic, bone																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																X		X	X		11
Alveolar/bronchiolar adenoma, multiple																						X				3
Alveolar/bronchiolar carcinoma																										2
Osteosarcoma, metastatic, bone																										1
Mediastinum, alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland		+																								1
Adenoma		X																								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma					X																				X	2
Lymphoma malignant																		X								1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 2,700 mg/kg

Number of Days on Study	0 0 4 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	0 0 9 4 2 2 2 2 2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 3 3
	6 7 7 7 8 8 8 8 8 8 8 8 8 8 1 1 1 1 1 1 1 1 1 1 1
Carcass ID Number	1 1 2 2 1 1 1 1 2 2 2 2 2 2 1 1 1 1 1 1 1 1 1 1 1
	8 9 2 1 8 8 9 9 0 0 1 2 2 3 8 8 8 8 8 9 9 9 9 9 9
	5 4 3 5 4 9 3 8 2 7 6 0 4 0 1 2 3 6 7 8 0 1 2 5 6
Alimentary System	
Esophagus	+ +
Gallbladder	+ + + + + + + + + + + + + + + + + + M + + + + + +
Intestine large, colon	+ +
Intestine large, rectum	+ +
Intestine large, cecum	+ +
Adenocarcinoma	
Intestine small, duodenum	+ +
Intestine small, jejunum	+ +
Intestine small, ileum	+ +
Liver	+ +
Hepatocellular carcinoma	X X
Hepatocellular adenoma	X X X X X X X X
Hepatocellular adenoma, multiple	X X X X X X X X X X X X
Mesentery	+
Pancreas	+ +
Salivary glands	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Adenoma	
Cardiovascular System	
Blood vessel	+ +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ +
Islets, pancreatic	+ +
Adenoma	X
Parathyroid gland	+ + + + + + + + + + + + + M + + + + + + + + + + +
Pituitary gland	+ + M + + + + + + M + + + + + + + + + M + + + + + +
Thyroid gland	+ +
Follicular cell, adenoma	
Follicular cell, carcinoma	
General Body System	
None	
Genital System	
Coagulating gland	
Epididymis	+ +
Preputial gland	+ +
Adenoma	
Prostate	+ +
Seminal vesicle	+ +
Testes	+ +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 2,700 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 9 7	1 9 9	2 0 0	2 0 1	2 0 3	2 0 4	2 0 5	2 0 6	2 0 8	2 0 9	2 1 0	2 1 1	2 1 2	2 1 3	2 1 4	2 2 5	2 2 6	2 2 7	2 2 8	2 2 9	2 1 7	2 1 8	2 1 9	2 2 1	2 2 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																									X	1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X									X	X					X						X			8
Hepatocellular adenoma			X	X				X				X						X		X	X					15
Hepatocellular adenoma, multiple	X				X	X	X		X	X	X		X						X			X	X	X	X	27
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																						X				1
Follicular cell, carcinoma															X											1
General Body System																										
None																										
Genital System																										
Coagulating gland																									+	1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 2,700 mg/kg (continued)

Number of Days on Study	0 0 4 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	0 0 9 4 2 2 2 2 2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 3 3
	0 6 7 7 7 8 8 8 8 8 8 8 8 8 8 1 1 1 1 1 1 1 1 1 1
Carcass ID Number	1 1 2 2 1 1 1 1 2 2 2 2 2 2 1 1 1 1 1 1 1 1 1 1 1
	1 8 9 2 1 8 8 9 9 0 0 1 2 2 3 8 8 8 8 8 9 9 9 9 9
	9 5 4 3 5 4 9 3 8 2 7 6 0 4 0 1 2 3 6 7 8 0 1 2 5 6
Hematopoietic System	
Bone marrow	+ +
Lymph node	
Lymph node, mandibular	+ M +
Lymph node, mesenteric	+ +
Hemangiosarcoma	
Spleen	+ +
Hemangiosarcoma	
Thymus	+ + + M + + + + M + + + + + M + + + + + + + + + +
Integumentary System	
Mammary gland	+ +
Skin	+ +
Subcutaneous tissue, plasma cell tumor benign	X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X
Alveolar/bronchiolar adenoma, multiple	X
Alveolar/bronchiolar carcinoma	X X
Alveolar/bronchiolar carcinoma, multiple	
Carcinoma, metastatic, tissue NOS	X
Nose	+ +
Trachea	+ +
Special Senses System	
Harderian gland	+ +
Adenoma	X X
Urinary System	
Kidney	+ +
Urinary bladder	+ +
Hemangioma	X
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant	
Lymphoma malignant lymphocytic	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 2,700 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 9 7	1 9 9	2 0 0	2 0 1	2 0 3	2 0 4	2 0 5	2 0 6	2 0 8	2 0 9	2 1 0	2 1 1	2 1 2	2 1 3	2 1 4	2 2 5	2 2 6	2 2 7	2 2 8	2 2 9	2 1 7	2 1 8	2 1 9	2 2 1	2 2 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+							+												+	+				4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																					X					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																					X					1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, plasma cell tumor benign																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X				X											4
Alveolar/bronchiolar adenoma, multiple					X																					2
Alveolar/bronchiolar carcinoma												X					X									4
Alveolar/bronchiolar carcinoma, multiple									X																	1
Carcinoma, metastatic, tissue NOS																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										2
Adenoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																						X				1
Lymphoma malignant lymphocytic									X																	1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	2/50 (4%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate[b]	5.0%	9.8%	2.4%	4.3%
Terminal rate[c]	2/40 (5%)	4/41 (10%)	1/41 (2%)	2/46 (4%)
First incidence (days)	728 (T)	728 (T)	728 (T)	728 (T)
Life table test[d]	P=0.371N	P=0.348	P=0.491N	P=0.644N
Logistic regression test[d]	P=0.371N	P=0.348	P=0.491N	P=0.644N
Cochran-Armitage test[d]	P=0.431N			
Fisher exact test[d]		P=0.339	P=0.500N	P=0.691N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate	7.5%	9.8%	2.4%	4.3%
Terminal rate	3/40 (8%)	4/41 (10%)	1/41 (2%)	2/46 (4%)
First incidence (days)	728 (T)	728 (T)	728 (T)	728 (T)
Life table test	P=0.240N	P=0.514	P=0.296N	P=0.436N
Logistic regression test	P=0.240N	P=0.514	P=0.296N	P=0.436N
Cochran-Armitage test	P=0.292N			
Fisher exact test		P=0.500	P=0.309N	P=0.500N
Liver: Hepatocellular Adenoma				
Overall rate	13/50 (26%)	32/50 (64%)	28/50 (56%)	42/50 (84%)
Adjusted rate	32.5%	76.2%	66.6%	87.5%
Terminal rate	13/40 (33%)	31/41 (76%)	27/41 (66%)	40/46 (87%)
First incidence (days)	728 (T)	666	678	497
Life table test	P<0.001	P<0.001	P=0.002	P<0.001
Logistic regression test	P<0.001	P<0.001	P=0.002	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P=0.002	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	13/50 (26%)	15/50 (30%)	23/50 (46%)	8/50 (16%)
Adjusted rate	29.2%	33.8%	51.0%	17.4%
Terminal rate	9/40 (23%)	12/41 (29%)	19/41 (46%)	8/46 (17%)
First incidence (days)	420	567	611	728 (T)
Life table test	P=0.094N	P=0.445	P=0.050	P=0.106N
Logistic regression test	P=0.154N	P=0.415	P=0.035	P=0.159N
Cochran-Armitage test	P=0.166N			
Fisher exact test		P=0.412	P=0.030	P=0.163N
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma				
Overall rate	24/50 (48%)	38/50 (76%)	38/50 (76%)	44/50 (88%)
Adjusted rate	54.3%	84.4%	82.6%	91.7%
Terminal rate	20/40 (50%)	34/41 (83%)	33/41 (80%)	42/46 (91%)
First incidence (days)	420	567	611	497
Life table test	P=0.004	P=0.008	P=0.010	P=0.001
Logistic regression test	P<0.001	P=0.004	P=0.005	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.004	P=0.004	P<0.001

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	13/50 (26%)	15/50 (30%)	23/50 (46%)	8/50 (16%)
Adjusted rate	29.2%	33.8%	51.0%	17.4%
Terminal rate	9/40 (23%)	12/41 (29%)	19/41 (46%)	8/46 (17%)
First incidence (days)	420	567	611	728 (T)
Life table test	P=0.094N	P=0.445	P=0.050	P=0.106N
Logistic regression test	P=0.154N	P=0.415	P=0.035	P=0.159N
Cochran-Armitage test	P=0.166N			
Fisher exact test		P=0.412	P=0.030	P=0.163N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	24/50 (48%)	38/50 (76%)	38/50 (76%)	44/50 (88%)
Adjusted rate	54.3%	84.4%	82.6%	91.7%
Terminal rate	20/40 (50%)	34/41 (83%)	33/41 (80%)	42/46 (91%)
First incidence (days)	420	567	611	497
Life table test	P=0.004	P=0.008	P=0.010	P=0.001
Logistic regression test	P<0.001	P=0.004	P=0.005	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.004	P=0.004	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	11/50 (22%)	11/50 (22%)	14/50 (28%)	6/50 (12%)
Adjusted rate	27.5%	26.8%	33.2%	13.0%
Terminal rate	11/40 (28%)	11/41 (27%)	13/41 (32%)	6/46 (13%)
First incidence (days)	728 (T)	728 (T)	648	728 (T)
Life table test	P=0.068N	P=0.572N	P=0.346	P=0.081N
Logistic regression test	P=0.078N	P=0.572N	P=0.361	P=0.081N
Cochran-Armitage test	P=0.132N			
Fisher exact test		P=0.595N	P=0.322	P=0.143N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/50 (6%)	8/50 (16%)	2/50 (4%)	5/50 (10%)
Adjusted rate	7.3%	18.4%	4.9%	10.9%
Terminal rate	2/40 (5%)	6/41 (15%)	2/41 (5%)	5/46 (11%)
First incidence (days)	689	588	728 (T)	728 (T)
Life table test	P=0.512N	P=0.115	P=0.489N	P=0.434
Logistic regression test	P=0.557	P=0.104	P=0.483N	P=0.392
Cochran-Armitage test	P=0.533			
Fisher exact test		P=0.100	P=0.500N	P=0.357
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	14/50 (28%)	18/50 (36%)	15/50 (30%)	11/50 (22%)
Adjusted rate	34.1%	41.7%	35.6%	23.9%
Terminal rate	13/40 (33%)	16/41 (39%)	14/41 (34%)	11/46 (24%)
First incidence (days)	689	588	648	728 (T)
Life table test	P=0.090N	P=0.289	P=0.533	P=0.192N
Logistic regression test	P=0.125N	P=0.284	P=0.551	P=0.218N
Cochran-Armitage test	P=0.185N			
Fisher exact test		P=0.260	P=0.500	P=0.322N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate	7.5%	0.0%	2.4%	0.0%
Terminal rate	3/40 (8%)	0/41 (0%)	1/41 (2%)	0/46 (0%)
First incidence (days)	728 (T)	—[e]	728 (T)	—
Life table test	P=0.074N	P=0.117N	P=0.296N	P=0.098N
Logistic regression test	P=0.074N	P=0.117N	P=0.296N	P=0.098N
Cochran-Armitage test	P=0.086N			
Fisher exact test		P=0.121N	P=0.309N	P=0.121N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adjusted rate	7.5%	0.0%	0.0%	2.2%
Terminal rate	3/40 (8%)	0/41 (0%)	0/41 (0%)	1/46 (2%)
First incidence (days)	728 (T)	—	—	728 (T)
Life table test	P=0.219N	P=0.117N	P=0.117N	P=0.257N
Logistic regression test	P=0.219N	P=0.117N	P=0.117N	P=0.257N
Cochran-Armitage test	P=0.247N			
Fisher exact test		P=0.121N	P=0.121N	P=0.309N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rate	10.0%	0.0%	0.0%	4.3%
Terminal rate	4/40 (10%)	0/41 (0%)	0/41 (0%)	2/46 (4%)
First incidence (days)	728 (T)	—	—	728 (T)
Life table test	P=0.294N	P=0.060N	P=0.060N	P=0.275N
Logistic regression test	P=0.294N	P=0.060N	P=0.060N	P=0.275N
Cochran-Armitage test	P=0.337N			
Fisher exact test		P=0.059N	P=0.059N	P=0.339N
All Organs: Malignant Lymphoma (Lymphocytic or Undifferentiated Cell Type)				
Overall rate	5/50 (10%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	12.1%	7.3%	2.4%	4.3%
Terminal rate	4/40 (10%)	3/41 (7%)	1/41 (2%)	2/46 (4%)
First incidence (days)	666	728 (T)	728 (T)	728 (T)
Life table test	P=0.106N	P=0.344N	P=0.098N	P=0.169N
Logistic regression test	P=0.118N	P=0.343N	P=0.095N	P=0.198N
Cochran-Armitage test	P=0.135N			
Fisher exact test		P=0.357N	P=0.102N	P=0.218N
All Organs: Benign Neoplasms				
Overall rate	26/50 (52%)	36/50 (72%)	32/50 (64%)	43/50 (86%)
Adjusted rate	65.0%	85.7%	74.3%	89.6%
Terminal rate	26/40 (65%)	35/41 (85%)	30/41 (73%)	41/46 (89%)
First incidence (days)	728 (T)	666	648	497
Life table test	P=0.008	P=0.021	P=0.168	P=0.003
Logistic regression test	P=0.001	P=0.022	P=0.194	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.032	P=0.156	P<0.001

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	25/50 (50%)	26/50 (52%)	28/50 (56%)	15/50 (30%)
Adjusted rate	53.2%	55.2%	60.8%	32.6%
Terminal rate	18/40 (45%)	20/41 (49%)	23/41 (56%)	15/46 (33%)
First incidence (days)	420	567	611	728 (T)
Life table test	P=0.008N	P=0.543	P=0.414	P=0.014N
Logistic regression test	P=0.026N	P=0.533	P=0.452	P=0.028N
Cochran-Armitage test	P=0.020N			
Fisher exact test		P=0.500	P=0.344	P=0.033N
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/50 (80%)	45/50 (90%)	41/50 (82%)	45/50 (90%)
Adjusted rate	85.1%	93.8%	87.2%	93.8%
Terminal rate	33/40 (83%)	38/41 (93%)	35/41 (85%)	43/46 (93%)
First incidence (days)	420	567	611	497
Life table test	P=0.349N	P=0.268	P=0.569N	P=0.543N
Logistic regression test	P=0.223	P=0.142	P=0.563N	P=0.137
Cochran-Armitage test	P=0.180			
Fisher exact test		P=0.131	P=0.500	P=0.131

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver and lung; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Hepatocellular Neoplasms in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	254/763 (33.3%)	127/763 (16.6%)	340/763 (44.6%)
Standard deviation	13.4%	4.5%	14.6%
Range	14%-58%	8%-24%	25%-72%

[a] Data as of 17 June 1994

TABLE C4b
Historical Incidence of Splenic Hemangiosarcoma in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	22/759 (2.9%)
Standard deviation	2.7%
Range	0%-8%

[a] Data as of 17 June 1994

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	2			
Moribund	5	4	3	4
Natural deaths	3	5	6	
Survivors				
Terminal sacrifice	40	41	41	46
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Basophilic focus		1 (10%)		
Clear cell focus	1 (10%)	1 (10%)		
Cytologic alterations		2 (20%)	8 (80%)	10 (100%)
Eosinophilic focus			2 (20%)	1 (10%)
Hematopoietic cell proliferation				1 (10%)
Vacuolization cytoplasmic	10 (100%)	7 (70%)	7 (70%)	
Pancreas	(10)	(10)	(10)	(10)
Inflammation, subacute			1 (10%)	
Salivary glands	(10)	(10)	(10)	(10)
Vacuolization cytoplasmic				1 (10%)
Submandibular gland, depletion secretory		2 (20%)		1 (10%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Hyperplasia		2 (20%)	1 (10%)	
Stomach, glandular	(10)	(10)	(10)	(10)
Atypia cellular			2 (20%)	
Cyst			2 (20%)	
Erosion	1 (10%)			
Mineralization		3 (30%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia		1 (10%)	1 (10%)	
Hypertrophy	1 (10%)	1 (10%)	1 (10%)	1 (10%)
Capsule, hyperplasia		1 (10%)		1 (10%)
Parathyroid gland	(10)	(10)	(8)	(10)
Cyst				1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)
Follicle, cyst		1 (10%)		
Follicle, degeneration	1 (10%)		1 (10%)	1 (10%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
15-Month Interim Evaluation (continued)				
Genital System				
Preputial gland	(10)	(10)	(10)	(10)
Duct, cyst	4 (40%)	8 (80%)	10 (100%)	7 (70%)
Testes	(10)	(10)	(10)	(10)
Atrophy		1 (10%)		
Thrombosis		1 (10%)		
Hematopoietic System				
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Angiectasis		1 (10%)		1 (10%)
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	2 (20%)	8 (80%)	10 (100%)	10 (100%)
Pigmentation, hemosiderin		4 (40%)	10 (100%)	10 (100%)
Thymus	(9)	(10)	(10)	(10)
Cyst		1 (10%)	3 (30%)	1 (10%)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Subcutaneous tissue, edema		1 (10%)		
Subcutaneous tissue, hemorrhage		1 (10%)		
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolus, infiltration cellular, histiocyte	1 (10%)			1 (10%)
Nose	(10)	(10)	(10)	(10)
Glands, cyst			4 (40%)	
Nasolacrimal duct, exudate		1 (10%)		
Olfactory epithelium, degeneration	1 (10%)	2 (20%)	8 (80%)	2 (20%)
Olfactory epithelium, hyperplasia			1 (10%)	
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	8 (80%)	3 (30%)	6 (60%)	2 (20%)
Pelvis, inflammation, subacute			1 (10%)	
Renal tubule, casts	1 (10%)			1 (10%)
Renal tubule, regeneration	7 (70%)	6 (60%)	8 (80%)	4 (40%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic		2 (20%)		
Transitional epithelium, hyperplasia		1 (10%)		
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Gallbladder	(49)	(48)	(49)	(48)
Fibrosis		1 (2%)		
Inflammation, suppurative			1 (2%)	
Epithelium, hyperplasia			1 (2%)	
Intestine large, cecum	(47)	(46)	(46)	(50)
Parasite metazoan	1 (2%)			
Intestine small, duodenum	(47)	(47)	(47)	(50)
Dilatation				1 (2%)
Inflammation, subacute			1 (2%)	
Necrosis			1 (2%)	
Ulcer			1 (2%)	
Intestine small, jejunum	(47)	(46)	(47)	(50)
Peyer's patch, hyperplasia, lymphoid			2 (4%)	
Intestine small, ileum	(47)	(46)	(46)	(50)
Inflammation, chronic				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)	1 (2%)	
Basophilic focus	1 (2%)	3 (6%)		
Clear cell focus	2 (4%)	14 (28%)	4 (8%)	8 (16%)
Clear cell focus, multiple			1 (2%)	3 (6%)
Developmental malformation		1 (2%)		
Eosinophilic focus	5 (10%)	17 (34%)	17 (34%)	13 (26%)
Eosinophilic focus, multiple	1 (2%)	2 (4%)	3 (6%)	9 (18%)
Fatty change, focal	1 (2%)			
Hemorrhage	1 (2%)	1 (2%)		
Hepatodiaphragmatic nodule			1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, subacute	3 (6%)	1 (2%)	1 (2%)	
Mineralization	2 (4%)		3 (6%)	
Mixed cell focus	2 (4%)	4 (8%)	1 (2%)	2 (4%)
Necrosis	3 (6%)	6 (12%)	5 (10%)	3 (6%)
Pigmentation, bile	1 (2%)			
Pigmentation, hemosiderin			1 (2%)	
Vacuolization cytoplasmic	3 (6%)	5 (10%)	1 (2%)	
Bile duct, cyst	2 (4%)			
Bile duct, hyperplasia			1 (2%)	
Mesentery	(4)	(4)	(1)	(1)
Hemorrhage		1 (25%)		
Inflammation, subacute		1 (25%)		
Fat, necrosis	3 (75%)	2 (50%)	1 (100%)	1 (100%)
Pancreas	(50)	(50)	(50)	(50)
Inflammation, subacute		1 (2%)		
Necrosis				1 (2%)
Polyarteritis		1 (2%)		
Acinus, atrophy		2 (4%)		
Acinus, depletion secretory	1 (2%)			
Duct, cyst		1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(49)	(50)
Cyst		1 (2%)		
Edema	1 (2%)		1 (2%)	
Hyperplasia	18 (36%)	11 (22%)	11 (22%)	10 (20%)
Inflammation, subacute	4 (8%)	5 (10%)	3 (6%)	2 (4%)
Mineralization		1 (2%)		
Ulcer	3 (6%)	3 (6%)	2 (4%)	
Stomach, glandular	(50)	(50)	(48)	(50)
Cyst			1 (2%)	
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Inflammation, subacute		2 (4%)		
Mineralization	1 (2%)	11 (22%)	9 (19%)	7 (14%)
Necrosis			1 (2%)	
Pigmentation	1 (2%)			
Polyarteritis		1 (2%)		
Ulcer	1 (2%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy			1 (2%)	
Embolus	1 (2%)			
Fibrosis			1 (2%)	
Mineralization	1 (2%)		1 (2%)	
Polyarteritis		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Accessory adrenal cortical nodule		1 (2%)	2 (4%)	
Embolus	1 (2%)			
Hemorrhage		1 (2%)	1 (2%)	
Hyperplasia	8 (16%)	11 (22%)	8 (16%)	6 (12%)
Hypertrophy	11 (22%)	11 (22%)	13 (27%)	12 (24%)
Necrosis		1 (2%)		
Vacuolization cytoplasmic	1 (2%)			
Capsule, hyperplasia	1 (2%)	6 (12%)		4 (8%)
Adrenal medulla	(50)	(49)	(49)	(50)
Embolus	1 (2%)			
Hemorrhage		1 (2%)		
Hyperplasia		2 (4%)		
Islets, pancreatic	(50)	(50)	(50)	(50)
Embolus	1 (2%)			
Hyperplasia	2 (4%)	4 (8%)	1 (2%)	3 (6%)
Parathyroid gland	(48)	(47)	(49)	(49)
Cyst				1 (2%)
Pituitary gland	(44)	(46)	(47)	(47)
Pars distalis, cyst		2 (4%)		
Pars distalis, hyperplasia			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
Polyarteritis		1 (2%)		
Follicle, cyst	6 (12%)	6 (12%)	12 (24%)	9 (18%)
Follicle, degeneration	3 (6%)	4 (8%)		3 (6%)
Follicular cell, hyperplasia	9 (18%)	4 (8%)	3 (6%)	2 (4%)
General Body System				
None				
Genital System				
Coagulating gland	(5)	(1)		(1)
Dilatation	5 (100%)	1 (100%)		1 (100%)
Inflammation, chronic				
Epididymis	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Granuloma sperm	1 (2%)			
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, chronic	1 (2%)			
Preputial gland	(49)	(49)	(49)	(50)
Congestion	1 (2%)			
Inflammation, subacute	2 (4%)	1 (2%)	1 (2%)	
Duct, cyst	45 (92%)	40 (82%)	31 (63%)	38 (76%)
Prostate	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Hyperplasia	1 (2%)			
Inflammation, subacute			1 (2%)	
Inflammation, suppurative	1 (2%)		1 (2%)	
Polyarteritis		1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(50)
Atrophy	2 (4%)		2 (4%)	2 (4%)
Dilatation	14 (28%)	2 (4%)	4 (8%)	
Inflammation, chronic	1 (2%)			1 (2%)
Epithelium, hyperplasia			1 (2%)	
Testes	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Mineralization	1 (2%)			
Interstitial cell, hyperplasia				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myeloid cell, hyperplasia	2 (4%)			
Lymph node	(3)	(3)	(3)	(4)
Inguinal, angiectasis		1 (33%)		
Inguinal, hyperplasia, lymphoid	1 (33%)	1 (33%)		1 (25%)
Inguinal, infiltration cellular, mast cell				
Inguinal, pigmentation		1 (33%)		
Mediastinal, angiectasis			1 (33%)	
Mediastinal, hematopoietic cell proliferation		1 (33%)		
Mediastinal, hyperplasia, lymphoid		1 (33%)	1 (33%)	1 (25%)
Pancreatic, angiectasis			1 (33%)	
Renal, hyperplasia, lymphoid				1 (25%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(50)	(49)	(49)	(49)
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Angiectasis	17 (34%)	17 (34%)	18 (36%)	12 (24%)
Hyperplasia, lymphoid	4 (8%)	3 (6%)	3 (6%)	3 (6%)
Infiltration cellular, histiocyte		1 (2%)		
Necrosis		1 (2%)		
Spleen	(50)	(50)	(49)	(50)
Atrophy	5 (10%)	1 (2%)	2 (4%)	
Congestion	1 (2%)	1 (2%)		1 (2%)
Hematopoietic cell proliferation	11 (22%)	16 (32%)	20 (41%)	13 (26%)
Hyperplasia, lymphoid	5 (10%)	12 (24%)	10 (20%)	7 (14%)
Pigmentation, hemosiderin	2 (4%)	25 (50%)	32 (65%)	47 (94%)
Capsule, inflammation, subacute		1 (2%)		
Thymus	(45)	(43)	(46)	(46)
Atrophy	3 (7%)	2 (5%)	1 (2%)	1 (2%)
Cyst	2 (4%)	3 (7%)	4 (9%)	1 (2%)
Polyarteritis		1 (2%)		
Thymocyte, necrosis	1 (2%)			1 (2%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, inflammation, chronic	1 (2%)			
Subcutaneous tissue, inflammation, subacute		1 (2%)		
Subcutaneous tissue, metaplasia, osseous				1 (2%)
Subcutaneous tissue, mineralization	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, hyperostosis	2 (4%)		1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	1 (2%)			
Embolus	1 (2%)			
Hydrocephalus				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Hyperplasia, macrophage		3 (6%)		1 (2%)
Alveolar epithelium, hyperplasia	4 (8%)	5 (10%)	5 (10%)	8 (16%)
Alveolus, foreign body	1 (2%)			
Alveolus, hemorrhage	1 (2%)			
Alveolus, infiltration cellular, histiocyte	3 (6%)		3 (6%)	1 (2%)
Mediastinum, hemorrhage	1 (2%)			
Mediastinum, inflammation, chronic		1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Glands, cyst	1 (2%)			
Glands, fibrosis		1 (2%)		
Lumen, inflammation, subacute		1 (2%)		
Respiratory epithelium, hyperplasia		1 (2%)		
Special Senses System				
Eye		(1)		
Cornea, inflammation, subacute		1 (100%)		
Harderian gland	(3)	(5)	(1)	(2)
Inflammation, chronic		1 (20%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Bacterium	1 (2%)		1 (2%)	
Fibrosis	1 (2%)	1 (2%)	1 (2%)	
Glomerulosclerosis	3 (6%)	1 (2%)	2 (4%)	
Infarct		2 (4%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocyte	1 (2%)			
Inflammation, chronic, suppurative			1 (2%)	
Inflammation, subacute	2 (4%)			
Metaplasia, osseous		1 (2%)		2 (4%)
Mineralization	37 (74%)	43 (86%)	40 (80%)	33 (66%)
Polyarteritis		1 (2%)		
Cortex, cyst	5 (10%)	1 (2%)	7 (14%)	1 (2%)
Cortex, medulla, inflammation, suppurative	1 (2%)			
Pelvis, necrosis	1 (2%)			
Renal tubule, casts	13 (26%)	11 (22%)	12 (24%)	3 (6%)
Renal tubule, degeneration	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Renal tubule, regeneration	38 (76%)	40 (80%)	40 (80%)	24 (48%)
Transitional epithelium, hyperplasia	1 (2%)			
Urethra			(1)	
Hemorrhage			1 (100%)	
Inflammation, subacute			1 (100%)	
Urinary bladder	(50)	(50)	(50)	(50)
Dilatation	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, subacute	1 (2%)			
Transitional epithelium, hyperplasia	1 (2%)			

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF SALICYLAZOSULFAPYRIDINE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	2		1	2
Moribund	5	6	8	6
Natural deaths	2	3	4	4
Survivors				
Died last week of study			1	
Terminal sacrifice	41	41	36	38
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma	1 (10%)			1 (10%)
Hepatocellular adenoma	1 (10%)		1 (10%)	1 (10%)
Hepatocellular adenoma, multiple				1 (10%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Squamous cell papilloma		1 (10%)		
Genital System				
Ovary	(10)	(10)	(10)	(10)
Cystadenoma	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study				
Alimentary System				
Intestine large, rectum	(49)	(50)	(49)	(46)
Histiocytic sarcoma			1 (2%)	
Leiomyosarcoma				1 (2%)
Intestine large, cecum	(49)	(49)	(48)	(46)
Leiomyosarcoma				1 (2%)
Intestine small, jejunum	(49)	(49)	(48)	(46)
Hemangiosarcoma				1 (2%)
Intestine small, ileum	(49)	(49)	(48)	(45)
Liver	(50)	(50)	(50)	(49)
Hemangioma	1 (2%)			
Hemangiosarcoma	2 (4%)	1 (2%)		
Hepatocellular carcinoma	2 (4%)	8 (16%)	9 (18%)	8 (16%)
Hepatocellular carcinoma, multiple		2 (4%)	1 (2%)	1 (2%)
Hepatocellular adenoma	9 (18%)	16 (32%)	13 (26%)	15 (31%)
Hepatocellular adenoma, multiple	3 (6%)	12 (24%)	12 (24%)	13 (27%)
Histiocytic sarcoma	1 (2%)		2 (4%)	
Osteosarcoma, metastatic, bone		1 (2%)		
Mesentery	(7)	(10)	(3)	(5)
Histiocytic sarcoma			1 (33%)	
Leiomyosarcoma, metastatic, uterus			1 (33%)	
Pancreas	(50)	(49)	(50)	(49)
Hemangioma			1 (2%)	
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(50)	(49)	(50)	(49)
Squamous cell papilloma	5 (10%)	1 (2%)	1 (2%)	
Stomach, glandular	(50)	(49)	(50)	(49)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Leiomyosarcoma, metastatic, intestine large, rectum				1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign	1 (2%)	2 (4%)		1 (2%)
Pituitary gland	(49)	(45)	(50)	(46)
Pars distalis, adenoma	7 (14%)	7 (16%)	7 (14%)	2 (4%)
Pars intermedia, adenoma	1 (2%)			2 (4%)
Thyroid gland	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Follicular cell, adenoma	1 (2%)		2 (4%)	1 (2%)
Follicular cell, carcinoma				1 (2%)
General Body System				
None				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Genital System				
Ovary	(49)	(49)	(49)	(49)
Cystadenoma	1 (2%)	5 (10%)	5 (10%)	2 (4%)
Granulosa cell tumor malignant		1 (2%)		
Granulosa cell tumor benign	1 (2%)			
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Luteoma		1 (2%)	3 (6%)	1 (2%)
Teratoma malignant			1 (2%)	
Thecoma malignant		1 (2%)		
Uterus	(50)	(50)	(50)	(49)
Histiocytic sarcoma	1 (2%)		3 (6%)	
Leiomyosarcoma			1 (2%)	
Polyp stromal				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Lymph node	(8)	(7)	(11)	(4)
Iliac, histiocytic sarcoma	1 (13%)			
Inguinal, histiocytic sarcoma			1 (9%)	
Inguinal, mast cell tumor NOS			1 (9%)	
Mediastinal, histiocytic sarcoma	1 (13%)			
Renal, histiocytic sarcoma	1 (13%)			
Renal, teratoma malignant, metastatic, ovary			1 (9%)	
Lymph node, mandibular	(49)	(50)	(50)	(49)
Histiocytic sarcoma	1 (2%)			
Lymph node, mesenteric	(49)	(50)	(50)	(48)
Histiocytic sarcoma	1 (2%)			
Spleen	(50)	(50)	(50)	(49)
Hemangioma			1 (2%)	
Hemangiosarcoma		2 (4%)	4 (8%)	1 (2%)
Histiocytic sarcoma	1 (2%)			
Thymus	(50)	(49)	(49)	(49)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoacanthoma			1 (2%)	
Carcinoma			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Squamous cell papilloma				2 (4%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	1 (2%)	
Subcutaneous tissue, hemangioma	1 (2%)			
Subcutaneous tissue, hemangiosarcoma	1 (2%)		1 (2%)	
Subcutaneous tissue, histiocytic sarcoma			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, osteosarcoma				1 (2%)
Vertebra, osteosarcoma		1 (2%)		
Skeletal muscle	(1)		(2)	(1)
Fibrosarcoma			1 (50%)	
Leiomyosarcoma, metastatic, uterus			1 (50%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone				1 (2%)
Spinal cord	(2)	(1)		(2)
Osteosarcoma, metastatic, bone		1 (100%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Adenoacanthoma, metastatic, mammary gland			1 (2%)	
Alveolar/bronchiolar adenoma	2 (4%)	3 (6%)	3 (6%)	4 (8%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)		
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	
Granulosa cell tumor malignant, metastatic, ovary		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Special Senses System				
Harderian gland	(2)		(1)	(2)
Adenoma	2 (100%)		1 (100%)	2 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Histiocytic sarcoma	1 (2%)			
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)		4 (8%)	
Lymphoma malignant	13 (26%)	6 (12%)	7 (14%)	6 (12%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	3	1	1	2
2-Year study	34	37	42	36
Total primary neoplasms				
15-Month interim evaluation	4	1	1	3
2-Year study	57	72	84	67
Total animals with benign neoplasms				
15-Month interim evaluation	3	1	1	2
2-Year study	22	32	34	32
Total benign neoplasms				
15-Month interim evaluation	3	1	1	2
2-Year study	35	48	49	46
Total animals with malignant neoplasms				
15-Month interim evaluation	1			1
2-Year study	19	19	26	17
Total malignant neoplasms				
15-Month interim evaluation	1			1
2-Year study	22	24	34	21
Total animals with metastatic neoplasms				
2-Year study	2	3	3	2
Total metastatic neoplasms				
2-Year study	2	4	6	2
Total animals with uncertain neoplasms — benign or malignant				
2-Year study			1	
Total uncertain neoplasms				
2-Year study			1	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control

Number of Days on Study	0 1 4	0 7 4	3 2 4	4 2 9	4 7 6	5 1 8	5 9 5	7 0 8	7 2 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	3 0 4	3 5 2	3 3 3	3 5 4	3 3 6	3 1 0	3 4 0	3 1 7	3 4 1	3 0 3	3 0 9	3 1 4	3 2 0	3 2 4	3 2 8	3 3 1	3 3 2	3 3 5	4 4 3	4 4 7	0 1 1	0 0 2	0 0 5	0 0 6	0 0 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																						X			
Hemangiosarcoma																							X		
Hepatocellular carcinoma																									
Hepatocellular adenoma										X				X	X					X					
Hepatocellular adenoma, multiple																								X	
Histiocytic sarcoma																									
Mesentery			+																						+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma											X		X									X	X		
Pars intermedia, adenoma											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Follicular cell, adenoma																									
General Body System																									
None																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 0 8	3 1 1	3 1 2	3 1 3	3 1 5	3 1 6	3 1 8	3 1 9	3 2 1	3 2 2	3 2 3	3 2 5	3 2 6	3 2 7	3 2 9	3 3 0	3 3 4	3 3 7	3 3 8	3 3 9	3 4 2	3 4 4	3 4 5	3 4 6	3 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma									X																	2
Hepatocellular carcinoma				X										X												2
Hepatocellular adenoma			X				X	X				X									X					9
Hepatocellular adenoma, multiple										X	X															3
Histiocytic sarcoma													X													1
Mesentery			+		+				+					+						+						7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X								X		X												X		5
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	M	+	M	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X														X	X								7
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Follicular cell, adenoma												X														1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	0 1 4	0 7 4	3 2 4	4 2 9	4 7 6	5 1 8	5 9 5	7 0 8	7 2 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	3 0 4	3 5 2	3 3 3	3 5 4	3 3 6	3 1 0	3 4 0	3 1 7	3 4 1	3 0 3	3 0 9	3 1 4	3 2 0	3 2 4	3 2 8	3 3 1	3 3 2	3 3 5	3 4 3	4 4 7	4 0 1	4 0 2	4 0 5	4 0 6	4 0 7
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Cystadenoma																									
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Hematopoietic System																									
Blood						+																			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node			+						+			+					+								
Iliac, histiocytic sarcoma																									
Mediastinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma				X																					
Subcutaneous tissue, hemangioma																						X			
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord			+		+																				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X									X		
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 0 8	3 1 1	3 1 2	3 1 3	3 1 5	3 1 6	3 1 8	3 1 9	3 2 1	3 2 2	3 2 3	3 2 5	3 2 6	3 2 7	3 2 9	3 3 0	3 3 4	3 3 7	3 3 8	3 3 9	3 4 2	3 4 4	3 4 5	3 4 6	3 4 8	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																X										1
Granulosa cell tumor benign																						X				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						1
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Lymph node								+	+				+		+											8
Iliac, histiocytic sarcoma													X													1
Mediastinal, histiocytic sarcoma													X													1
Renal, histiocytic sarcoma													X													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma													X													1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma													X													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, hemangiosarcoma																X										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma										X																1
Hepatocellular carcinoma, metastatic, liver				X										X												2
Histiocytic sarcoma													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	0 1 4	0 7 4	3 2 4	4 2 9	4 7 6	5 1 8	5 9 5	7 0 8	7 2 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	3 0 4	3 5 2	3 3 3	3 5 4	3 3 6	3 1 0	3 4 0	3 1 7	3 4 1	3 0 3	3 0 9	3 1 4	3 2 0	3 2 4	3 2 8	3 3 1	3 3 2	3 3 5	3 4 3	4 4 7	4 0 1	4 0 2	4 0 5	4 0 6	4 0 7
Special Senses System																										
Ear			+																							
Harderian gland																				+						
Adenoma																				X						
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Lymphoma malignant								X	X	X	X	X					X									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 0 8	3 1 1	3 1 2	3 1 3	3 1 5	3 1 6	3 1 8	3 1 9	3 2 1	3 2 2	3 2 3	3 2 5	3 2 6	3 2 7	3 2 9	3 3 0	3 3 4	3 3 7	3 3 8	3 3 9	3 4 2	3 4 4	3 4 5	3 4 6	3 4 8	Total Tissues/ Tumors	
Special Senses System																											
Ear																										1	
Harderian gland																		+								2	
Adenoma																		X								2	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma													X													1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma													X							X						2	
Lymphoma malignant					X		X	X	X	X					X							X				13	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 675 mg/kg

Number of Days on Study	2 2 4 4 5 5 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 2 9 7 9 3 5 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 7 1 3 9 1 0 3 2 5 5 5 5 5 5 5 5 5 5 7 7 7 7 8 8
Carcass ID Number	3 3 4 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 4 3 3 3 3 3 3 7 7 0 8 9 9 9 6 8 6 6 7 7 8 8 9 9 0 0 6 6 6 6 6 6 0 1 1 7 0 2 8 3 1 4 8 4 8 3 8 4 9 4 8 1 2 5 6 7 9
Alimentary System	
Esophagus	+ +
Gallbladder	+ +
Intestine large, colon	+ +
Intestine large, rectum	+ +
Intestine large, cecum	+ + + + + + A + + + + + + + + + + + + + + + + + +
Intestine small, duodenum	+ + + + + + A + + + + + + + + + + + + + + + + + +
Intestine small, jejunum	+ + + + + + A + + + + + + + + + + + + + + + + + +
Intestine small, ileum	+ + + + + + A + + + + + + + + + + + + + + + + + +
Liver	+ +
Hemangiosarcoma	X
Hepatocellular carcinoma	X X X X X
Hepatocellular carcinoma, multiple	X X
Hepatocellular adenoma	X X X X X X X
Hepatocellular adenoma, multiple	X X X X
Osteosarcoma, metastatic, bone	X
Mesentery	+ + + +
Pancreas	+ + + + + A + + + + + + + + + + + + + + + + + + +
Salivary glands	+ +
Stomach, forestomach	+ + + + + + A + + + + + + + + + + + + + + + + + +
Squamous cell papilloma	X
Stomach, glandular	+ + + + + + A + + + + + + + + + + + + + + + + + +
Cardiovascular System	
Blood vessel	+ +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adenoma	
Adrenal medulla	+ +
Pheochromocytoma benign	X X
Islets, pancreatic	+ +
Parathyroid gland	M +
Pituitary gland	+ + + M M M I + + + + + + + + + + + + + + + + + +
Pars distalis, adenoma	X X X
Thyroid gland	+ +
General Body System	
None	
Genital System	
Clitoral gland	+ +
Ovary	+ M + + + +
Cystadenoma	X X
Granulosa cell tumor malignant	
Luteoma	X
Thecoma malignant	X
Uterus	+ +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 675 mg/kg (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	3 7 2	3 7 3	3 7 5	3 7 6	3 7 7	3 7 9	3 8 0	3 8 2	3 8 4	3 8 5	3 8 6	3 8 9	3 9 1	3 9 3	3 9 5	3 9 6	3 9 7	4 0 0	4 0 2	4 0 3	4 0 5	4 0 6	4 0 7	4 0 9	4 1 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma					X															X			X			8
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma		X					X						X	X	X	X			X				X	X		16
Hepatocellular adenoma, multiple	X		X	X				X		X							X				X					12
Osteosarcoma, metastatic, bone																										1
Mesentery	+								+			+					+						+		+	10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Pars distalis, adenoma			X		X						X														X	7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma								X							X						X					5
Granulosa cell tumor malignant										X																1
Luteoma																										1
Thecoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 675 mg/kg (continued)

Number of Days on Study	2 2 4 4 5 5 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 2 9 7 9 3 5 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 7 1 3 9 1 0 3 2 5 5 5 5 5 5 5 5 5 5 7 7 7 7 8 8
Carcass ID Number	3 3 4 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 4 3 3 3 3 3 3 7 7 0 8 9 9 9 6 8 6 6 7 7 8 8 9 9 0 0 6 6 6 6 6 6 0 1 1 7 0 2 8 3 1 4 8 4 8 3 8 4 9 4 8 1 2 5 6 7 9
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ + + + + + + + + + + + +
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ +
Spleen	+ +
Hemangiosarcoma	X X
Thymus	+ + + + + + + + + + + + + + M + + + + + + + + + +
Integumentary System	
Mammary gland	+ +
Skin	+ +
Subcutaneous tissue, fibrosarcoma	
Musculoskeletal System	
Bone	+ +
Vertebra, osteosarcoma	X
Nervous System	
Brain	+ +
Spinal cord	+
Osteosarcoma, metastatic, bone	X
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X
Alveolar/bronchiolar carcinoma	X
Granulosa cell tumor malignant, metastatic, ovary	
Hepatocellular carcinoma, metastatic, liver	
Nose	+ +
Trachea	+ +
Special Senses System	
None	
Urinary System	
Kidney	+ +
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant	X X X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 675 mg/kg (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	3 7 2	3 7 3	3 7 5	3 7 6	3 7 7	3 7 9	3 8 0	3 8 2	3 8 4	3 8 5	3 8 6	3 8 9	3 9 1	3 9 3	3 9 5	3 9 6	3 9 7	4 0 0	4 0 2	4 0 3	4 0 5	4 0 6	4 0 7	4 0 9	4 1 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node										+																7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Osteosarcoma, metastatic, bone																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X									3
Alveolar/bronchiolar carcinoma																										1
Granulosa cell tumor malignant, metastatic, ovary										X																1
Hepatocellular carcinoma, metastatic, liver																				X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant										X				X										X		6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg

Number of Days on Study	0 0 9	1 7 1	3 1 6	4 2 0	4 6 5	5 8 8	6 1 8	6 6 0	6 6 1	6 6 3	6 8 6	6 9 3	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 7	7 3 7
Carcass ID Number	4 2 9	4 2 5	4 4 3	4 7 9	4 6 9	4 3 4	4 3 1	4 5 5	4 5 8	4 2 3	4 2 6	4 4 8	4 5 4	4 2 4	4 3 0	4 3 6	4 4 0	4 4 4	4 4 7	4 5 2	4 5 6	4 6 0	4 6 5	4 2 1	4 2 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X			X				X	X		X	
Hepatocellular carcinoma, multiple																		X							
Hepatocellular adenoma							X								X	X					X				
Hepatocellular adenoma, multiple														X				X				X		X	
Histiocytic sarcoma													X												
Mesentery						+							+												
Histiocytic sarcoma													X												
Leiomyosarcoma, metastatic, uterus						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X			X					X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X							X							
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Cystadenoma							X									X	X								
Leiomyosarcoma, metastatic, uterus						X																			
Luteoma																									
Teratoma malignant		X																							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 2 7	4 2 8	4 3 2	4 3 3	4 3 5	4 3 7	4 3 8	4 3 9	4 4 1	4 4 2	4 4 5	4 4 6	4 4 9	4 5 0	4 5 1	4 5 3	4 5 7	4 5 9	4 6 1	4 6 2	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma												X														1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X						X		X		X										9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma				X	X	X				X					X					X		X		X	X	13
Hepatocellular adenoma, multiple		X	X				X		X		X			X			X				X					12
Histiocytic sarcoma												X														2
Mesentery														+												3
Histiocytic sarcoma																										1
Leiomyosarcoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma												X			X		X						X			7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																X								X		5
Leiomyosarcoma, metastatic, uterus																										1
Luteoma								X									X							X		3
Teratoma malignant																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg (continued)

Number of Days on Study	0	1	3	4	4	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	0	7	1	2	6	8	1	6	6	6	8	9	3	3	3	3	3	3	3	3	3	3	3	3
	9	1	6	0	5	8	8	0	1	3	6	3	2	5	5	5	5	5	5	5	5	5	7	7
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	2	2	4	7	6	3	3	5	5	2	2	4	5	2	3	3	4	4	4	5	5	6	6	2	2
	9	5	3	9	9	4	1	5	8	3	6	8	4	4	0	6	0	4	7	2	6	0	5	1	2
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X										X		
Leiomyosarcoma						X																			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node		+		+			+	+			+								+		+				
Inguinal, histiocytic sarcoma				X																					
Inguinal, mast cell tumor NOS																									
Renal, teratoma malignant, metastatic, ovary		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma											X														
Hemangiosarcoma									X																
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma																									
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma											X														
Subcutaneous tissue, hemangiosarcoma									X																
Subcutaneous tissue, histiocytic sarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+																	+		
Fibrosarcoma																							X		
Leiomyosarcoma, metastatic, uterus						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma, metastatic, mammary gland																									
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma, multiple																									
Histiocytic sarcoma													X												
Leiomyosarcoma, metastatic, uterus						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																							+		
Adenoma																							X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 2 7	4 2 8	4 3 2	4 3 3	4 3 5	4 3 7	4 3 8	4 3 9	4 4 1	4 4 2	4 4 5	4 4 6	4 4 9	4 5 0	4 5 1	4 5 3	4 5 7	4 5 9	4 6 1	4 6 2	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma												X														3
Leiomyosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							1
Lymph node								+	+						+			+								11
Inguinal, histiocytic sarcoma																										1
Inguinal, mast cell tumor NOS									X																	1
Renal, teratoma malignant, metastatic, ovary																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma			X			X						X														4
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma																			X							1
Carcinoma																					X					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Fibrosarcoma																										1
Leiomyosarcoma, metastatic, uterus																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma, metastatic, mammary gland																			X							1
Alveolar/bronchiolar adenoma										X															X	3
Alveolar/bronchiolar carcinoma, multiple															X											1
Histiocytic sarcoma																										1
Leiomyosarcoma, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Adenoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg (continued)

Number of Days on Study	0	1	3	4	4	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	7	1	2	6	8	1	6	6	6	8	9	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	1	6	0	5	8	8	0	1	3	6	3	2	5	5	5	5	5	5	5	5	5	7	7	
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	2	2	4	7	6	3	3	5	5	2	2	4	5	2	3	3	4	4	4	5	5	6	6	2	2
	9	5	3	9	9	4	1	5	8	3	6	8	4	4	0	6	0	4	7	2	6	0	5	1	2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X									X										X		
Lymphoma malignant							X	X									X	X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 1,350 mg/kg (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 2 7	4 2 8	4 3 2	4 3 3	4 3 5	4 3 7	4 3 8	4 3 9	4 4 1	4 4 2	4 4 5	4 4 6	4 4 9	4 5 0	4 5 1	4 5 3	4 5 7	4 5 9	4 6 1	4 6 2	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma			-									X														4
Lymphoma malignant								X										X					X			7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 2,700 mg/kg

Number of Days on Study	0 0 0 0 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7
	0 6 7 7 8 0 0 1 5 5 6 9 3 3 3 3 3 3 3 3 3 3 3 3 3
	2 7 0 2 3 3 4 0 5 9 0 5 5 5 5 5 5 5 5 5 5 6 6 6
Carcass ID Number	4 5 5 4 5 4 5 4 5 4 5 5 4 4 4 5 5 5 5 5 5 5 4 4 4
	9 0 1 9 1 9 0 8 2 9 1 2 8 8 9 0 1 1 1 2 2 2 8 8 8
	8 6 7 9 2 4 4 8 4 1 9 7 4 9 5 3 0 1 6 0 3 8 1 2 3
Alimentary System	
Esophagus	+ +
Gallbladder	+ + A +
Intestine large, colon	+ A A + A + + + A + + + + + + + + + + + + + + + +
Intestine large, rectum	+ A A + A + + + A + + + + + + + + + + + + + + + +
Leiomyosarcoma	
Intestine large, cecum	+ A A + A + + + A + + + + + + + + + + + + + + + +
Leiomyosarcoma	
Intestine small, duodenum	+ A A + A + + + A + + + + + + + + + + + + + + + +
Intestine small, jejunum	+ A A + A + + + A + + + + + + + + + + + + + + + +
Hemangiosarcoma	X
Intestine small, ileum	+ A A M A + + + A + + + + + + + + + + + + + + + +
Liver	+ + A +
Hepatocellular carcinoma	X
Hepatocellular carcinoma, multiple	X
Hepatocellular adenoma	X X X X X X X X
Hepatocellular adenoma, multiple	X X X X
Mesentery	+ +
Pancreas	+ + A +
Salivary glands	+ +
Stomach, forestomach	+ + + + + + + + A + + + + + + + + + + + + + + + +
Stomach, glandular	+ + + + + + + + A + + + + + + + + + + + + + + + +
Cardiovascular System	
Blood vessel	+ +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Leiomyosarcoma, metastatic, intestine large, rectum	
Adrenal medulla	+ +
Pheochromocytoma benign	
Islets, pancreatic	+ +
Parathyroid gland	+ + + + + + + + + M + + + + + + + + + + + + + + +
Pituitary gland	+ + + + M + + + + + + + + + + + + + M + + + + + +
Pars distalis, adenoma	X
Pars intermedia, adenoma	
Thyroid gland	+ +
Follicular cell, adenoma	X
Follicular cell, carcinoma	
General Body System	
None	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 2,700 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 8 5	4 8 6	4 8 7	4 9 0	4 9 2	4 9 3	4 9 6	4 9 7	5 0 0	5 0 1	5 0 2	5 0 5	5 0 7	5 0 8	5 0 9	5 1 3	5 1 4	5 1 5	5 1 8	5 2 1	5 2 2	5 2 5	5 2 6	5 2 9	5 3 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyosarcoma															X											1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyosarcoma															X											1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangiosarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma	X							X						X	X			X	X				X			8
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma				X						X					X					X	X		X			15
Hepatocellular adenoma, multiple					X			X	X		X		X	X				X	X					X		13
Mesentery																		+							+	5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine large, rectum															X											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																		X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma			X																							2
Pars intermedia, adenoma		X					X																			2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
Follicular cell, carcinoma																							X			1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 2,700 mg/kg (continued)

Number of Days on Study	0 0 0 0 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 0 6 7 7 8 0 0 1 5 5 6 9 3 3 3 3 3 3 3 3 3 3 3 3 3 2 7 0 2 3 3 4 0 5 9 0 5 5 5 5 5 5 5 5 5 5 6 6 6
Carcass ID Number	4 5 5 4 5 4 5 4 5 4 5 5 4 4 4 5 5 5 5 5 5 5 4 4 4 9 0 1 9 1 9 0 8 2 9 1 2 8 8 9 0 1 1 1 2 2 2 8 8 8 8 6 7 9 2 4 4 8 4 1 9 7 4 9 5 3 0 1 6 0 3 8 1 2 3
Genital System	
Clitoral gland	+ +
Ovary	+ + A +
Cystadenoma	X
Luteoma	
Uterus	+ + A +
Polyp stromal	
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ + + + +
Lymph node, mandibular	+ + A +
Lymph node, mesenteric	+ + A + + + + + M + + + + + + + + + + + + + + + +
Spleen	+ + A +
Hemangiosarcoma	
Thymus	+ + + + + + + + + + + + + + M + + + + + + + + + +
Integumentary System	
Mammary gland	+ +
Skin	+ +
Squamous cell papilloma	X
Musculoskeletal System	
Bone	+ +
Cranium, osteosarcoma	X
Skeletal muscle	+
Nervous System	
Brain	+ +
Osteosarcoma, metastatic, bone	X
Spinal cord	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X
Nose	+ +
Trachea	+ +
Special Senses System	
Harderian gland	
Adenoma	
Urinary System	
Kidney	+ + A +
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant	X X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine: 2,700 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 8 5	4 8 6	4 8 7	4 9 0	4 9 2	4 9 3	4 9 6	4 9 7	5 0 0	5 0 1	5 0 2	5 0 5	5 0 7	5 0 8	5 0 9	5 1 3	5 1 4	5 1 5	5 1 8	5 2 1	5 2 2	5 2 5	5 2 6	5 2 9	5 3 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma				X																						2
Luteoma				X																						1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal		X																								1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																	+									4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma				X																						1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X											2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteosarcoma																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X			X									X												4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland														+				+								2
Adenoma														X				X								2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X										X					X		X						6

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Liver: Hepatocellular Adenoma				
Overall rate[a]	12/50 (24%)	28/50 (56%)	25/50 (50%)	28/49 (57%)
Adjusted rate[b]	29.3%	63.6%	65.7%	71.7%
Terminal rate[c]	12/41 (29%)	25/41 (61%)	24/37 (65%)	27/38 (71%)
First incidence (days)	735 (T)	539	618	655
Life table test[d]	P<0.001	P=0.001	P=0.001	P<0.001
Logistic regression test[d]	P=0.002	P=0.001	P=0.002	P<0.001
Cochran-Armitage test[d]	P=0.004			
Fisher exact test[d]		P=0.001	P=0.006	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	2/50 (4%)	10/50 (20%)	10/50 (20%)	9/49 (18%)
Adjusted rate	4.9%	23.7%	27.0%	23.7%
Terminal rate	2/41 (5%)	9/41 (22%)	10/37 (27%)	9/38 (24%)
First incidence (days)	735 (T)	551	735 (T)	735 (T)
Life table test	P=0.051	P=0.016	P=0.009	P=0.019
Logistic regression test	P=0.059	P=0.017	P=0.009	P=0.019
Cochran-Armitage test	P=0.071			
Fisher exact test		P=0.014	P=0.014	P=0.023
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	14/50 (28%)	32/50 (64%)	28/50 (56%)	29/49 (59%)
Adjusted rate	34.1%	71.1%	73.6%	74.3%
Terminal rate	14/41 (34%)	28/41 (68%)	27/37 (73%)	28/38 (74%)
First incidence (days)	735 (T)	539	618	655
Life table test	P=0.002	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.005	P<0.001	P=0.001	P<0.001
Cochran-Armitage test	P=0.011			
Fisher exact test		P<0.001	P=0.004	P=0.002
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted rate	4.9%	7.0%	8.1%	10.5%
Terminal rate	2/41 (5%)	2/41 (5%)	3/37 (8%)	4/38 (11%)
First incidence (days)	735 (T)	620	735 (T)	735 (T)
Life table test	P=0.237	P=0.502	P=0.453	P=0.302
Logistic regression test	P=0.254	P=0.507	P=0.453	P=0.302
Cochran-Armitage test	P=0.273			
Fisher exact test		P=0.500	P=0.500	P=0.339
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted rate	7.3%	9.4%	10.8%	10.5%
Terminal rate	3/41 (7%)	3/41 (7%)	4/37 (11%)	4/38 (11%)
First incidence (days)	735 (T)	620	735 (T)	735 (T)
Life table test	P=0.395	P=0.502	P=0.444	P=0.458
Logistic regression test	P=0.418	P=0.509	P=0.444	P=0.458
Cochran-Armitage test	P=0.446			
Fisher exact test		P=0.500	P=0.500	P=0.500

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Ovary: Luteoma				
Overall rate	0/49 (0%)	1/49 (2%)	3/49 (6%)	1/49 (2%)
Adjusted rate	0.0%	2.5%	8.3%	2.6%
Terminal rate	0/40 (0%)	1/40 (3%)	3/36 (8%)	1/38 (3%)
First incidence (days)	—[e]	735 (T)	735 (T)	735 (T)
Life table test	P=0.331	P=0.500	P=0.103	P=0.490
Logistic regression test	P=0.331	P=0.500	P=0.103	P=0.490
Cochran-Armitage test	P=0.351			
Fisher exact test		P=0.500	P=0.121	P=0.500
Ovary: Cystadenoma				
Overall rate	1/49 (2%)	5/49 (10%)	5/49 (10%)	2/49 (4%)
Adjusted rate	2.5%	12.5%	13.1%	5.3%
Terminal rate	1/40 (3%)	5/40 (13%)	4/36 (11%)	2/38 (5%)
First incidence (days)	735 (T)	735 (T)	618	735 (T)
Life table test	P=0.524	P=0.103	P=0.087	P=0.482
Logistic regression test	P=0.548	P=0.103	P=0.100	P=0.482
Cochran-Armitage test	P=0.558			
Fisher exact test		P=0.102	P=0.102	P=0.500
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/49 (14%)	7/45 (16%)	7/50 (14%)	2/46 (4%)
Adjusted rate	17.5%	17.5%	17.8%	5.0%
Terminal rate	7/40 (18%)	7/40 (18%)	5/37 (14%)	1/35 (3%)
First incidence (days)	735 (T)	735 (T)	663	603
Life table test	P=0.097N	P=0.615	P=0.553	P=0.112N
Logistic regression test	P=0.079N	P=0.615	P=0.603	P=0.102N
Cochran-Armitage test	P=0.069N			
Fisher exact test		P=0.545	P=0.597N	P=0.095N
Spleen: Hemangiosarcoma				
Overall rate	0/50 (0%)	2/50 (4%)	4/50 (8%)	1/49 (2%)
Adjusted rate	0.0%	4.7%	10.3%	2.6%
Terminal rate	0/41 (0%)	1/41 (2%)	3/37 (8%)	1/38 (3%)
First incidence (days)	—	620	661	735 (T)
Life table test	P=0.391	P=0.242	P=0.055	P=0.485
Logistic regression test	P=0.411	P=0.235	P=0.061	P=0.485
Cochran-Armitage test	P=0.414			
Fisher exact test		P=0.247	P=0.059	P=0.495
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	5/50 (10%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	12.2%	2.4%	2.7%	0.0%
Terminal rate	5/41 (12%)	1/41 (2%)	1/37 (3%)	0/38 (0%)
First incidence (days)	735 (T)	735 (T)	735 (T)	—
Life table test	P=0.020N	P=0.103N	P=0.128N	P=0.040N
Logistic regression test	P=0.020N	P=0.103N	P=0.128N	P=0.040N
Cochran-Armitage test	P=0.016N			
Fisher exact test		P=0.102N	P=0.102N	P=0.028N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted rate	7.3%	4.7%	10.3%	5.3%
Terminal rate	3/41 (7%)	1/41 (2%)	3/37 (8%)	2/38 (5%)
First incidence (days)	735 (T)	620	661	735 (T)
Life table test	P=0.522N	P=0.498N	P=0.450	P=0.535N
Logistic regression test	P=0.495N	P=0.493N	P=0.487	P=0.535N
Cochran-Armitage test	P=0.479N			
Fisher exact test		P=0.500N	P=0.500	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	2/50 (4%)	6/50 (12%)	2/50 (4%)
Adjusted rate	9.8%	4.7%	15.1%	5.3%
Terminal rate	4/41 (10%)	1/41 (2%)	4/37 (11%)	2/38 (5%)
First incidence (days)	735 (T)	620	661	735 (T)
Life table test	P=0.439N	P=0.337N	P=0.316	P=0.372N
Logistic regression test	P=0.406N	P=0.329N	P=0.356	P=0.372N
Cochran-Armitage test	P=0.389N			
Fisher exact test		P=0.339N	P=0.370	P=0.339N
All Organs: Malignant Lymphoma				
Overall rate	13/50 (26%)	6/50 (12%)	7/50 (14%)	6/50 (12%)
Adjusted rate	30.2%	13.7%	17.4%	14.7%
Terminal rate	11/41 (27%)	4/41 (10%)	5/37 (14%)	4/38 (11%)
First incidence (days)	708	493	618	583
Life table test	P=0.113N	P=0.068N	P=0.160N	P=0.095N
Logistic regression test	P=0.083N	P=0.057N	P=0.112N	P=0.069N
Cochran-Armitage test	P=0.076N			
Fisher exact test		P=0.062N	P=0.105N	P=0.062N
All Organs: Histiocytic Sarcoma				
Overall rate	2/50 (4%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate	4.9%	0.0%	9.9%	0.0%
Terminal rate	2/41 (5%)	0/41 (0%)	2/37 (5%)	0/38 (0%)
First incidence (days)	735 (T)	—	420	—
Life table test	P=0.366N	P=0.238N	P=0.303	P=0.255N
Logistic regression test	P=0.338N	P=0.238N	P=0.337	P=0.254N
Cochran-Armitage test	P=0.337N			
Fisher exact test		P=0.247N	P=0.339	P=0.247N
All Organs: Benign Neoplasms				
Overall rate	22/50 (44%)	32/50 (64%)	34/50 (68%)	32/50 (64%)
Adjusted rate	53.7%	72.7%	82.9%	79.9%
Terminal rate	22/41 (54%)	29/41 (71%)	30/37 (81%)	30/38 (79%)
First incidence (days)	735 (T)	539	618	603
Life table test	P=0.009	P=0.030	P=0.002	P=0.007
Logistic regression test	P=0.017	P=0.032	P=0.003	P=0.010
Cochran-Armitage test	P=0.049			
Fisher exact test		P=0.035	P=0.013	P=0.035

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	19/50 (38%)	19/50 (38%)	26/50 (52%)	17/50 (34%)
Adjusted rate	43.1%	41.3%	57.4%	41.1%
Terminal rate	16/41 (39%)	14/41 (34%)	18/37 (49%)	14/38 (37%)
First incidence (days)	429	493	171	583
Life table test	P=0.505	P=0.569N	P=0.075	P=0.521N
Logistic regression test	P=0.467N	P=0.557N	P=0.110	P=0.447N
Cochran-Armitage test	P=0.432N			
Fisher exact test		P=0.582N	P=0.114	P=0.418N
All Organs: Benign or Malignant Neoplasms				
Overall rate	34/50 (68%)	37/50 (74%)	42/50 (84%)	36/50 (72%)
Adjusted rate	77.2%	78.7%	91.3%	85.6%
Terminal rate	31/41 (76%)	31/41 (76%)	33/37 (89%)	32/38 (84%)
First incidence (days)	429	493	171	583
Life table test	P=0.157	P=0.351	P=0.015	P=0.214
Logistic regression test	P=0.262	P=0.379	P=0.035	P=0.356
Cochran-Armitage test	P=0.361			
Fisher exact test		P=0.330	P=0.050	P=0.414

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and spleen; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4a
Historical Incidence of Hepatocellular Neoplasms in Female B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	99/759 (13.0%)	38/759 (5.0%)	131/759 (17.3%)
Standard deviation	8.4%	3.7%	9.8%
Range	2%-28%	0%-14%	4%-37%

[a] Data as of 17 June 1994

TABLE D4b
Historical Incidence of Splenic Hemangiosarcoma in Female B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	6/756 (0.8%)
Standard deviation	1.3%
Range	0%-4%

[a] Data as of 17 June 1994

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	2		1	2
Moribund	5	6	8	6
Natural deaths	2	3	4	4
Survivors				
Died last week of study			1	
Terminal sacrifice	41	41	36	38
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Cytologic alterations		3 (30%)	6 (60%)	8 (80%)
Eosinophilic focus	1 (10%)	1 (10%)		1 (10%)
Inflammation, subacute				1 (10%)
Mixed cell focus			1 (10%)	1 (10%)
Vacuolization cytoplasmic	1 (10%)			
Mesentery		(1)		
Fat, necrosis		1 (100%)		
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy			1 (10%)	
Stomach, forestomach	(10)	(10)	(10)	(10)
Hyperplasia	1 (10%)	1 (10%)	2 (20%)	
Inflammation, subacute		1 (10%)		
Stomach, glandular	(10)	(10)	(10)	(10)
Cyst	1 (10%)			
Hyperplasia				1 (10%)
Mineralization				3 (30%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)		
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, hyperplasia	1 (10%)			1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)
Follicle, degeneration	2 (20%)	4 (40%)	3 (30%)	4 (40%)
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Duct, cyst	3 (30%)	4 (40%)	5 (50%)	3 (30%)
Ovary	(10)	(10)	(10)	(10)
Cyst	1 (10%)	1 (10%)	2 (20%)	
Uterus	(10)	(10)	(10)	(10)
Dilatation		1 (10%)	3 (30%)	
Hyperplasia, cystic	9 (90%)	9 (90%)	9 (90%)	10 (100%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mandibular	(10)	(10)	(10)	(10)
Pigmentation		1 (10%)		
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Necrosis	2 (20%)			2 (20%)
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	2 (20%)	7 (70%)	10 (100%)	10 (100%)
Hyperplasia, lymphoid	2 (20%)			
Pigmentation, hemosiderin		10 (100%)	10 (100%)	10 (100%)
Thymus	(10)	(10)	(10)	(10)
Cyst			2 (20%)	
Thymocyte, necrosis	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, subacute			1 (10%)	
Alveolar epithelium, hyperplasia	1 (10%)		1 (10%)	
Alveolus, infiltration cellular, histiocyte	2 (20%)	1 (10%)		
Nose	(10)	(10)	(10)	(10)
Glands, cyst		2 (20%)	4 (40%)	
Olfactory epithelium, degeneration	8 (80%)	10 (100%)	10 (100%)	6 (60%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Fibrosis				1 (10%)
Glomerulosclerosis				1 (10%)
Metaplasia, osseous			1 (10%)	
Mineralization		1 (10%)		
Renal tubule, casts	3 (30%)	4 (40%)	4 (40%)	5 (50%)
Renal tubule, regeneration	2 (20%)	2 (20%)		
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			1 (2%)
Perforation	1 (2%)			
Intestine large, cecum	(49)	(49)	(48)	(46)
Edema	1 (2%)			
Inflammation, subacute	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Intestine small, duodenum	(50)	(49)	(48)	(46)
Hyperplasia				1 (2%)
Necrosis				1 (2%)
Intestine small, jejunum	(49)	(49)	(48)	(46)
Dilatation				1 (2%)
Peyer's patch, hyperplasia, lymphoid		2 (4%)		
Intestine small, ileum	(49)	(49)	(48)	(45)
Dilatation				1 (2%)
Inflammation, subacute		1 (2%)		
Liver	(50)	(50)	(50)	(49)
Angiectasis	2 (4%)		1 (2%)	
Basophilic focus	1 (2%)		1 (2%)	1 (2%)
Clear cell focus		1 (2%)	1 (2%)	1 (2%)
Congestion	1 (2%)			1 (2%)
Depletion glycogen			1 (2%)	
Eosinophilic focus	5 (10%)	13 (26%)	13 (26%)	15 (31%)
Eosinophilic focus, multiple		4 (8%)	2 (4%)	4 (8%)
Fibrosis			1 (2%)	
Hematopoietic cell proliferation		1 (2%)	1 (2%)	1 (2%)
Hemorrhage			1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Inflammation, chronic		1 (2%)		
Inflammation, subacute	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Mineralization			1 (2%)	
Mixed cell focus	2 (4%)		1 (2%)	
Necrosis		3 (6%)	5 (10%)	2 (4%)
Pigmentation, bile	1 (2%)	1 (2%)		
Thrombosis		1 (2%)		
Vacuolization cytoplasmic	2 (4%)		1 (2%)	1 (2%)
Bile duct, cyst	2 (4%)		1 (2%)	
Mesentery	(7)	(10)	(3)	(5)
Cyst	1 (14%)			
Inflammation, subacute	1 (14%)			
Polyarteritis	2 (29%)			
Fat, inflammation, subacute				1 (20%)
Fat, necrosis	4 (57%)	10 (100%)	1 (33%)	4 (80%)
Pancreas	(50)	(49)	(50)	(49)
Edema	1 (2%)	1 (2%)		
Fibrosis				1 (2%)
Hemorrhage			1 (2%)	
Inflammation, chronic			1 (2%)	
Inflammation, subacute				1 (2%)
Polyarteritis	1 (2%)			
Acinus, atrophy		1 (2%)	3 (6%)	1 (2%)
Acinus, depletion secretory	1 (2%)		1 (2%)	
Acinus, necrosis		1 (2%)		1 (2%)
Duct, cyst	1 (2%)	1 (2%)		1 (2%)
Salivary glands	(49)	(50)	(50)	(50)
Acinus, atrophy	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(49)	(50)	(49)
Diverticulum	1 (2%)	1 (2%)		
Edema				1 (2%)
Hyperplasia	12 (24%)	6 (12%)	4 (8%)	4 (8%)
Inflammation, subacute	2 (4%)	1 (2%)		1 (2%)
Mineralization	1 (2%)		1 (2%)	
Polyarteritis	1 (2%)			
Ulcer	2 (4%)			1 (2%)
Stomach, glandular	(50)	(49)	(50)	(49)
Cyst	2 (4%)		1 (2%)	1 (2%)
Edema			2 (4%)	
Erosion				1 (2%)
Hyperplasia		1 (2%)		
Inflammation, subacute		2 (4%)		
Mineralization	3 (6%)	8 (16%)	4 (8%)	2 (4%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy		1 (2%)		
Congestion			1 (2%)	
Degeneration	1 (2%)			
Fibrosis	1 (2%)	1 (2%)	1 (2%)	
Foreign body	1 (2%)			
Hemorrhage		1 (2%)		
Mineralization	1 (2%)		1 (2%)	
Pericardium, inflammation, chronic	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)			
Cyst	2 (4%)		1 (2%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia		2 (4%)	3 (6%)	4 (8%)
Hypertrophy		1 (2%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic, focal			1 (2%)	
Capsule, hyperplasia	1 (2%)			
Spindle cell, hyperplasia	1 (2%)			1 (2%)
X-zone, vacuolization cytoplasmic		1 (2%)	3 (6%)	2 (4%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)		1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)		
Pituitary gland	(49)	(45)	(50)	(46)
Pars distalis, cyst	1 (2%)			
Pars distalis, hyperplasia	12 (24%)	12 (27%)	7 (14%)	7 (15%)
Pars intermedia, hyperplasia			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Polyarteritis	1 (2%)			
Follicle, cyst	6 (12%)	4 (8%)	3 (6%)	
Follicle, degeneration	1 (2%)	5 (10%)	6 (12%)	10 (20%)
Follicular cell, hyperplasia	20 (40%)	5 (10%)	2 (4%)	1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Atrophy			1 (2%)	
Hemorrhage				1 (2%)
Necrosis				1 (2%)
Duct, cyst	13 (26%)	17 (34%)	19 (38%)	12 (24%)
Ovary	(49)	(49)	(49)	(49)
Cyst	8 (16%)	12 (24%)	12 (24%)	5 (10%)
Hemorrhage	1 (2%)			
Mineralization			1 (2%)	
Thrombosis			1 (2%)	
Uterus	(50)	(50)	(50)	(49)
Cyst			1 (2%)	
Dilatation	4 (8%)	17 (34%)	11 (22%)	11 (22%)
Hemorrhage			3 (6%)	1 (2%)
Hydrometra			1 (2%)	
Hyperplasia, cystic	42 (84%)	39 (78%)	42 (84%)	40 (82%)
Inflammation, suppurative	1 (2%)			
Mineralization			1 (2%)	
Thrombosis			2 (4%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			
Lymph node	(8)	(7)	(11)	(4)
Hyperplasia, lymphoid				1 (25%)
Inguinal, hyperplasia, lymphoid		1 (14%)		1 (25%)
Mediastinal, hyperplasia, lymphoid	2 (25%)	2 (29%)	3 (27%)	
Renal, hyperplasia, lymphoid		1 (14%)		
Lymph node, mandibular	(49)	(50)	(50)	(49)
Angiectasis	2 (4%)			
Hyperplasia, lymphoid	4 (8%)	1 (2%)	2 (4%)	4 (8%)
Lymph node, mesenteric	(49)	(50)	(50)	(48)
Angiectasis	3 (6%)		2 (4%)	
Hyperplasia, lymphoid	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Spleen	(50)	(50)	(50)	(49)
Atrophy	1 (2%)		1 (2%)	2 (4%)
Congestion		1 (2%)	1 (2%)	
Cyst	1 (2%)			
Hematopoietic cell proliferation	7 (14%)	21 (42%)	19 (38%)	23 (47%)
Hyperplasia, lymphoid	16 (32%)	28 (56%)	17 (34%)	15 (31%)
Pigmentation, hemosiderin	14 (28%)	37 (74%)	39 (78%)	46 (94%)
Polyarteritis	1 (2%)			
Thymus	(50)	(49)	(49)	(49)
Atrophy	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, granulomatous			1 (2%)	
Thymocyte, necrosis				1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Duct, cyst			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)		
Hyperkeratosis			1 (2%)	
Inflammation, chronic	1 (2%)			
Inflammation, subacute		1 (2%)	1 (2%)	
Subcutaneous tissue, abscess		1 (2%)		
Subcutaneous tissue, edema			1 (2%)	
Subcutaneous tissue, fibrosis		1 (2%)		
Subcutaneous tissue, foreign body		1 (2%)		
Subcutaneous tissue, hemorrhage			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, fibrous osteodystrophy	1 (2%)			2 (4%)
Cranium, hyperostosis				1 (2%)
Femur, fibrous osteodystrophy	3 (6%)		2 (4%)	
Skeletal muscle	(1)		(2)	(1)
Abscess	1 (100%)			
Foreign body	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	1 (2%)		2 (4%)	
Cyst epithelial inclusion		1 (2%)	1 (2%)	
Hemorrhage		1 (2%)		
Vacuolization cytoplasmic	1 (2%)	1 (2%)		
Spinal cord	(2)	(1)		(2)
Vacuolization cytoplasmic	1 (50%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Foreign body	1 (2%)	1 (2%)		1 (2%)
Hemorrhage		2 (4%)		2 (4%)
Hyperplasia, macrophage		1 (2%)		
Inflammation, subacute		1 (2%)		
Pigmentation		1 (2%)		
Alveolar epithelium, hyperplasia	2 (4%)		2 (4%)	
Alveolus, infiltration cellular, histiocyte		2 (4%)		
Mediastinum, inflammation, chronic	1 (2%)			1 (2%)
Nose	(50)	(50)	(50)	(50)
Glands, mineralization		1 (2%)	2 (4%)	
Lumen, exudate	1 (2%)	2 (4%)	1 (2%)	
Lumen, foreign Body		1 (2%)		
Olfactory epithelium, degeneration		1 (2%)	2 (4%)	
Respiratory epithelium, mineralization		2 (4%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
2-Year Study (continued)				
Special Senses System				
None				
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Glomerulosclerosis		2 (4%)		
Metaplasia, osseous		5 (10%)	1 (2%)	1 (2%)
Mineralization	14 (28%)	26 (52%)	24 (48%)	13 (27%)
Polyarteritis	1 (2%)			
Cortex, cyst				1 (2%)
Pelvis, mineralization		1 (2%)		
Renal tubule, casts	23 (46%)	22 (44%)	22 (44%)	29 (59%)
Renal tubule, degeneration		3 (6%)	1 (2%)	
Renal tubule, dilatation			1 (2%)	
Renal tubule, pigmentation, hemosiderin		1 (2%)		
Renal tubule, regeneration	15 (30%)	15 (30%)	14 (28%)	17 (35%)
Urinary bladder	(50)	(50)	(50)	(50)
Dilatation	1 (2%)		1 (2%)	
Polyarteritis	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1988). Salicylazosulfapyridine was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA1535 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of five doses of salicylazosulfapyridine. The high dose was limited by toxicity.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which is not dose-related, is not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Bishop *et al.* (1990). Salicylazosulfapyridine was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of salicylazosulfapyridine; the high dose was limited by toxicity. A single flask per dose was used.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with salicylazosulfapyridine in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing salicylazosulfapyridine was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with salicylazosulfapyridine, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no salicylazosulfapyridine, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically

significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with salicylazosulfapyridine for 10 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with salicylazosulfapyridine and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 11 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included "simple" (breaks and terminal deletions), "complex" (rearrangements and translocations), and "other" (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose-response curve and individual dose points. For a single trial, a statistically significant ($P\leq0.05$) difference for one dose point and a significant trend ($P\leq0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. In the absence of a statistically significant increase at any one dose point, a positive trend led to an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female $B6C3F_1$ mice at the end of the 13-week toxicity study (Table E4). Smears were immediately prepared and fixed in absolute methanol, stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned at 630× or 1,000× magnification using a semi-automated image analysis system to determine the frequency of micronuclei in at least 2,000 polychromatic erythrocytes (PCEs) and 10,000 normochromatic erythrocytes (NCEs) in each of 10 animals per dose group. The criteria of Schmid (1976) were used in defining micronuclei, with the additional requirement that micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 540 nm ultraviolet illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell. In addition, the percentage of PCEs among the total erythrocyte population was determined.

Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was determined by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent control using a Student's *t*-test. The frequency of micronucleated cells among PCEs was analyzed by the Cochran-Armitage trend test, and individual dose groups were compared to the concurrent solvent control by Kastenbaum-Bowman's binomial test. The percentage of PCEs among total erythrocytes was determined by an analysis of variance on ranks (classed by sex), and individual dose groups were compared with the concurrent solvent control using a *t*-test on ranks.

MOUSE BONE MARROW CHROMOSOMAL ABERRATIONS TEST PROTOCOLS

Standard Protocol: A dose range-finding study was performed in the absence of adequate toxicity information from the literature, and the high dose was limited by toxicity to 1,000 mg/kg. Salicylazosulfapyridine was tested for induction of Abs in mouse bone marrow cells using a harvest time of 17 hours.

Male B6C3F$_1$ mice (eight animals per dose group) were administered salicylazosulfapyridine once by corn oil gavage (Table E5). Solvent control mice were administered corn oil by gavage. The positive control, dimethylbenz(a)anthracene, was intraperitoneally injected. The mice were subcutaneously implanted with a BrdU tablet (McFee *et al.*, 1983) 18 hours before the scheduled harvest. (For a standard 17-hour exposure time, this required BrdU implantation to precede treatment with salicylazosulfapyridine by 1 hour.) The use of BrdU allowed selection of the appropriate cell population for scoring. (Abs induced by chemical administration are present in maximum number at the first metaphase following treatment; they decline in number during subsequent nuclear divisions due to cell death.) Two hours before sacrifice, the mice received an intraperitoneal injection of colchicine in saline. The animals were killed 17 hours after salicylazosulfapyridine treatment (18 hours after BrdU dosing). One or both femurs were removed and the marrow was flushed out with phosphate-buffered saline (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained with Giemsa and scored (Goto *et al.*, 1978).

Fifty first-division metaphase cells were scored from each of eight animals per treatment group. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The data were analyzed by a trend test (Margolin *et al.*, 1986).

Nonstandard Protocol: Because positive results were observed in micronucleus experiments that employed multiple dosing protocols (standard for a micronucleus test), and because the standard single-dose rat and mouse bone marrow chromosomal aberrations protocol yielded negative results, salicylazosulfapyridine was tested for induction of Abs in a nonstandard, triple-treatment protocol that used three gavage administrations separated by 24-hour intervals in an attempt to mimic the same exposure environment that produced the positive micronucleus test results (Table E9). The highest dose used in this experiment was 4,000 mg/kg.

RAT AND MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

Preliminary range-finding studies were performed for the initial mouse bone marrow micronucleus test. Factors affecting dose selection included chemical solubility, toxicity, and the extent of cell cycle delay induced by salicylazosulfapyridine exposure. Based on the results of the range finding studies, male B6C3F$_1$ mice were administered salicylazosulfapyridine by corn oil gavage twice, at 24-hour intervals (Table E6). The total dosing volume was 0.4 mL. Solvent control animals received 0.4 mL corn oil, and the positive control mice received injections of dimethylbenz(a)anthracene. The mice were killed 24 hours after the second injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 PCEs were scored for frequency of micronucleated cells in each of five animals per dose group.

Doses of salicylazosulfapyridine used in subsequent micronucleus tests in male Fisher 344/N rats (Table E10) and male and female B6C3F$_1$ mice (Table E8) were based on the accumulated information available from all toxicity studies performed with salicylazosulfapyridine. Salicylazosulfapyridine was administered by gavage in these additional micronucleus tests, and the number of gavage treatments administered to each dose group varied from one to three; multiple treatments were administered at 24-hour intervals. Bone marrow sampling was performed 24 hours after the final dosing, and slide preparation and scoring were performed as described above.

The results were tabulated as the mean of the pooled results from all animals within a treatment group, plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups using a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (Margolin *et al.*, 1990). In the presence of excess binomial variation as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if 1) the trend test P value is ≤0.025, or 2) the P value for any single exposure group is ≤0.025/N, where N=the number of exposure groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, reproducibility of any effects observed, and the magnitudes of those effects.

Mouse Bone Marrow Micronucleus Test with Kinetochore Analysis Protocol

This specialized micronucleus test was conducted at SITEK Research Laboratories (Rockville, MD) (Table E7). Male B6C3F$_1$ mice (five per treatment group) were fasted for 12 hours prior to treatment. They were administered salicylazosulfapyridine in corn oil by gavage three times at 24-hour intervals. Solvent control animals were administered corn oil by gavage, and two groups of positive control mice were used. One group received triethylenemelamine, a clastogen which produces mainly kinetochore-negative micronuclei, and the other group received vincristine sulfate, an aneuploidogen which produces micronuclei that contain kinetochores. Both these positive control chemicals were dissolved in deionized distilled water and administered by a single intraperitoneal injection.

Mice were killed 24 hours after the final treatment, and bone marrow was flushed from the femurs into tubes containing fetal bovine serum. The marrow preparation was pelleted by centrifugation and passed through a cellulose column to isolate the erythrocytes (Romagna and Staniforth, 1989). The separated erythrocytes were cytocentrifuged onto slides and fixed immediately in ethanol. Slides were immersed in phosphate-buffered saline and processed for indirect immunofluorescence as described by Gudi *et al.* (1990). Briefly, slides were overlaid with antikinetochore-specific antibodies, rinsed in phosphate-buffered saline and stained with a fluorescent antibody tag (fluorescein isothiocyanate-conjugated goat anti-human IgG). Counterstaining with propidium iodide was performed to allow visualization of the micronuclei. This procedure allows differentiation of the PCE and NCE populations as well as simultaneous visualization of micronuclei and kinetochores. PCEs appear pale red and NCEs appear light green. Kinetochores are bright yellow dots in redstained micronuclei.

Two thousand PCEs were scored for frequency of micronucleated cells in each of five mice per dose group. Data were analyzed as described previously.

Results

Salicylazosulfapyridine (33-6,666 μg/plate) was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, or TA1535 when tested in a preincubation protocol with and without induced rat or hamster liver S9 metabolic activation enzymes (Table E1). It did not induce SCEs (Table E2) or Abs (Table E3) in cultured Chinese hamster ovary cells, with or without induced rat liver S9 (Bishop *et al.*, 1990). In contrast to the negative results obtained *in vitro*, results from *in vivo* genotoxicity tests with salicylazosulfapyridine yielded generally positive results.

Salicylazosulfapyridine gave a strongly positive response in a micronucleus assay conducted with peripheral blood smears obtained from mice used in the 13-week toxicity study (Table E4; Bishop *et al.*, 1990). Significant increases in the frequency of micronucleated PCEs were observed in male and female mice administered 2,700 mg salicylazosulfapyridine/kg body weight. Significantly elevated micronucleus frequencies were also observed in NCEs in male and female mice administered 675, 1,350, or 2,700 mg/kg. A dose-related increase in the percentage of PCEs was also observed in all dosed groups of males and females, indicating that erythropoiesis was stimulated in animals treated with salicylazosulfapyridine.

Salicylazosulfapyridine was subsequently tested for induction of Abs in bone marrow cells of male mice following single gavage administrations of 250 to 1,000 mg/kg (Table E5; B shop *et al.*, 1990). These doses, selected on the basis of results from a preliminary range-finding study, were less than all but the lowest dose tested in the 13-week study. No significant increases in Abs were noted in the two trials conducted.

Subsequent micronucleus tests with salicylazosulfapyridine confirmed the positive response observed in the initial 13-week peripheral blood test. A small but significant increase in PCEs was observed in the bone marrow of male mice administered 250 to 2,000 mg salicylazosulfapyridine/kg body weight in corn oil by gavage, twice at 24-hour intervals; sampling was performed 24 hours after administration of the second dose (Table E6; Bishop *et al.*, 1990).

A specialized micronucleus test was performed with salicylazosulfapyridine to investigate the aneuploidy-inducing potential of the compound, implied by the positive results from micronuclei assays (which detect both numerical and structural chromosomal aberrations) and the negative results from the *in vitro* and *in vivo* Abs assays (which detect only structural damage). In this micronucleus/kinetochore-staining assay (Table E7; Witt *et al.*, 1992b), salicylazosulfapyridine induced dose-related increases in the number of total micronucleated PCEs; in addition, the micronuclei that were induced were predominantly kinetochore-positive (contained a fluorescent signal indicating the presence of a kinetochore and presumably, therefore, an entire chromosome rather than a fragment). Salicylazosulfapyridine also induced a significant increase in kinetochore-negative micronuclei, but only at the highest dose tested in the second trial; the majority of induced micronuclei stained positive for the presence of a kinetochore. These results imply that salicylazosulfapyridine produces aneuploidogenic rather than clastogenic chromosomal effects.

Because positive results were observed in micronucleus experiments that employed multiple dosing protocols (standard for a micronucleus assay), and because results from the single-dose chromosomal aberrations protocol were negative, salicylazosulfapyridine was tested for induction of micronuclei and chromosomal aberrations in nonstandard protocols that were designed to measure the influence of treatment schedules. Table E8 presents results from a series of bone marrow micronucleus tests performed with male and female mice. Significant increases in micronucleated PCEs were observed in each of two trials in which female mice were dosed with salicylazosulfapyridine three times by gavage. Male mice were administered salicylazosulfapyridine either by single (Trial 1) or triple (Trial 2) gavage protocols. Results of the first experiment were negative, whereas results obtained in the second trail using the triple-treatment protocol were positive, thus underscoring the relationship between dosing schedule and detection of a genotoxic response.

Salicylazosulfapyridine was further tested for induction of chromosomal aberrations in a nonstandard, triple treatment protocol that used three gavage administrations separated by 24-hour intervals in an attempt to mimic the same exposure environment that produced the positive micronucleus test results. The highest dose used in this experiment was 4,000 mg/kg. Again, no induction of Abs by salicylazosulfapyridine was

noted in mouse bone marrow cells (Table E9). These results further support the hypothesis that salicylazosulfapyridine is aneuploidogenic.

Because the carcinogenicity of salicylazosulfapyridine was being evaluated by the NTP in both rats and mice, a micronucleus test was also performed in male rats using the triple-treatment protocol (Table E10). The overall results were considered to be equivocal because the weakly positive response obtained in the first trial with doses as great as 2,700 mg/kg did not repeat in the second trial when doses as great as 3,000 mg/kg were tested. Thus, there appears to be a species difference in response to bone marrow erythrocyte micronucleus induction by salicylazosulfapyridine.

TABLE E1
Mutagenicity of Salicylazosulfapyridine in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA100	0	94 ± 6.7	96 ± 4.6	100 ± 8.7	124 ± 9.0	132 ± 4.7
	33			105 ± 10.4		105 ± 2.0
	100	101 ± 4.8	97 ± 4.8	102 ± 2.4	118 ± 6.6	96 ± 3.2
	333	78 ± 1.8	94 ± 6.4	107 ± 4.7	101 ± 8.5	113 ± 8.5
	1,000	93 ± 1.2	101 ± 4.4	117 ± 9.5	137 ± 8.7	116 ± 5.9
	3,333	87 ± 3.8	94 ± 4.3[c]	103 ± 13.8	101 ± 3.8[c]	117 ± 5.3
	6,666	84 ± 4.4[c]	102 ± 7.0[c]		102 ± 7.0[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,276 ± 14.0	1,264 ± 64.3	2,153 ± 47.9	1,038 ± 35.8	787 ± 16.7
TA1535	0	13 ± 1.2	14 ± 0.9	11 ± 2.8	14 ± 1.5	14 ± 0.6
	33			10 ± 2.4		11 ± 1.7
	100	16 ± 1.2	13 ± 1.5	14 ± 4.1	15 ± 1.2	13 ± 2.5
	333	15 ± 2.0	9 ± 0.7	15 ± 2.6	10 ± 2.0	12 ± 0.9
	1,000	19 ± 3.2	12 ± 2.0	11 ± 0.7	10 ± 0.0	14 ± 1.7
	3,333	16 ± 0.7	12 ± 0.3[c]	11 ± 3.2	11 ± 1.9[c]	12 ± 1.5
	6,666	17 ± 1.9[c]	17 ± 2.1[c]		17 ± 0.9[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		1,063 ± 12.5	153 ± 9.5	461 ± 16.3	117 ± 11.7	165 ± 4.4
TA97	0	89 ± 7.0	138 ± 3.8	144 ± 6.1	148 ± 9.5	138 ± 16.2
	33			144 ± 12.2		154 ± 3.6
	100	88 ± 3.8	143 ± 9.8	146 ± 11.9	119 ± 7.0	140 ± 12.5
	333	85 ± 6.0	129 ± 4.7	130 ± 2.1	151 ± 3.0	158 ± 3.8
	1,000	83 ± 1.5	149 ± 4.4	134 ± 4.9	140 ± 3.4	163 ± 1.5
	3,333	86 ± 5.5	113 ± 10.8[c]	140 ± 4.2	111 ± 7.2[c]	143 ± 7.8
	6,666	83 ± 2.8[c]	91 ± 4.4[c]		109 ± 6.5[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		542 ± 20.5	904 ± 14.5	1,039 ± 17.2	736 ± 29.6	489 ± 24.3
TA98	0	25 ± 2.0	39 ± 3.8	32 ± 1.2	33 ± 3.5	31 ± 3.2
	33			28 ± 6.1		31 ± 5.2
	100	27 ± 3.6	35 ± 1.5	28 ± 2.0	38 ± 2.6	30 ± 1.5
	333	29 ± 2.9	35 ± 3.4	34 ± 4.7	43 ± 1.5	25 ± 3.9
	1,000	24 ± 3.4	40 ± 1.7	37 ± 0.7	44 ± 1.8	31 ± 3.0
	3,333	24 ± 2.0	21 ± 1.5[c]	29 ± 3.1	29 ± 3.2	17 ± 0.9
	6,666	10 ± 1.9	17 ± 1.2[c]		21 ± 1.3[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		1,292 ± 65.1	1,720 ± 32.0	2,086 ± 18.8	1,210 ± 11.3	699 ± 8.4

[a] Study performed at Microbiological Associates, Inc. The detailed protocol and these data are presented in Zeiger *et al.* (1988).
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Salicylazosulfapyridine[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Summary: Negative								
Dimethylsulfoxide		50	1,033	475	0.45	9.5	26.0	
Mitomycin-C	0.0007	50	1,039	667	0.64	13.3	26.0	39.61*
	0.0050	10	207	247	1.19	24.7	26.0	159.50*
Salicylazosulfapyridine	1.6	50	1,029	381	0.37	7.6	26.0	-19.48
	16.0	50	1,032	395	0.38	7.9	26.0	-16.76
	50.0	50	1,030	388	0.37	7.8	26.0	-18.08
	160.0	50	1,022	444	0.43	8.9	26.0	-5.52
					P=0.835[c]			
+S9								
Summary: Negative								
Dimethylsulfoxide		50	1,047	398	0.38	8.0	26.0	
Cyclophosphamide	0.1000	50	1,049	485	0.46	9.7	26.0	21.63*
	0.6000	10	210	137	0.65	13.7	26.0	71.62*
Salicylazosulfapyridine	50	50	1,034	398	0.38	8.0	26.0	1.26
	160	50	1,036	415	0.40	8.3	26.0	5.38
	500	50	1,034	364	0.35	7.3	26.0	-7.39
	1,000	50	1,029	380	0.36	7.6	26.0	-2.85
					P=0.825			

* Positive response (≥20% increase over solvent control)
[a] Study performed at Environmental Health Research and Testing, Inc. The detailed protocol and these data are presented in Bishop *et al.* (1990). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine.
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Salicylazosulfapyridine[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 12.0 hours					Harvest time: 13.0 hours				
Summary: Negative					Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	1	0.01	0.5		200	4	0.02	1.5
Mitomycin-C					Cyclophosphamide				
0.125	200	54	0.27	21.5	5.0	200	29	0.15	13.5
0.250	50	33	0.66	34.0	7.5	50	23	0.46	42.0
Salicylazosulfapyridine					Salicylazosulfapyridine				
300	200	0	0.00	0.0	300	200	1	0.01	0.5
500	200	1	0.01	0.5	500	200	1	0.01	0.5
1,000	200	2	0.01	1.0	1,000	200	0	0.00	0.0
				P=0.182[b]					P=0.965

[a] Study performed at Environmental Health Research and Testing, Inc. The detailed protocol and these data are presented in Bishop *et al.* (1990). Abs=aberrations.
[b] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE E4
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with Salicylazosulfapyridine by Gavage for 13 Weeks[a]

Compound	Dose (mg/kg)	Micronucleated Cells/1,000 Cells PCEs	Micronucleated Cells/1,000 Cells NCEs	PCEs (%)	Number of Mice
Male					
Salicylazosulfapyridine					
	0[b]	1.71 ± 0.32	1.07 ± 0.08	2.33 ± 0.14	10
	675	2.27 ± 0.42	2.46 ± 0.17**	3.94 ± 0.16**	10
	1,350	3.42 ± 0.45	2.94 ± 0.22**	4.35 ± 0.21**	10
	2,700	3.66 ± 0.41**	2.78 ± 0.20**	5.23 ± 0.24**	10
		P=0.001[c]	P<0.0001[d]	P<0.0001[e]	
Female					
Salicylazosulfapyridine					
	0	1.45 ± 0.21	0.86 ± 0.01	1.62 ± 0.15	10
	675	2.30 ± 0.41	1.93 ± 0.18**	2.51 ± 0.20**	10
	1,350	2.48 ± 0.54	2.24 ± 0.19**	2.76 ± 0.17**	10
	2,700	2.72 ± 0.36*	2.04 ± 0.12**	3.14 ± 0.28**	10
		P=0.0315	P<0.0001	P<0.0001	

* P=0.026
** P≤0.01
[a] Study performed at USDA, Western Regional Research Center. The detailed protocol and these data are presented in Bishop *et al.* (1990). PCE=polychromatic erythrocyte; NCE=normochromatic erythrocyte. At least 2,000 PCEs and 10,000 NCEs were scored for micronuclei per animal. Data are presented as mean ± standard error.
[b] Corn oil (solvent) control
[c] Cochran-Armitage trend test
[d] Linear contrasts from analysis of variance
[e] Analysis of variance

TABLE E5
Induction of Chromosomal Aberrations in Bone Marrow Cells of Male Mice Treated Once with Salicylazosulfapyridine by Gavage: Standard Protocol[a]

Compound	Dose (mg/kg)	Total Abs	Abs/Cell (without gaps)	Cells with Abs[b] (%) (without gaps)
Trial 1				
Corn oil[c]		1	0.003	0.250 ± 0.25
Dimethylbenz(a)anthracene[d]	100	12	0.030	2.750 ± 0.92
Salicylazosulfapyridine	250	3	0.008	0.750 ± 0.37
	500	7	0.018	1.750 ± 1.49
	1,000	0	0	0.00 ± 0.00
				P=0.637[e]
Trial 2				
Corn oil		5	0.013	1.250 ± 0.53
Dimethylbenz(a)anthracene	100	24	0.060	5.000 ± 1.51
Salicylazosulfapyridine	250	4	0.010	1.000 ± 0.65
	500	3	0.008	0.750 ± 0.37
	1,000	0	0	0.00 ± 0.00
				P=0.984

[a] Study performed at Environmental Health Research and Testing, Inc. The detailed protocol and these data are presented in Bishop *et al.* (1990). Fifty first-division metaphase cells were scored in each of eight animals in each dose group. Abs=chromosomal aberrations.
[b] Data are presented as mean ± standard error.
[c] Solvent control
[d] Positive control
[e] One-tailed trend analysis (Margolin *et al.*, 1986); significant at $P < 0.025$

TABLE E6
Frequency of Micronuclei in Polychromatic Bone Marrow Cells of Male Mice Treated Twice with Salicylazosulfapyridine by Gavage: Initial Assay[a]

Dose (mg/kg)	Micronucleated Cells/1,000 PCEs			Mice per Dose
	Trial 1	Trial 2	Trial 3	
Corn oil[b]	1.4 ± 0.3	1.1 ± 0.4	0.6 ± 0.2	5
Dimethylbenz(a)anthracene[c]				
12.5			1.8 ± 0.2	5
100	29.5 ± 4.4	34.5 ± 4.0	33.3 ± 4.9	5
Salicylazosulfapyridine				
250	2.1 ± 0.7	1.2 ± 0.3		5
500	2.2 ± 1.1	2.0 ± 0.8		5
1,000	2.9 ± 0.8	2.0 ± 0.6	1.8 ± 0.2*	5
2,000			1.8 ± 0.6*	5
	P=0.770[d]	P=0.032	P=0.01	

* Significantly different (P≤0.01) from the solvent control
[a] Study performed at Environmental Health Research and Testing, Inc. The protocol and these data are presented in Bishop *et al.* (1990). PCE=polychromatic erythrocyte; 2,000 PCEs were scored in each of five animals in each dose group. Data are presented as mean ± standard error.
[b] Solvent control
[c] Positive control
[d] Significance of micronucleated cells/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (Margolin *et al.*, 1990).

TABLE E7
Frequency of Kinetochore Positive and Kinetochore Negative Micronuclei in Polychromatic Bone Marrow Cells of Male Mice Treated Three Times with Salicylazosulfapyridine by Gavage[a]

Compound	Dose (mg/kg)	Micronucleated Cells/1,000 PCEs		
		Total	Kinetochore Negative	Kinetochore Positive
Trial 1				
Triethylenemelamine[b]				
	1.0	100.2 ± 4.94	96.3 ± 4.68	3.9 ± 0.58
Vincristine sulfate[c]				
	0.125	83.0 ± 2.91	6.7 ± 0.94	76.3 ± 3.00
Salicylazosulfapyridine				
	0[d]	1.6 ± 0.19	1.6 ± 0.19	0.0
	1,875	4.5 ± 0.52	2.2 ± 0.20	2.3 ± 0.44
	2,721	5.3 ± 0.34	2.8 ± 0.34	2.5 ± 0.27
	3,649	6.3 ± 0.68	2.1 ± 0.29	4.2 ± 0.58
		P<0.001[e]	P=0.122	P<0.001
Trial 2				
Triethylenemelamine				
	1.0	63.1 ± 6.54	54.0 ± 4.16	9.1 ± 2.63
Vincristine sulfate				
	0.125	79.9 ± 6.67	3.9 ± 1.24	76.0 ± 5.62
Salicylazosulfapyridine				
	0	1.1 ± 0.29	0.8 ± 0.26	0.3 ± 0.12
	1,289	7.2 ± 0.20	1.3 ± 0.26	5.9 ± 0.33
	2,797	9.1 ± 0.19	1.3 ± 0.26	7.8 ± 0.26
	5,634	10.7 ± 0.75	2.7 ± 0.60	8.0 ± 0.22
		P<0.001	P<0.005	P<0.001

[a] Study performed at SITEK, Inc. The detailed protocol and these data are presented by Witt *et al.* (1992b). PCE=polychromatic erythrocyte; 2,000 PCEs were scored in each of five animals in each dose group. Data are presented as mean ± standard error.
[b] Clastogenic positive control
[c] Aneuploidogenic positive control
[d] Corn oil (solvent) control
[e] Trend test

TABLE E8
Frequency of Micronuclei in Polychromatic Bone Marrow Cells of Mice Treated with Salicylazosulfapyridine by Gavage: Subsequent Assay[a]

Dose (mg/kg)	Micronucleated Cells/1,000 PCEs		Mice per Dose
	Trial 1	Trial 2	
Male			
	1 × Gavage[b]	3 × Gavage	
Dimethylbenz(a)anthracene[c]			
12.5	3.8 ± 0.58*	5.3 ± 0.82*	5
Salicylazosulfapyridine			
0[d]	0.9 ± 0.29	1.5 ± 0.42	5
1,000	0.3 ± 0.12	4.3 ± 0.62*	5
2,000	0.9 ± 0.29	4.7 ± 0.70*	5
4,000	0.8 ± 0.26	3.9 ± 0.33*	5
	P=0.389[e]	P=0.010	
Female			
	3 × Gavage	3 × Gavage	
Dimethylbenz(a)anthracene			
12.5	3.8 ± 0.77*	1.5 ± 0.59[f]	5
Salicylazosulfapyridine			
0	0.4 ± 0.29	1.0 ± 0.27	5
1,000	5.4 ± 0.80*	5.2 ± 0.54*	5
2,000	6.7 ± 0.58*	7.5 ± 0.98*	5
4,000	4.8 ± 0.78	5.7 ± 0.96*	5
	P<0.001	P<0.001	

* Significantly different (P<0.001) from the solvent control
a Study performed at Environmental Health Research and Testing, Inc. The protocol is presented in Shelby *et al.* (1993). PCE=polychromatic erythrocyte; 2,000 PCEs were scored in each of five animals in each dose group. Data are presented as mean ± standard error.
b This trial was performed using a single gavage administration of salicylazosulfapyridine instead of the triple treatment protocol used in the other trials presented in this table.
c Positive control
d Corn oil (solvent) control
e Significance of micronucleated cells/1,000 PCEs tested by the one-tailed trend test (Margolin *et al.*, 1990).
f Positive control failure; experiment considered valid due to response registered in the treated groups.

TABLE E9
Induction of Chromosomal Aberrations in Bone Marrow Cells of Male Mice Treated with Salicylazosulfapyridine by Gavage: Nonstandard Protocol[a]

Compound	Dose (mg/kg)	Total Abs	Abs/Cell (without gaps)	Cells with Abs[b] (%) (without gaps)
Trial 1				
Dimethylbenz(a)anthracene[c]	150	12.5	0.09	8.00 ± 1.51*
Salicylazosulfapyridine[d]	0[e]	0.8	0.00	0.50 ± 0.33
	1,000	1.8	0.01	1.25 ± 0.53
	2,000	1.9	0.01	1.00 ± 0.53
	4,000	1.1	0.01	0.75 ± 0.37
				P=0.464[f]
Trial 2				
Dimethylbenz(a)anthracene	100	18.8	0.17	15.25 ± 3.14*
Salicylazosulfapyridine[g]	0	1.3	0.00	0.50 ± 0.33
	1,000	1.1	0.00	0.50 ± 0.33
	2,000	0.3	0.00	0.25 ± 0.25
	4,000	0.8	0.00	0.00 ± 0.00
				P=0.925

* Significantly different ($P<0.001$) from the solvent control
[a] Study performed at Environmental Health Research and Testing, Inc. Fifty first-division metaphase cells were scored in each of eight animals in each dose group. Abs=chromosomal aberrations.
[b] Data are presented as mean ± standard error.
[c] Positive control
[d] Results from single-dose gavage treatment
[e] Corn oil (solvent) control
[f] Trend test
[g] Results from triple-dose gavage treatment

TABLE E10
Frequency of Micronuclei in Polychromatic Bone Marrow Cells of Male Rats Treated Three Times with Salicylazosulfapyridine by Gavage[a]

Dose (mg/kg)	Micronucleated Cells/1,000 PCEs		Rats per Dose
	Trial 1	Trial 2	
Corn oil[b]	0.8 ± 0.2	2.2 ± 0.6	5
Dimethylbenz(a)anthracene[c]			
50	5.2 ± 1.7	11.9 ± 1.4	5
100	7.7 ± 1.7		5
Salicylazosulfapyridine			
337.5	0.7 ± 0.5		5
675.0	2.1 ± 0.4		5
1,000		1.8 ± 0.3	5
1,350	0.6 ± 0.2		5
2,000		1.3 ± 0.3	5
2,700	2.4 ± 0.5*		5
3,000		1.8 ± 0.5	5
	P=0.005[d]	P=0.817	

* Significantly different (P=0.004) from the solvent control
[a] Study performed at Integrated Laboratory Systems, Inc. The protocol is presented in Shelby *et al.* (1993). PCE=polychromatic erythrocyte; 2,000 PCEs were scored in each of five animals in each dose group. Data are presented as mean ± standard error.
[b] Solvent control
[c] Positive control
[d] Significance of micronucleated cells/1,000 PCEs tested by the one-tailed trend test (Margolin *et al.*, 1990).

APPENDIX F
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
n	5	5	5	5
Male				
Necropsy body wt	215 ± 5	204 ± 4	160 ± 4**	147 ± 4**
Brain				
Absolute	1.803 ± 0.016	1.770 ± 0.022	1.715 ± 0.015**	1.680 ± 0.022**
Relative	8.41 ± 0.14	8.69 ± 0.20	10.76 ± 0.25**	11.49 ± 0.28**
Heart				
Absolute	0.718 ± 0.011	0.708 ± 0.025	0.572 ± 0.017**	0.510 ± 0.014**
Relative	3.35 ± 0.04	3.47 ± 0.12	3.59 ± 0.10	3.48 ± 0.06
R. Kidney				
Absolute	0.787 ± 0.025	0.762 ± 0.030	0.691 ± 0.030*	0.637 ± 0.010**
Relative	3.67 ± 0.09	3.73 ± 0.10	4.33 ± 0.20**	4.35 ± 0.08**
Liver				
Absolute	10.067 ± 0.282	8.653 ± 0.218**	6.832 ± 0.303**	7.298 ± 0.254**
Relative	46.87 ± 0.81	42.39 ± 0.41	42.93 ± 2.33	49.78 ± 1.14
Lung				
Absolute	1.181 ± 0.108	1.158 ± 0.050	0.930 ± 0.030*	0.921 ± 0.056*
Relative	5.48 ± 0.43	5.68 ± 0.25	5.83 ± 0.17	6.28 ± 0.33
R. Testis				
Absolute	1.217 ± 0.028	1.182 ± 0.036	1.076 ± 0.033**	1.028 ± 0.027**
Relative	5.67 ± 0.13	5.79 ± 0.11	6.75 ± 0.25**	7.01 ± 0.03**
Thymus				
Absolute	0.455 ± 0.027	0.404 ± 0.020	0.236 ± 0.017**	0.133 ± 0.004**
Relative	2.12 ± 0.10	1.98 ± 0.09	1.47 ± 0.09**	0.91 ± 0.03**
Female				
Necropsy body wt	147 ± 3	133 ± 2**	129 ± 4**	111 ± 3**
Brain				
Absolute	1.714 ± 0.031	1.665 ± 0.025	1.638 ± 0.037	1.584 ± 0.015**
Relative	11.64 ± 0.17	12.58 ± 0.25*	12.73 ± 0.15**	14.36 ± 0.35**
Heart				
Absolute	0.535 ± 0.025	0.491 ± 0.016	0.494 ± 0.026	0.443 ± 0.033
Relative	3.62 ± 0.13	3.71 ± 0.09	3.84 ± 0.18	4.00 ± 0.23
R. Kidney				
Absolute	0.533 ± 0.013	0.547 ± 0.009	0.543 ± 0.011	0.539 ± 0.018
Relative	3.62 ± 0.06	4.13 ± 0.08**	4.22 ± 0.10**	4.88 ± 0.12**
Liver				
Absolute	5.573 ± 0.051	5.182 ± 0.072	5.510 ± 0.320	6.019 ± 0.277
Relative	37.87 ± 0.75	39.14 ± 0.66	42.73 ± 1.72*	54.34 ± 1.51**
Lung				
Absolute	0.936 ± 0.023[b]	0.823 ± 0.025**	0.863 ± 0.022**	0.755 ± 0.009**
Relative	6.42 ± 0.17[b]	6.23 ± 0.28	6.72 ± 0.19	6.84 ± 0.14
Thymus				
Absolute	0.362 ± 0.013	0.306 ± 0.019	0.269 ± 0.023**	0.132 ± 0.020**
Relative	2.45 ± 0.06	2.32 ± 0.16	2.08 ± 0.16	1.21 ± 0.21**

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168.8 mg/kg	337.5 mg/kg
n	10	10	10	10
Male				
Necropsy body wt	357 ± 7	344 ± 4	345 ± 5	341 ± 6
Brain				
Absolute	1.968 ± 0.014	1.952 ± 0.015	1.964 ± 0.015	1.941 ± 0.020
Relative	5.53 ± 0.10	5.68 ± 0.08	5.71 ± 0.11	5.70 ± 0.09
Heart				
Absolute	0.994 ± 0.016	1.004 ± 0.008	1.005 ± 0.017	1.022 ± 0.027
Relative	2.79 ± 0.04	2.92 ± 0.04	2.92 ± 0.05	3.00 ± 0.07*
R. Kidney				
Absolute	1.075 ± 0.023	1.073 ± 0.025	1.094 ± 0.027	1.089 ± 0.028
Relative	3.01 ± 0.03	3.12 ± 0.07	3.18 ± 0.07	3.19 ± 0.07
Liver				
Absolute	13.779 ± 0.247	13.266 ± 0.272	13.389 ± 0.313	12.875 ± 0.267
Relative	38.66 ± 0.48	38.57 ± 0.73	38.84 ± 0.63	37.73 ± 0.51
Lung				
Absolute	1.692 ± 0.043	1.617 ± 0.047	1.733 ± 0.057	1.647 ± 0.038
Relative	4.74 ± 0.08	4.70 ± 0.11	5.02 ± 0.10	4.83 ± 0.12
R. Testis				
Absolute	1.485 ± 0.028	1.505 ± 0.016	1.501 ± 0.018	1.467 ± 0.035
Relative	4.17 ± 0.06	4.38 ± 0.06	4.36 ± 0.10	4.30 ± 0.10
Thymus				
Absolute	0.323 ± 0.016	0.283 ± 0.013	0.291 ± 0.012	0.286 ± 0.024[b]
Relative	0.91 ± 0.05	0.82 ± 0.04	0.84 ± 0.03	0.84 ± 0.07[b]
Female				
Necropsy body wt	199 ± 3	190 ± 2**	189 ± 2**	188 ± 2**
Brain				
Absolute	1.817 ± 0.020	1.792 ± 0.019	1.763 ± 0.015	1.814 ± 0.017
Relative	9.14 ± 0.11	9.44 ± 0.11	9.37 ± 0.14	9.67 ± 0.15*
Heart				
Absolute	0.660 ± 0.014	0.643 ± 0.011	0.639 ± 0.011	0.661 ± 0.014
Relative	3.32 ± 0.05	3.39 ± 0.06	3.39 ± 0.06	3.52 ± 0.07
R. Kidney				
Absolute	0.616 ± 0.010	0.621 ± 0.009	0.605 ± 0.009	0.660 ± 0.011**
Relative	3.09 ± 0.03	3.27 ± 0.04*	3.21 ± 0.05*	3.52 ± 0.04**
Liver				
Absolute	6.134 ± 0.151	6.141 ± 0.135	6.173 ± 0.165	6.467 ± 0.176
Relative	30.81 ± 0.55	32.32 ± 0.54	32.72 ± 0.68*	34.41 ± 0.73**
Lung				
Absolute	1.178 ± 0.046	1.190 ± 0.037	1.188 ± 0.024	1.147 ± 0.036
Relative	5.91 ± 0.20	6.26 ± 0.16	6.30 ± 0.11	6.11 ± 0.21
Thymus				
Absolute	0.241 ± 0.008	0.253 ± 0.011	0.238 ± 0.011	0.252 ± 0.008
Relative	1.21 ± 0.04	1.33 ± 0.06	1.26 ± 0.05	1.34 ± 0.04

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 6-Month Interim Evaluation in the Stop-Exposure Evaluation of Salicylazosulfapyridine[a]

	Vehicle Control	337.5 mg/kg
n	10	10
Necropsy body wt	396 ± 9	382 ± 9
R. Kidney		
Absolute	1.335 ± 0.026	1.339 ± 0.038
Relative	3.37 ± 0.05	3.50 ± 0.06
Liver		
Absolute	14.775 ± 0.518	14.165 ± 0.461
Relative	37.26 ± 0.88	37.04 ± 0.71
Spleen		
Absolute	0.676 ± 0.022	0.656 ± 0.018
Relative	1.71 ± 0.05	1.72 ± 0.02
R. Testis		
Absolute	1.442 ± 0.023	1.449 ± 0.026
Relative	3.65 ± 0.09	3.80 ± 0.06
Thyroid Gland		
Absolute	0.012 ± 0.001	0.013 ± 0.001
Relative	0.03 ± 0.00	0.03 ± 0.00

[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error). Differences from the vehicle control were not significant by Williams' or Dunnett's test.

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
n	10	10	10	10	10
Male					
Necropsy body wt	491 ± 8	478 ± 10	485 ± 8	459 ± 8*	488 ± 11
R. Kidney					
Absolute	1.639 ± 0.061	1.556 ± 0.060	1.586 ± 0.035	1.590 ± 0.029	1.563 ± 0.028
Relative	3.33 ± 0.10	3.25 ± 0.10	3.27 ± 0.07	3.47 ± 0.05	3.21 ± 0.07
Liver					
Absolute	16.660 ± 0.544	15.488 ± 0.483	15.895 ± 0.399	15.713 ± 0.370	15.125 ± 0.421*
Relative	33.89 ± 0.92	32.42 ± 0.84	32.76 ± 0.57	34.24 ± 0.69	30.97 ± 0.40**
Spleen					
Absolute	0.803 ± 0.026	0.787 ± 0.033	0.739 ± 0.031	0.727 ± 0.015	0.747 ± 0.022[b]
Relative	1.63 ± 0.04	1.65 ± 0.07	1.52 ± 0.06	1.58 ± 0.02	1.52 ± 0.02*[b]
L. Testis					
Absolute	1.641 ± 0.055	1.660 ± 0.068	1.794 ± 0.131	1.842 ± 0.167	1.690 ± 0.035
Relative	3.34 ± 0.08	3.47 ± 0.11	3.71 ± 0.28	4.01 ± 0.35	3.47 ± 0.09
R. Testis					
Absolute	1.559 ± 0.040	1.634 ± 0.072	1.739 ± 0.177	1.743 ± 0.157	1.750 ± 0.207
Relative	3.17 ± 0.06	3.43 ± 0.17	3.58 ± 0.35	3.79 ± 0.32	3.64 ± 0.50
Thyroid Gland					
Absolute	0.025 ± 0.003	0.018 ± 0.003	0.016 ± 0.001*	0.022 ± 0.002	0.020 ± 0.002
Relative	0.05 ± 0.01	0.04 ± 0.00	0.03 ± 0.00*	0.05 ± 0.00	0.04 ± 0.00
Female					
Necropsy body wt	265 ± 4	261 ± 4	253 ± 4	237 ± 8**	
R. Kidney					
Absolute	0.800 ± 0.017	0.839 ± 0.021	0.829 ± 0.019	0.908 ± 0.038*	
Relative	3.02 ± 0.07	3.22 ± 0.06*	3.28 ± 0.05*	3.83 ± 0.08**	
Liver					
Absolute	7.986 ± 0.188	8.121 ± 0.136	8.132 ± 0.352	8.023 ± 0.300	
Relative	30.12 ± 0.62	31.17 ± 0.50	32.10 ± 1.23	33.92 ± 0.98**	
Spleen					
Absolute	0.467 ± 0.006[b]	0.507 ± 0.041	0.454 ± 0.011[b]	0.431 ± 0.016[b]	
Relative	1.78 ± 0.03[b]	1.95 ± 0.17	1.79 ± 0.03[b]	1.81 ± 0.07[b]	
Thyroid Gland					
Absolute	0.016 ± 0.001	0.014 ± 0.001	0.014 ± 0.001	0.014 ± 0.001	
Relative	0.06 ± 0.00	0.05 ± 0.00	0.06 ± 0.00	0.06 ± 0.00	

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Male				
n	5	5	5	5
Necropsy body wt	23.6 ± 0.4	23.0 ± 0.4	24.2 ± 0.5	24.1 ± 0.4
Brain				
Absolute	0.455 ± 0.004	0.452 ± 0.004	0.464 ± 0.008	0.464 ± 0.004
Relative	19.27 ± 0.33	19.62 ± 0.20	19.19 ± 0.34	19.24 ± 0.46
Heart				
Absolute	0.122 ± 0.002	0.117 ± 0.004	0.136 ± 0.003*	0.122 ± 0.003
Relative	5.19 ± 0.07	5.10 ± 0.15	5.61 ± 0.07	5.04 ± 0.16
R. Kidney				
Absolute	0.211 ± 0.012	0.205 ± 0.008	0.217 ± 0.004	0.201 ± 0.006
Relative	8.93 ± 0.37	8.92 ± 0.27	8.97 ± 0.08	8.34 ± 0.18
Liver				
Absolute	1.263 ± 0.043	1.254 ± 0.048	1.378 ± 0.064	1.395 ± 0.058
Relative	53.45 ± 1.19	54.41 ± 1.42	56.91 ± 2.24	57.74 ± 1.83
Lung				
Absolute	0.208 ± 0.015	0.204 ± 0.017	0.219 ± 0.006	0.201 ± 0.005
Relative	8.79 ± 0.63	8.83 ± 0.67	9.06 ± 0.27	8.35 ± 0.22
R. Testis				
Absolute	0.099 ± 0.003	0.091 ± 0.006	0.099 ± 0.003	0.100 ± 0.001
Relative	4.18 ± 0.13	3.96 ± 0.21	4.09 ± 0.12	4.16 ± 0.11
Thymus				
Absolute	0.048 ± 0.006	0.046 ± 0.002	0.049 ± 0.006	0.042 ± 0.003
Relative	2.01 ± 0.24	1.99 ± 0.10	2.03 ± 0.21	1.75 ± 0.12
Female				
n	5	4	5	4
Necropsy body wt	19.6 ± 0.3	20.8 ± 0.2	20.1 ± 0.3	20.3 ± 0.7
Brain				
Absolute	0.458 ± 0.010	0.456 ± 0.008	0.459 ± 0.006	0.450 ± 0.007
Relative	23.43 ± 0.72	21.95 ± 0.49	22.80 ± 0.40	22.29 ± 0.82
Heart				
Absolute	0.108 ± 0.005	0.105 ± 0.002	0.114 ± 0.004	0.112 ± 0.005
Relative	5.52 ± 0.30	5.05 ± 0.11	5.64 ± 0.15	5.56 ± 0.37
R. Kidney				
Absolute	0.159 ± 0.003	0.157 ± 0.002	0.157 ± 0.004	0.153 ± 0.003
Relative	8.12 ± 0.25	7.57 ± 0.16	7.78 ± 0.14	7.59 ± 0.27
Liver				
Absolute	1.060 ± 0.040	1.194 ± 0.027	1.154 ± 0.030	1.228 ± 0.084
Relative	54.17 ± 2.15	57.46 ± 1.11	57.30 ± 1.59	60.43 ± 2.43
Lung				
Absolute	0.184 ± 0.007	0.210 ± 0.013	0.222 ± 0.019	0.207 ± 0.009
Relative	9.40 ± 0.50	10.09 ± 0.61	10.98 ± 0.88	10.22 ± 0.47
Thymus				
Absolute	0.071 ± 0.004	0.065 ± 0.003	0.071 ± 0.003	0.063 ± 0.003
Relative	3.61 ± 0.22	3.14 ± 0.15	3.55 ± 0.19	3.10 ± 0.10

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
n	10	10	10	10
Male				
Necropsy body wt	30.2 ± 0.5	29.8 ± 0.4	29.2 ± 0.4	29.9 ± 0.5
Brain				
Absolute	0.457 ± 0.002	0.464 ± 0.003	0.466 ± 0.002*	0.457 ± 0.002
Relative	15.17 ± 0.23	15.56 ± 0.23	16.02 ± 0.28	15.34 ± 0.27
Heart				
Absolute	0.142 ± 0.004	0.150 ± 0.003	0.149 ± 0.002	0.154 ± 0.005
Relative	4.71 ± 0.12	5.05 ± 0.11	5.11 ± 0.08	5.17 ± 0.15*
R. Kidney				
Absolute	0.259 ± 0.009	0.264 ± 0.007	0.260 ± 0.005	0.253 ± 0.005
Relative	8.56 ± 0.24	8.84 ± 0.16	8.91 ± 0.20	8.47 ± 0.15
Liver				
Absolute	1.244 ± 0.026	1.491 ± 0.044**	1.531 ± 0.023**	1.636 ± 0.047**
Relative	41.24 ± 0.80	49.92 ± 1.09**	52.54 ± 0.88**	54.71 ± 0.91**
Lung				
Absolute	0.187 ± 0.006	0.203 ± 0.007	0.193 ± 0.005	0.198 ± 0.005
Relative	6.20 ± 0.15	6.81 ± 0.26	6.61 ± 0.16	6.62 ± 0.14
R. Testis				
Absolute	0.115 ± 0.003	0.112 ± 0.002	0.109 ± 0.004	0.111 ± 0.002
Relative	3.82 ± 0.11	3.74 ± 0.06	3.74 ± 0.13	3.73 ± 0.06
Thymus				
Absolute	0.030 ± 0.004	0.036 ± 0.003	0.036 ± 0.002	0.034 ± 0.002
Relative	0.98 ± 0.13	1.21 ± 0.10	1.23 ± 0.06	1.14 ± 0.06
Female				
Necropsy body wt	26.1 ± 0.5	26.2 ± 0.3	26.0 ± 0.3	26.1 ± 0.4
Brain				
Absolute	0.478 ± 0.017	0.472 ± 0.005	0.466 ± 0.004	0.465 ± 0.005
Relative	18.43 ± 0.74	18.03 ± 0.18	17.95 ± 0.23	17.83 ± 0.19
Heart				
Absolute	0.122 ± 0.003	0.133 ± 0.003	0.134 ± 0.008	0.127 ± 0.002
Relative	4.69 ± 0.12	5.09 ± 0.11	5.16 ± 0.31	4.88 ± 0.06
R. Kidney				
Absolute	0.185 ± 0.003	0.185 ± 0.004	0.180 ± 0.003	0.188 ± 0.004
Relative	7.10 ± 0.12	7.06 ± 0.10	6.92 ± 0.08	7.22 ± 0.14
Liver				
Absolute	1.314 ± 0.029	1.488 ± 0.034**	1.498 ± 0.031**	1.634 ± 0.038**
Relative	50.50 ± 1.02	56.81 ± 0.89**	57.68 ± 1.13**	62.69 ± 1.66**
Lung				
Absolute	0.195 ± 0.007	0.192 ± 0.006	0.186 ± 0.006	0.192 ± 0.005
Relative	7.50 ± 0.32	7.32 ± 0.23	7.16 ± 0.18	7.38 ± 0.21
Thymus				
Absolute	0.054 ± 0.002	0.046 ± 0.004	0.047 ± 0.004	0.057 ± 0.003
Relative	2.07 ± 0.10	1.76 ± 0.15	1.82 ± 0.14	2.17 ± 0.09

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE F7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
n	10	10	10	10
Male				
Necropsy body wt	53.9 ± 1.1	52.8 ± 1.5	54.8 ± 1.5	44.9 ± 1.3**
R. Kidney				
Absolute	0.424 ± 0.018	0.372 ± 0.008*	0.397 ± 0.017	0.359 ± 0.011**
Relative	7.87 ± 0.30	7.09 ± 0.21	7.26 ± 0.26	8.05 ± 0.30
Liver				
Absolute	2.328 ± 0.106	2.609 ± 0.199	2.920 ± 0.174*	2.305 ± 0.062
Relative	43.02 ± 1.15	49.62 ± 3.98	53.16 ± 2.45*	51.55 ± 1.19*
Spleen				
Absolute	0.100 ± 0.008	0.103 ± 0.008	0.117 ± 0.005	0.119 ± 0.006
Relative	1.86 ± 0.17	1.95 ± 0.14	2.14 ± 0.10	2.67 ± 0.15**
R. Testis				
Absolute	0.113 ± 0.004[b]	0.113 ± 0.003	0.112 ± 0.002	0.108 ± 0.005
Relative	2.11 ± 0.08[b]	2.14 ± 0.06	2.07 ± 0.07	2.44 ± 0.14
Thyroid Gland				
Absolute	0.003 ± 0.000	0.004 ± 0.000	0.004 ± 0.000	0.004 ± 0.000
Relative	0.06 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.08 ± 0.01
Female				
Necropsy body wt	53.0 ± 2.1	51.9 ± 2.3	48.1 ± 2.0	42.8 ± 1.4**
R. Kidney				
Absolute	0.264 ± 0.008	0.265 ± 0.007	0.273 ± 0.006	0.280 ± 0.012
Relative	5.02 ± 0.19	5.19 ± 0.25	5.76 ± 0.29*	6.56 ± 0.23**
Liver				
Absolute	1.805 ± 0.247	1.895 ± 0.089	2.034 ± 0.055	2.125 ± 0.070
Relative	33.68 ± 3.79	36.60 ± 0.88	42.62 ± 1.40**	49.79 ± 1.30**
Spleen				
Absolute	0.102 ± 0.010	0.114 ± 0.003	0.164 ± 0.008**	0.191 ± 0.009**
Relative	1.92 ± 0.16	2.24 ± 0.13	3.47 ± 0.25**	4.48 ± 0.20**
Thyroid Gland				
Absolute	0.004 ± 0.000	0.004 ± 0.000	0.003 ± 0.000	0.003 ± 0.000
Relative	0.08 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.08 ± 0.01

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1
Clinical Chemistry Data for Rats in the 16-Day Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
n	5	5	5	5
Male				
Thyroid-stimulating hormone (ng/mL)	401 ± 38	398 ± 35	567 ± 44	2,919 ± 351**
Triiodothyronine (ng/dL)	67 ± 3	53 ± 1	57 ± 3	18 ± 2**
Thyroxine (μg/dL)	2.7 ± 0.3	2.2 ± 0.2	1.3 ± 0.1*	0.8 ± 0.1**
Female				
Thyroid-stimulating hormone (ng/mL)	595 ± 240	393 ± 17	685 ± 96	2,852 ± 836**
Triiodothyronine (ng/dL)	72 ± 6	54 ± 4	69 ± 5	36 ± 8*
Thyroxine (μg/dL)	1.8 ± 0.0	1.4 ± 0.1	1.5 ± 0.2	1.0 ± 0.1**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168.8 mg/kg	337.5 mg/kg
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	46.4 ± 0.4	46.5 ± 0.3	46.8 ± 0.3	46.8 ± 0.3
Hemoglobin (g/dL)	16.2 ± 0.1	16.2 ± 0.1	16.4 ± 0.1	16.4 ± 0.1
Erythrocytes ($10^6/\mu L$)	9.15 ± 0.05	9.10 ± 0.08	9.07 ± 0.05	9.01 ± 0.07
Reticulocytes ($10^6/\mu L$)	0.10 ± 0.01[b]	0.12 ± 0.01	0.09 ± 0.01	0.12 ± 0.02
Mean cell volume (fL)	50.7 ± 0.3	51.1 ± 0.3	51.6 ± 0.3	52.0 ± 0.2**
Mean cell hemoglobin (pg)	17.8 ± 0.1	17.8 ± 0.1	18.1 ± 0.1*	18.2 ± 0.2*
Mean cell hemoglobin concentration (g/dL)	35.0 ± 0.2	34.9 ± 0.1	35.0 ± 0.1	35.0 ± 0.3
Leukocytes ($10^3/\mu L$)	8.83 ± 0.34	9.58 ± 0.40	9.47 ± 0.27	9.78 ± 0.38
Segmented neutrophils ($10^3/\mu L$)	1.15 ± 0.12	1.26 ± 0.17	1.19 ± 0.11	1.17 ± 0.11
Lymphocytes ($10^3/\mu L$)	7.51 ± 0.35	8.12 ± 0.38	8.13 ± 0.34	8.40 ± 0.37
Monocytes ($10^3/\mu L$)	0.12 ± 0.03	0.14 ± 0.02	0.12 ± 0.04	0.14 ± 0.04
Eosinophils ($10^3/\mu L$)	0.05 ± 0.02	0.06 ± 0.03	0.04 ± 0.02	0.06 ± 0.03
Methemoglobin (g/dL)	0.80 ± 0.08	0.90 ± 0.11	0.87 ± 0.10	0.95 ± 0.09
Clinical Chemistry				
Urea nitrogen (mg/dL)	18.9 ± 0.7	17.7 ± 1.0	18.4 ± 1.0	18.0 ± 0.9
Creatinine (mg/dL)	0.55 ± 0.03	0.60 ± 0.04	0.51 ± 0.03	0.53 ± 0.02
Glucose (mg/dL)	152 ± 3	150 ± 4	156 ± 4	149 ± 3
Total protein (g/dL)	6.7 ± 0.1[b]	6.9 ± 0.2[b]	7.0 ± 0.1	7.1 ± 0.2[b]
Albumin (g/dL)	4.8 ± 0.1	5.0 ± 0.2	4.9 ± 0.1	5.0 ± 0.1
Alanine aminotransferase (IU/L)	92 ± 8	73 ± 3	72 ± 5	81 ± 8
Alkaline phosphatase (IU/L)	257 ± 12	249 ± 11	251 ± 12	266 ± 9
Aspartate aminotransferase (IU/L)	153 ± 16	121 ± 7	124 ± 11	134 ± 12
Thyroid-stimulating hormone (ng/mL)	528 ± 43	543 ± 33	597 ± 26	789 ± 64**
Triiodothyronine (ng/dL)	92 ± 2	87 ± 3	78 ± 3**	72 ± 4**
Thyroxine ($\mu g/dL$)	3.6 ± 0.1	3.2 ± 0.2	3.1 ± 0.1**	2.6 ± 0.2**
Urinalysis				
Volume (mL/16 hr)	2.9 ± 0.6	2.7 ± 0.4	4.3 ± 0.5	3.7 ± 0.5
Specific gravity	1.043 ± 0.004	1.045 ± 0.003	1.040 ± 0.004	1.041 ± 0.003

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	84 mg/kg	168.8 mg/kg	337.5 mg/kg
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	45.0 ± 0.3	44.4 ± 0.6	44.4 ± 0.4	44.3 ± 0.5
Hemoglobin (g/dL)	16.2 ± 0.2	16.1 ± 0.3	16.2 ± 0.2	15.8 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.09 ± 0.06	7.98 ± 0.12	8.01 ± 0.09	7.98 ± 0.07
Reticulocytes ($10^6/\mu L$)	0.08 ± 0.02[c]	0.08 ± 0.01[c]	0.07 ± 0.01	0.08 ± 0.02[c]
Mean cell volume (fL)	55.8 ± 0.2	55.6 ± 0.2	55.3 ± 0.2	55.5 ± 0.2
Mean cell hemoglobin (pg)	20.0 ± 0.3	20.2 ± 0.3	20.3 ± 0.4	19.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	35.9 ± 0.4	36.4 ± 0.4	36.6 ± 0.5	35.8 ± 0.3
Leukocytes ($10^3/\mu L$)	6.83 ± 0.17	7.35 ± 0.31	6.84 ± 0.42	7.12 ± 0.41
Segmented neutrophils ($10^3/\mu L$)	0.79 ± 0.09	0.60 ± 0.08[c]	0.86 ± 0.07	0.65 ± 0.07
Lymphocytes ($10^3/\mu L$)	5.92 ± 0.17	6.35 ± 0.28[c]	5.86 ± 0.41	6.30 ± 0.39
Monocytes ($10^3/\mu L$)	0.08 ± 0.02	0.11 ± 0.02[c]	0.06 ± 0.02	0.09 ± 0.02
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.08 ± 0.03[c]	0.04 ± 0.02	0.08 ± 0.03
Methemoglobin (g/dL)	0.85 ± 0.13	0.86 ± 0.11	1.03 ± 0.09	1.07 ± 0.17
Clinical Chemistry				
Urea nitrogen (mg/dL)	14.3 ± 0.9	15.9 ± 0.8	14.6 ± 0.6	15.6 ± 0.7
Creatinine (mg/dL)	0.44 ± 0.02	0.42 ± 0.03	0.40 ± 0.02	0.45 ± 0.05
Glucose (mg/dL)	148 ± 2	147 ± 3	147 ± 4	148 ± 3
Total protein (g/dL)	6.7 ± 0.1	6.4 ± 0.1	6.6 ± 0.1	6.5 ± 0.1
Albumin (g/dL)	4.9 ± 0.1	4.5 ± 0.1*	4.7 ± 0.2	4.6 ± 0.1
Alanine aminotransferase (IU/L)	50 ± 3	62 ± 4	50 ± 4	58 ± 5
Alkaline phosphatase (IU/L)	246 ± 13	252 ± 20	224 ± 16	212 ± 13
Aspartate aminotransferase (IU/L)	95 ± 6	116 ± 9	95 ± 7	109 ± 6
Thyroid-stimulating hormone (ng/mL)	941 ± 187	552 ± 70	1,221 ± 195	989 ± 166
Triiodothyronine (ng/dL)	75 ± 3	72 ± 4	72 ± 4	69 ± 2
Thyroxine ($\mu g/dL$)	2.3 ± 0.1	2.1 ± 0.1*	2.2 ± 0.1	1.8 ± 0.1**
Urinalysis				
Volume (mL/16 hr)	4.52 ± 1.31	4.06 ± 1.23	4.84 ± 1.50	7.77 ± 1.35
Specific gravity	1.029 ± 0.004	1.035 ± 0.006	1.028 ± 0.004	1.026 ± 0.005

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8
[c] n=9

TABLE G3
Clinical Chemistry Data for Rats at the 6- and 15-Month Interim Evaluations and at Study Termination in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168 mg/kg	337.5 mg/kg	337.5 mg/kg (Stop-Exposure)
n	10	10	10	10	10
Male					
Thyroid-stimulating hormone (ng/mL)					
6-Month interim evaluation	1 ± 0	—[b]	—	—	1 ± 0
15-Month interim evaluation	1 ± 0	—	—	1 ± 0	—
2-Year study	2 ± 0[c]	2 ± 0	2 ± 0[d]	2 ± 0[d]	2 ± 0
Triiodothyronine (ng/dL)					
6-Month interim evaluation	80 ± 6	—	—	—	68 ± 6
15-Month interim evaluation	84 ± 7[d]	—	—	68 ± 8[d]	—
2-Year study	121 ± 4	120 ± 8[d]	115 ± 10	127 ± 6	118 ± 7
Reverse triiodothyronine (ng/mL)					
6-Month interim evaluation	0.224 ± 0.010	—	—	—	0.242 ± 0.020
15-Month interim evaluation	0.164 ± 0.011	—	—	0.172 ± 0.010	—
2-Year study	0.081 ± 0.017	0.074 ± 0.012	0.087 ± 0.019	0.042 ± 0.014[d]	0.078 ± 0.020
Thyroxine (μg/dL)					
6-Month interim evaluation	3.4 ± 0.3	—	—	—	3.1 ± 0.1
15-Month interim evaluation	2.7 ± 0.1	—	—	2.7 ± 0.2	—
2-Year study	4.3 ± 0.3	3.7 ± 0.2	3.7 ± 0.3	3.3 ± 0.1**	3.6 ± 0.3
Female					
2-Year study					
Thyroid-stimulating hormone (ng/mL)	2 ± 0	2 ± 0[d]	2 ± 1[d]	1 ± 0[d]	
Triiodothyronine (ng/dL)	93 ± 7	106 ± 3	100 ± 4	108 ± 7	
Reverse triiodothyronine (ng/mL)	0.029 ± 0.009	0.055 ± 0.013	0.063 ± 0.015	0.062 ± 0.018	
Thyroxine (μg/dL)	2.8 ± 0.1	2.7 ± 0.2	2.6 ± 0.2	2.9 ± 0.3	

** Significantly different (P≤0.01) from the control group by Shirley's test
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] Not measured at this dose level
[c] n=8
[d] n=9

TABLE G4
Clinical Chemistry Data for Mice in the 16-Day Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Male				
n	5	5	5	5
Thyroid-stimulating hormone (ng/mL)	164[b]	275 ± 73[c]	283 ± 61[c]	246 ± 37[c]
Triiodothyronine (ng/dL)	67 ± 1	73 ± 2	68 ± 5	62 ± 4
Thyroxine (μg/dL)	2.7 ± 0.2	2.4 ± 0.1	2.4 ± 0.3	2.3 ± 0.2
Female				
n	5	4	5	4
Thyroid-stimulating hormone (ng/mL)	232 ± 78[d]	123 ± 17[c]	242 ± 41[e]	142 ± 25[c]
Triiodothyronine (ng/dL)	70 ± 6	68 ± 8	62 ± 6	65 ± 4
Thyroxine (μg/dL)	3.9 ± 0.4	3.5 ± 0.4	3.1 ± 0.2	2.9 ± 0.2

[a] Mean ± standard error. Statistical tests were performed on unrounded data. Differences from the vehicle control group are not significant by Dunn's or Shirley's test.
[b] n=1; no standard error calculated
[c] n=3
[d] n=2
[e] n=4

TABLE G5
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	45.8 ± 1.0	45.7 ± 0.9	45.1 ± 0.6	44.9 ± 0.5
Erythrocytes ($10^6/\mu L$)	9.57 ± 0.14	9.37 ± 0.17	9.15 ± 0.11	9.23 ± 0.10
Reticulocytes ($10^6/\mu L$)	0.08 ± 0.02	0.15 ± 0.03	0.18 ± 0.05*	0.31 ± 0.04**
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.03 ± 0.02	0.02 ± 0.01	0.01 ± 0.01
Mean cell volume (fL)	48.0 ± 0.5	48.6 ± 0.3	49.2 ± 0.4	48.6 ± 0.3
Leukocytes ($10^3/\mu L$)	4.97 ± 0.70	5.73 ± 0.61	6.40 ± 0.60	9.03 ± 0.50**
Segmented neutrophils ($10^3/\mu L$)	1.05 ± 0.21	1.39 ± 0.22	1.33 ± 0.21	2.17 ± 0.34*
Lymphocytes ($10^3/\mu L$)	3.67 ± 0.48	4.10 ± 0.50	4.78 ± 0.44	6.41 ± 0.31**
Monocytes ($10^3/\mu L$)	0.03 ± 0.02	0.05 ± 0.02	0.08 ± 0.02	0.11 ± 0.03
Eosinophils ($10^3/\mu L$)	0.22 ± 0.06	0.17 ± 0.05	0.18 ± 0.04	0.31 ± 0.08
Methemoglobin (g/dL)	0.71 ± 0.19[b]	0.99 ± 0.20[c]	0.70 ± 0.12[d]	0.85 ± 0.12[e]
Clinical Chemistry				
Urea nitrogen (mg/dL)	24.7 ± 1.5	25.9 ± 2.1[f]	27.1 ± 1.8	20.5 ± 1.4
Creatinine (mg/dL)	0.34 ± 0.05	0.37 ± 0.04[f]	0.40 ± 0.04	0.32 ± 0.03
Glucose (mg/dL)	217 ± 10[f]	189 ± 9[f]	202 ± 9[g]	205 ± 13
Total protein (g/dL)	5.0 ± 0.2	5.0 ± 0.1[f]	5.0 ± 0.1	5.1 ± 0.1
Albumin (g/dL)	3.6 ± 0.0	3.7 ± 0.1[f]	3.8 ± 0.1	3.7 ± 0.1
Alanine aminotransferase (IU/L)	20 ± 2[f]	25 ± 2[f]	27 ± 2**	31 ± 4**
Alkaline phosphatase (IU/L)	58 ± 1	60 ± 2[f]	69 ± 3**[f]	64 ± 1**
Aspartate aminotransferase (IU/L)	52 ± 4[h]	51 ± 4[f]	52 ± 4[f]	65 ± 12
Thyroid-stimulating hormone (ng/mL)	333 ± 23[d]	232 ± 20*[f]	283 ± 36[h]	304 ± 34[c]
Triiodothyronine (ng/dL)	84 ± 3	72 ± 4[g]	87 ± 4[f]	79 ± 8[f]
Thyroxine (μg/dL)	3.9 ± 0.2	2.8 ± 0.2**	2.6 ± 0.1**	2.7 ± 0.1**
Urinalysis				
Volume (mL/16 hr)	1.2 ± 0.1	1.0 ± 0.2[f]	0.6 ± 0.1*	1.2 ± 0.1
Specific gravity	1.023 ± 0.004[f]	1.039 ± 0.003*[h]	1.051 ± 0.003**[f]	1.044 ± 0.004**

TABLE G5
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Gavage Study of Salicylazosulfapyridine (continued)

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	47.7 ± 0.5	44.9 ± 1.0*	45.7 ± 0.4	45.8 ± 0.7
Hemoglobin (g/dL)	16.2 ± 0.2	15.4 ± 0.3	15.8 ± 0.2	15.8 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.54 ± 0.09	8.93 ± 0.17*[f]	9.18 ± 0.08	8.98 ± 0.15*
Reticulocytes ($10^6/\mu L$)	0.10 ± 0.01	0.16 ± 0.02**[f]	0.22 ± 0.02**	0.20 ± 0.03**[g]
Mean cell volume (fL)	50.0 ± 0.4	50.2 ± 0.3	49.8 ± 0.4	50.9 ± 0.3
Mean cell hemoglobin (pg)	17.0 ± 0.2	17.3 ± 0.1	17.2 ± 0.2	17.6 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	34.0 ± 0.2	34.3 ± 0.3	34.6 ± 0.2	34.5 ± 0.2
Leukocytes ($10^3/\mu L$)	5.37 ± 0.49	5.27 ± 0.39	6.60 ± 0.44	8.26 ± 0.40**
Segmented neutrophils ($10^3/\mu L$)	0.69 ± 0.10	0.80 ± 0.08	0.74 ± 0.08	1.08 ± 0.26
Lymphocytes ($10^3/\mu L$)	4.46 ± 0.45	4.25 ± 0.35	5.57 ± 0.42	6.81 ± 0.46**
Monocytes ($10^3/\mu L$)	0.05 ± 0.01	0.04 ± 0.02	0.10 ± 0.02	0.11 ± 0.04
Eosinophils ($10^3/\mu L$)	0.16 ± 0.04	0.17 ± 0.04	0.18 ± 0.04	0.25 ± 0.04
Methemoglobin (g/dL)	0.70 ± 0.13[g]	0.82 ± 0.11[f]	1.12 ± 0.09**[h]	1.47 ± 0.21**[b]
Clinical Chemistry				
Urea nitrogen (mg/dL)	24.9 ± 0.9	24.4 ± 2.2	23.6 ± 1.7	24.3 ± 1.8
Creatinine (mg/dL)	0.40 ± 0.03[f]	0.30 ± 0.03	0.34 ± 0.04[f]	0.40 ± 0.06[f]
Glucose (mg/dL)	190 ± 10[h]	189 ± 5[f]	176 ± 9[g]	194 ± 12
Total protein (g/dL)	5.4 ± 0.1	5.6 ± 0.2	5.5 ± 0.1	5.4 ± 0.1
Albumin (g/dL)	4.2 ± 0.1	4.2 ± 0.1	4.0 ± 0.1	4.1 ± 0.1
Alanine aminotransferase (IU/L)	26 ± 2	38 ± 10	36 ± 9[f]	36 ± 3
Alkaline phosphatase (IU/L)	109 ± 3	119 ± 5[f]	112 ± 4	113 ± 3
Aspartate aminotransferase (IU/L)	69 ± 8[f]	67 ± 13	67 ± 11[f]	78 ± 7
Thyroid-stimulating hormone (ng/mL)	320 ± 16[e]	280 ± 26[h]	256 ± 13[d]	255 ± 16[c]
Triiodothyronine (ng/dL)	79 ± 3	86 ± 4[f]	82 ± 2	87 ± 3
Thyroxine (μg/dL)	3.9 ± 0.1	3.3 ± 0.2*[f]	3.3 ± 0.1**	2.7 ± 0.2**
Urinalysis				
Volume (mL/16 hr)	1.0 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Specific gravity	1.019 ± 0.004[f]	1.034 ± 0.004*	1.038 ± 0.003**[f]	1.036 ± 0.004**[f]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data. Special study animals were used for the thyroid-stimulating hormone, triiodothyronine, and thyroxine analyses.
[b] n=3
[c] n=5
[d] n=6
[e] n=4
[f] n=9
[g] n=8
[h] n=7

TABLE G6
Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation and at Study Termination in the 2-Year Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
n	10	10	9	10
Male				
Thyroid-stimulating hormone (ng/mL)				
15-Month interim evaluation	463 ± 54	—[b]	—	287 ± 65*
2-Year study	470 ± 142[c]	493 ± 72	483 ± 80	327 ± 100[d]
Triiodothyronine (ng/dL)				
15-Month interim evaluation	171 ± 5[e]	—	—	183 ± 8
2-Year study	179 ± 12[e]	200 ± 13[e]	188 ± 11	206 ± 10[f]
Reverse triiodothyronine (ng/mL)				
15-Month interim evaluation	0.193 ± 0.007	—	—	0.173 ± 0.008
2-Year study	0.316 ± 0.084[d]	0.128 ± 0.009**[d]	0.166 ± 0.018	0.136 ± 0.007*[g]
Thyroxine (μg/dL)				
15-Month interim evaluation	7.3 ± 0.3	—	—	7.2 ± 0.4
2-Year study	9.2 ± 0.8	9.1 ± 0.7	8.6 ± 0.4[h]	9.9 ± 1.0[e]
Female				
2-Year study				
Thyroid-stimulating hormone (ng/mL)	422 ± 82	299 ± 59[f]	155 ± 12**	241 ± 40
Triiodothyronine (ng/dL)	146 ± 8	168 ± 13	159 ± 8	175 ± 12
Reverse triiodothyronine (ng/mL)	0.203 ± 0.027[d]	0.222 ± 0.041[i]	0.148 ± 0.013[f]	0.150 ± 0.017[c]
Thyroxine (μg/dL)	6.1 ± 0.3	6.9 ± 0.7	7.8 ± 1.6[h]	7.2 ± 0.5

* Significantly different (P≤0.05) from the control group by Dunn's test
** P≤0.01
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] Not measured at this dose level
[c] n=7
[d] n=6
[e] n=9
[f] n=8
[g] n=5
[h] n=10
[i] n=4

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	84 mg/kg	168.8 mg/kg	337.5 mg/kg
Male				
n	10	10	10	10
Weights (g)				
Necropsy body wt	357 ± 7	344 ± 4	345 ± 5	341 ± 6
R. cauda	0.146 ± 0.005	0.145 ± 0.004	0.139 ± 0.005	0.142 ± 0.004
R. epididymis	0.444 ± 0.007	0.455 ± 0.010	0.438 ± 0.005	0.430 ± 0.010
R. testis	1.485 ± 0.028	1.505 ± 0.016	1.501 ± 0.018	1.467 ± 0.035
Epididymal spermatozoal parameters				
Motility (%)	84.92 ± 2.09	75.68 ± 1.20**	71.86 ± 4.08**	71.34 ± 2.55**
Concentration (10^6/g cauda epididymal tissue)	808.1 ± 46.1	778.0 ± 51.2	758.4 ± 54.2	675.4 ± 54.0
Abnormal (%)	0.720 ± 0.090	0.860 ± 0.095	0.900 ± 0.054	1.080 ± 0.120
Female				
n	10	10	10	10
Necropsy body wt	199 ± 3	190 ± 2**	189 ± 2**	188 ± 2**
Estrous cycle length (days)	4.80 ± 0.25	5.11 ± 0.20[b]	4.89 ± 0.20[b]	4.89 ± 0.26[b]
Estrous stage (% of cycle)				
Diestrus	37.1	30.0	35.7	34.3
Proestrus	17.1	21.4	20.0	17.1
Estrus	24.3	27.1	27.1	25.7
Metestrus	21.4	21.4	17.1	22.9

** Significantly different ($P \leq 0.01$) from the vehicle control group by Shirley's test (epididymal spermatozoal motility) or Williams' or Dunnett's test (weights)

[a] Weights, epididymal spermatozoal parameters, and estrous cycle lengths are presented as mean ± standard error. Statistical tests were performed on unrounded data. Differences from the vehicle control group for epididymal spermatozoal concentration and abnormality are not significant by Dunn's test. By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in relative length of time spent in the estrous stages.

[b] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

TABLE H2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Gavage Study of Salicylazosulfapyridine[a]

	Vehicle Control	675 mg/kg	1,350 mg/kg	2,700 mg/kg
Male				
n	10	9	10	10
Weights (g)				
Necropsy body wt	30.2 ± 0.5	29.8 ± 0.4[b]	29.2 ± 0.4	29.9 ± 0.5
R. cauda	0.017 ± 0.001	0.016 ± 0.001	0.014 ± 0.001**	0.015 ± 0.000
R. epididymis	0.048 ± 0.001	0.044 ± 0.001**	0.041 ± 0.001**	0.042 ± 0.001**
R. testis	0.115 ± 0.003	0.112 ± 0.002	0.109 ± 0.004	0.111 ± 0.002
Epididymal spermatozoal parameters				
Motility (%)	82.02 ± 2.43	81.61 ± 1.41	77.06 ± 2.20	77.68 ± 1.66
Concentration (10^6/g cauda epididymal tissue)	1,318 ± 92	1,169 ± 79	1,367 ± 125	1,319 ± 116
Abnormal (%)	1.14 ± 0.17	1.11 ± 0.12	1.34 ± 0.17	1.48 ± 0.28
Female				
n	10	10	10	10
Necropsy body wt	26.1 ± 0.5	26.2 ± 0.3	26.0 ± 0.3	26.1 ± 0.4
Estrous cycle length (days)	4.89 ± 0.20[c]	4.88 ± 0.30[d]	4.89 ± 0.31[c]	5.13 ± 0.30[d]
Estrous stage (% of cycle)				
Diestrus	18.6	34.3	32.9	28.6
Proestrus	22.9	20.0	18.6	20.0
Estrus	41.4	27.1	27.1	30.0
Metestrus	17.1	18.6	21.4	21.4

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' or Dunnett's test
[a] Weights, epididymal spermatozoal parameters, and estrous cycle lengths are presented as mean ± standard error. Statistical tests were performed on unrounded data. Differences from the vehicle control group for epididymal spermatozoal parameters are not significant by Dunn's test. By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in relative length of time spent in the estrous stages.
[b] n=10
[c] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.
[d] Estrous cycle was longer than 7 days or was unclear in 2 of 10 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF SALICYLAZOSULFAPYRIDINE

Salicylazosulfapyridine was obtained from Salisbury Labs, Inc. (Charles City, IA) in one lot (1089), which was used during the 16-day and 13-week studies. For the 2-year studies, one lot (61838) was obtained from Pharmacia, Inc. (Piscataway, NJ). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory and confirmed by the study laboratories. Reports on analyses performed in support of the salicylazosulfapyridine studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, an orange powder, were identified as salicylazosulfapyridine by infrared, ultraviolet/visible, and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with the literature spectra (Florey, 1976; Nygård *et al.*, 1966) of salicylazosulfapyridine. The infrared and NMR spectra are shown in Figures I1 and I2. The observed melting point of 247° to 248° C for lot 1089 was consistent with the literature reference (*Merck Index,* 1983).

The purity of each lot was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). For functional group titration of lots 1089 and 61838, samples of salicylazosulfapyridine were dissolved in pyridine, titrated with aqueous 0.1 N sodium hydroxide and monitored potentiometrically using a combination pH/mV electrode filled with 3 M or 4 M potassium chloride. Samples were also dissolved in dimethylformamide and titrated with 0.1 N tetrabutylammonium hydroxide in 2-propanol and monitored potentiometrically using a glass indicating electrode versus a calomel reference electrode filled with 1 M tetrabutylammonium chloride in methanol. TLC for lot 1089 was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) methyl ethyl ketone:acetone:water (16:16:1) and 2) chloroform:*n*-butanol: acetone:glacial acetic acid (4:1:1:1). Salicylic acid was used as a reference standard. The plates were examined with visible and ultraviolet light (254 and 366 nm) and with a spray of potassium iodoplatinate reagent. TLC for lot 61838 was performed on Silica Gel 60A K6F 60 plates with two solvent systems: 1) methyl ethyl ketone:acetone:water (16:16:1) and 2) chloroform:isopropanol:acetone:glacial acetic acid (4:1:1:1). Salicylic acid was used as a reference standard. The plates were examined with visible and ultraviolet light (254 and 366 nm) and with a spray of ferricyanide-ferric chloride reagent. HPLC for lot 1089 was performed with a Waters Nova Pak C_{18} column using ultraviolet light detection (254 and 365 nm) and an isocratic solvent system of 1% phosphoric acid in water:1% phosphoric acid in methanol (45:55) at a flow rate of 1 mL/minute. HPLC for lot 61838 was performed with the same system used for lot 1089 except with a solvent ratio of 53:47.

Elemental analyses for carbon, hydrogen, nitrogen, and sulfur agreed with theoretical values for both lots. Karl Fischer water analysis indicated 0.50% ± 0.04% water in lot 1089 and 0.5% ± 0.1% water in lot 61838. Functional group titration for lot 1089 by two methods indicated purities of 99.3% ± 0.6% and 100.6% ± 0.8%. Functional group titration for lot 61838 by two methods indicated purities of 100.6% ± 0.3% and 101.0% ± 0.4%. For lot 1089, TLC by each system indicated a major spot and a trace impurity. For lot 61838, TLC indicated a major spot with a trace and two slight trace impurities by system 1. System 2 indicated a major spot with two trace impurities and a slight trace impurity. Using a detection wavelength of 254 nm, HPLC revealed a major peak and three impurities with a combined area of 2.3% relative to the major peak area for lot 1089. At a detection wavelength of 365 nm, two impurities with a combined area of 1.9% relative to the major peak were observed for lot 1089. HPLC using a detection wavelength of 254 nm resolved a major peak and two impurity peaks with a combined area of 1.7% relative to the major peak area for lot 61838. When 365 nm was used as the detection wavelength, three impurity peaks were observed with a combined area of 1.2% relative to the major peak for lot 61838.

The overall purity was determined to be approximately 96% to 97% for lot 1089 and approximately 98% for lot 61838.

The analytical chemistry laboratory analyzed lot 1089 to determine if it met United States Pharmacopeia XX (USP) purity requirements. The complete battery of USP analyses was performed as a supplement to the chemical characterization of salicylazosulfapyridine. The chemical met the USP requirements for the identification tests, which included infrared and visible absorption spectroscopy. The loss on drying was 0.30% ± 0.01%, which met the USP requirement. The residue on ignition was 0.18% ± 0.04%, which met the USP requirement. The chemical met the USP requirements for the chloride, sulfate, and heavy metals tests. The USP purity assay indicated that lot 1089 had a purity of 96.5% ± 1.7%, calculated on the anhydrous basis, relative to the USP salicylazosulfapyridine reference standard. This purity was consistent with USP requirements.

Each lot was concomitantly analyzed with the USP standard for salicylazosulfapyridine content using the HPLC system described for the purity analyses except with a solvent ratio of 42:58 (lot 1089) or 50:50 (lot 61838). Relative to the USP standard, lot 1089 was determined to contain 96.3% ± 0.7% salicylazosulfapyridine, and lot 61838 was found to contain 97.0% ± 0.9% salicylazosulfapyridine.

Stability studies of the bulk chemical for lot 1089 were performed by the analytical chemistry laboratory. HPLC was performed using the system described for the purity studies except with a solvent ratio of 42:58, valerophenone as an internal standard, and detection at 254 nm. These studies indicated that salicylazosulfapyridine was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. Stability was monitored by HPLC and potentiometric titration prior to the start of the 16-day and 13-week studies, twice during the 13-week studies, and at least every 4 months by HPLC only during the 2-year studies. To ensure stability, the bulk chemical was stored in sealed amber plastic bags at 5° C during the 16-day and 13-week studies and in metal cans protected from light at room temperature during the 2-year studies.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared by mixing salicylazosulfapyridine with corn oil to give the required concentrations (Table I1). The dose formulations were prepared weekly during the 16-day studies and every 2 weeks during the 13-week and 2-year studies and stored for up to 3 weeks at 0° ± 5° C in clear (16-day studies) or amber glass (13-week and 2-year studies) bottles.

The corn oil vehicle used in the studies was analyzed every 1 to 3 months for peroxide levels. All analyses determined that the peroxide levels were within the specified limits except for two lots (2-year studies) that were replaced as soon as possible.

Homogeneity studies of the 500 mg/kg dose formulation were performed by the analytical chemistry laboratory. Extracts were prepared by mixing samples with N,N-dimethylformamide. Aliquots of the extracts were mixed with 5 mL of internal standard solution (2-bromo-4,6-dinitroaniline, 3 mg/mL in methanol) and 3 mL of deionized water, and then diluted to 250 mL with HPLC mobile phase. HPLC was performed with a Brownlee RP-18 (100 × 4.6 MM ID) column using ultraviolet detection (365 nm) and a mobile phase solvent system of methanol:water:phosphoric acid (60.5:38.5:1) at a flow rate of 1.0 mL/minute. Homogeneity was confirmed.

Stability studies of the 60 mg/g dose formulation were performed using the HPLC system described for the homogeneity studies. Stability was confirmed for 3 weeks when stored in the dark at room temperature and for 3 hours when stored open to air and light.

Periodic analyses of the dose formulations of salicylazosulfapyridine were conducted at the study laboratories using HPLC. The dose formulations were analyzed at the beginning of the 16-day studies, and all formulations (4/4) were within 10% of the target concentrations (Table I2). During the 13-week studies, the dose formulations were analyzed at the beginning, midpoint, and end of the studies, and all formulations (15/15) were within 10% of the target concentrations (Table I3). During the 2-year studies, the dose formulations were analyzed every 6 to 12 weeks. Of the dose formulations analyzed for the 2-year studies, 98% (103/105) were within 10% of the target concentrations. The dose formulations not within 10% of the target concentrations were remixed and found to be within 10% of the target concentrations (Table I4). Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table I5).

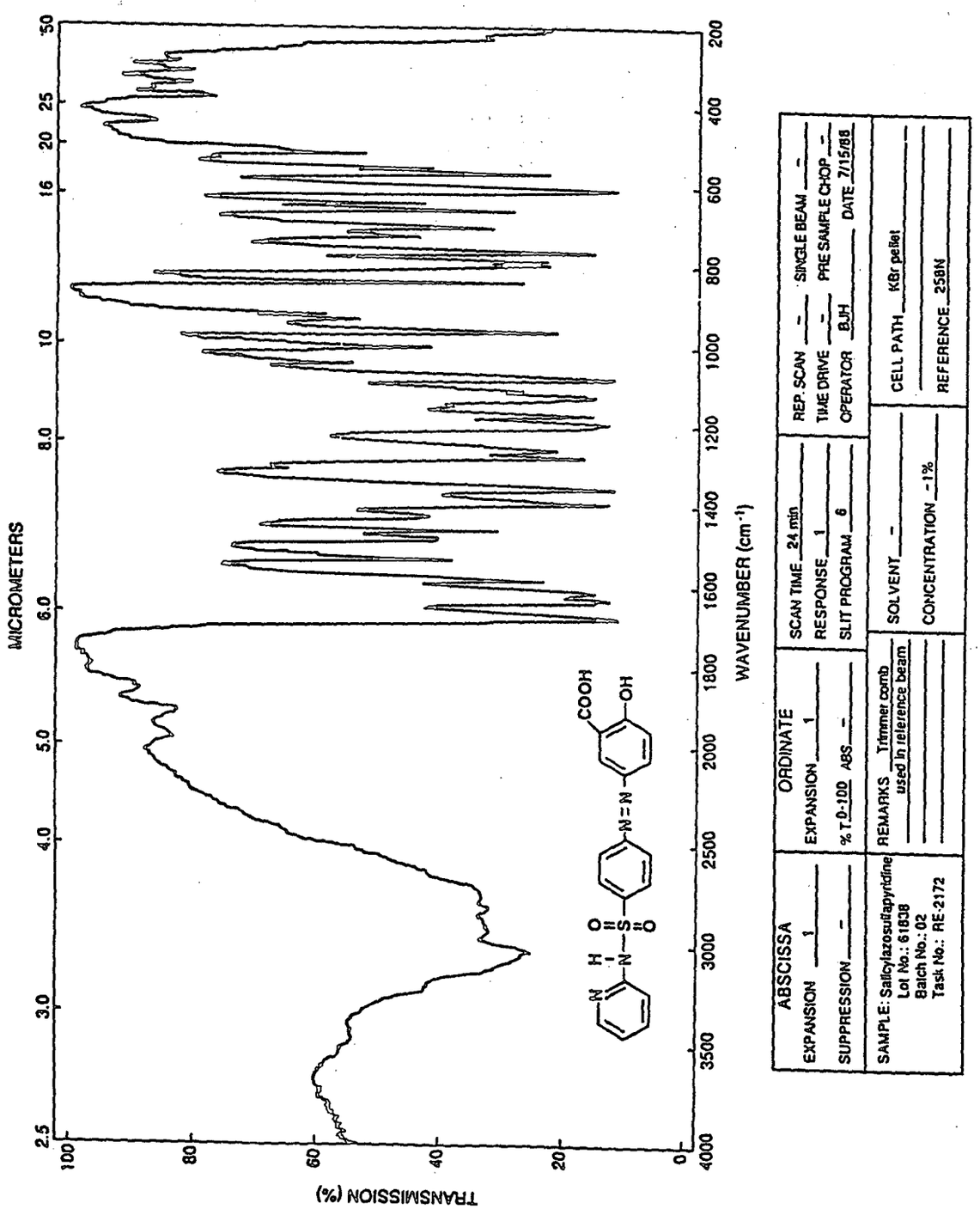

FIGURE 11
Infrared Absorption Spectrum of Salicylazosulfapyridine

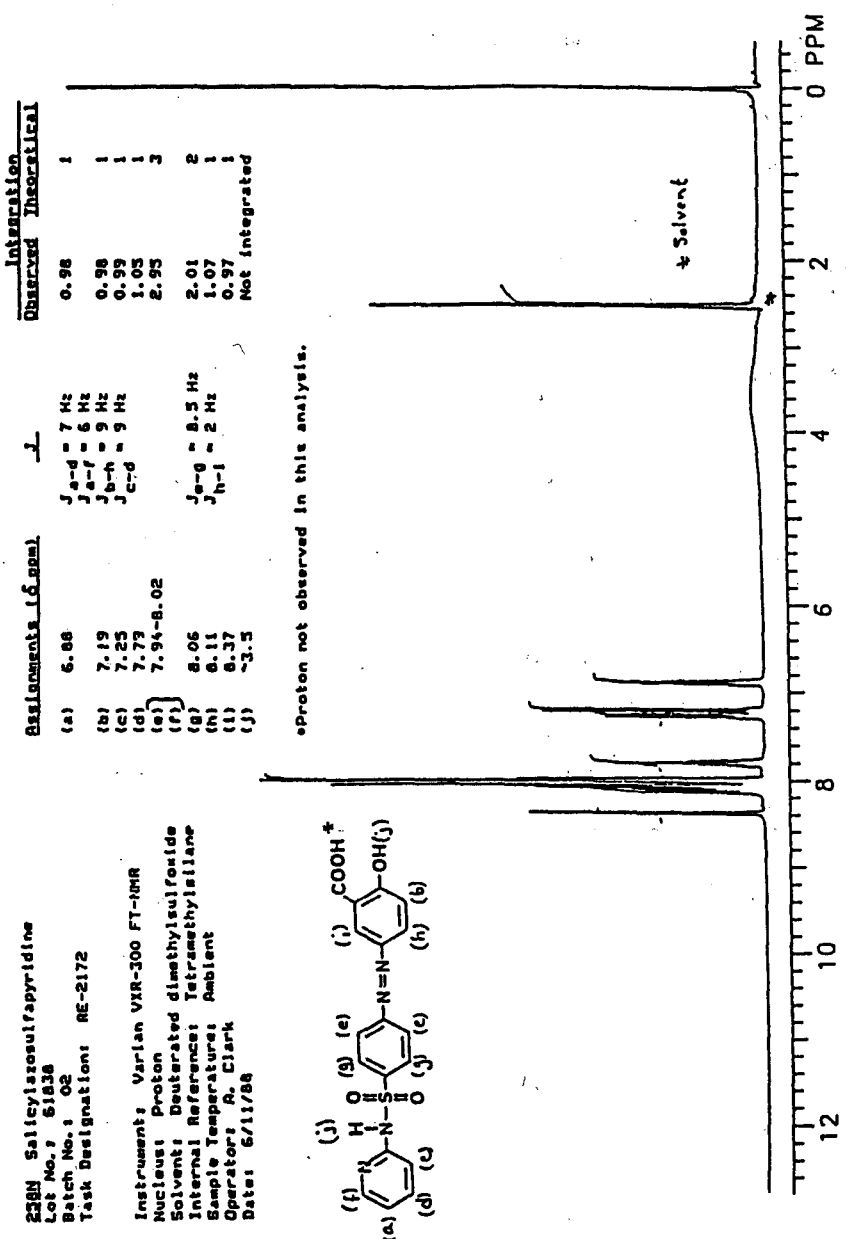

FIGURE I2
Nuclear Magnetic Resonance Spectrum of Salicylazosulfapyridine

TABLE I1
Preparation and Storage of Dose Formulations in the Gavage Studies of Salicylazosulfapyridine

16-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Salicylazosulfapyridine (finely powdered) was slowly added to corn oil in a graduated, light-protected Erlenmeyer flask. The corn oil was continuously stirred at room temperature and medium speed by a magnetic stir bar. Stirring was continued for up to 5 minutes, until the suspension appeared homogeneous. The mixture was then blended in a Brinkman Polytron blender for 3 minutes.	Same as 16-day studies	Same as 16-day studies
Chemical Lot Number		
1089	Same as 16-day studies	61838
Maximum Storage Time		
3 weeks	3 weeks	3 weeks
Storage Conditions		
Stored in sealed glass containers protected from light at 0° ± 5° C	Same as 16-day studies	Same as 16-day studies
Study Laboratory		
EG&G Mason Research Institute (Worchester, MA)	EG&G Mason Research Institute (Worchester, MA)	Southern Research Institute (Birmingham, AL)
Referee Laboratory		
Midwest Research Institute (Kansas City, MO)	Same as 16-day studies	Same as 16-day studies

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 16-Day Gavage Studies of Salicylazosulfapyridine

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)[a]	% Difference from Target
17 September 1985	19 September 1985	72	73.42	+2
		141	141.95	+1
		269	273.10	+2
		496	497.35	0
	10 October 1985[b]	72	73.29	+2
		141	142.26	+1
		269	272.08	+1
		496	506.74	+2

[a] Results of duplicate analyses. Dosing volume for rats = 5 mL/kg; 141 mg/g = 675 mg/kg; 269 mg/g = 1,350 mg/kg; 496 mg/g = 2,700 mg/kg. Dosing volume for mice = 10 mL/kg; 72 mg/g = 675 mg/kg; 141 mg/g = 1,350 mg/kg; 269 mg/g = 2,700 mg/kg.
[b] Animal room samples

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Salicylazosulfapyridine

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)[a]	% Difference from Target
Rats				
24 March 1986	26 March 1986	18.2	17.23	-5
		36.4	35.69	-2
		72.0	72.99	+1
	23 April 1986[b]	18.2	19.94	+10
		36.4	39.25	+8
		72.0	73.61	+2
13 May 1986	14 May 1986	18.2	18.21	0
		36.4	36.54	0
		72.0	72.78	+1
	11 June 1986[b]	18.2	18.34	+1
		36.4	36.80	+1
		72.0	72.42	+1
23 June 1986	24 June 1986	18.2	17.93	-2
		36.4	36.23	0
		72.0	72.39	+1
	12 August 1986[b]	18.2	18.09	-1
		36.4	36.11	-1
		72.0	72.57	+1
Mice				
24 March 1986	26 March 1986	72.0	72.99	+1
		140.8	141.8	+1
		269.4	269.6	0
	23 April 1986[b]	72.0	78.68	+9
		140.8	147.6	+5
		269.4	259.5	-4

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Salicylazosulfapyridine (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Mice (continued)				
13 May 1986	14 May 1986	72.0	72.78	+1
		140.8	141.8	+1
		269.4	273.6	+2
	11 June 1986[b]	72.0	72.94	+1
		140.8	142.5	+1
		269.4	273.8	+2
23 June 1986	24 June 1986	72.0	72.39	+1
		140.8	142.6	+1
		269.4	274.6	+2
	12 August 1986[b]	72.0	72.57	+1
		140.8	139.6	-1
		269.4	270.3	0

[a] Results of duplicate analyses. Dosing volume for rats = 5 mL/kg; 18.2 mg/g = 84 mg/kg; 36.4 mg/g = 168.8 mg/kg; 72.0 mg/g = 337.5 mg/kg. Dosing volume for mice = 10 mL/kg; 72.0 mg/g = 675 mg/kg; 140.75 mg/g = 1,350 mg/kg; 269.39 mg/g = 2,700 mg/kg.
[b] Animal room samples

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Salicylazosulfapyridine

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)[a]	% Difference from Target
Rats				
6 December 1988	7 December 1988	18.3[b]	18.2	-1
		18.3[c]	17.6	-4
		18.3[d]	18.2	-1
		18.3	17.8	-3
		36.6	36.8	+1
		73.4	74.0	+1
		73.4	74.4	+1
	27 December 1988[e]	18.3	18.4	+1
		36.6	36.9	+1
		73.4	78.3	+7
28 February 1989	1-2 March 1989	18.3	19.0	+4
		36.6	38.0	+4
		73.4	75.2	+2
		73.4	74.0	+1
11 April 1989	13-14 April 1989	18.3	18.2	-1
		36.6	37.1	+1
		73.4	72.8	-1
		73.4	73.7	0
6 June 1989	7-8 June 1989	18.3	16.4	-10
		36.6	37.0	+1
		73.4	72.2	-2
		73.4	74.3	+1
	29-30 June 1989[e]	18.3	18.3	0
		36.6	35.8	-2
		73.4	74.8	+2
		73.4	75.5	+3
1 August 1989	1-2 August 1989	18.3	18.0	-2
		36.6	37.5	+2
		73.4	75.0	+2
		73.4	74.0	+1
26 September 1989	26-27 September 1989	18.3	19.0	+4
		36.6	38.0	+4
		73.4	74.6	+2
		73.4	74.8	+2

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Salicylazosulfapyridine (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Rats (continued)				
7 November 1989	8-9 November 1989	18.3	19.0	+4
		36.6	36.4	-1
		73.4	72.2	-2
		73.4	73.0	-1
	29-30 November 1989[e]	18.3	20.6	+13
		36.6	37.2	+2
		73.4	90.8	+24
		73.4	97.8	+33
16 January 1990	16-17 January 1990	18.3	19.4	+6
		36.6	38.5	+5
		73.4	76.8	+5
		73.4	76.0	+4
27 February 1990	27-28 February 1990	18.3	18.4	+1
		36.6	36.8	+1
		73.4	73.8	+1
		73.4	74.0	+1
24 April 1990	24-25 April 1989	18.3	18.3	0
		36.6	36.4	-1
		73.4	73.8	+1
		73.4	74.4	+1
	15 May 1990[e]	18.3	19.0	+4
		36.6	49.8	+36
		73.4	82.9	+13
3 July 1990	5 July 1990	18.3	19.8	+8
		36.6	37.4	+2
		73.4	73.4	0
		73.4	72.8	-1
11 September 1990	11-13 September 1990	18.3	17.5	-4
		36.6	33.4	-9
		73.4	71.5	-3
		73.4	70.8	-4
6 November 1990	6-7 November 1990	18.3	18.5	+1
		36.6	37.7	+3
		73.4	74.6	+2
	29 November 1990[e]	18.3	18.4	+1
		36.6	36.6	0
		73.4	73.2	0

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Salicylazosulfapyridine (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Rats (continued)				
15 January 1991	15 January 1991	73.4	73.5	0
12 March 1991	12 March 1991	73.4	73.7	0
7 May 1991	7-9 May 1991	73.4	74.41	+1
Mice				
21 December 1988	27 December 1988	73.4	73.6	0
		146.9	148	+1
		293.8	291	-1
	10 January 1989[e]	73.4	72.2	-2
		146.9	150	+2
		293.8	293	0
28 February 1989	1-2 March 1989	73.4	75.0	+2
		146.9	146	-1
		293.8	296	+1
11 April 1989	13-14 April 1989	73.4	71.4	-3
		146.9	145	-1
		293.8	294	0
6 June 1989	7-8 June 1989	73.4	74.6	+2
		146.9	150	+2
		293.8	296	+1
	29-30 June 1989[e]	73.4	75.2	+2
		146.9	150	+2
		293.8	296	+1
1 August 1989	1-2 August 1989	73.4	74.4	+1
		146.9	150	+2
		293.8	294	0
26 September 1989	26-27 September 1989	73.4	74.9	+2
		146.9	150	+2
		293.8	296	+1
7 November 1989	8-9 November 1989	73.4	72.2	-2
		146.9	143	-3
		293.8	289	-2
	29-30 November 1989[e]	73.4	73	-1
		146.9	146	-1
		293.8	286	-3

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Salicylazosulfapyridine (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Mice (continued)				
16 January 1990	16-17 January 1990	73.4	76.2	+4
		146.9	83.2	-43
		293.8	304	+3
18 January 1990[f]	19 January 1990	146.9	174	+18
19 January 1990[g]	19 January 1990	146.9	150	+2
27 February 1990	27-28 February 1990	73.4	73.4	0
		146.9	147	0
		293.8	294	0
24 April 1990	24-25 April 1990	73.4	74.4	+1
		146.9	147	0
		293.8	292	-1
	15 May 1990[e]	73.4	82.6	+13
		146.9	158	+8
		293.8	294	0
3 July 1990	5 July 1990	73.4	72.4	-1
		146.9	145	-1
		293.8	289	-2
11 September 1990	11-13 September 1990	73.4	70.0	-5
		146.9	146	-1
		293.8	302	+3
6 November 1990	6-7 November 1990	73.4	74.1	+1
		146.9	148	+1
		293.8	287	-2
	29 November 1990[e]	73.4	74.3	+1
		146.9	148	+1
		293.8	291	-1
15 January 1991	15 January 1991	293.8	289.2	-2
12 March 1991	12 March 1991	293.8	292.6	0
7 May 1991	7-9 May 1991	293.8	292.1	-1
2 July 1991	2 July 1991	293.8	286.7	-2
30 July 1991	31 July-1 August 1991	293.8	292.7	0
	19-20 August 1991[e]	293.8	291.7	-1

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Salicylazosulfapyridine (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Mice (continued)				
24 September 1991	24-25 September 1991	293.8	292	-1
	14-16 October 1991[e]	293.8	293	0
3 December 1991	3 December 1991	293.8	295	0

[a] Results of duplicate analyses. Dosing volume for rats = 5 mL/kg; 18.3 mg/g = 84 mg/kg; 36.6 mg/g = 168.8 mg/kg; 73.4 mg/g = 337.5 mg/kg. Dosing volume for mice = 10 mL/kg; 73.4 mg/g = 675 mg/kg; 146.9 mg/g = 1,350 mg/kg; 293.8 mg/g = 2,700 mg/kg.
[b] Sample from top of mixing container
[c] Sample from middle of mixing container
[d] Sample from bottom of mixing container
[e] Animal room samples
[f] First remix of 146.9 mg/g concentration; used for dosing although more than 10% different from target concentration
[g] Second remix of 146.9 mg/g concentration

TABLE I5
Results of Referee Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Gavage Studies of Salicylazosulfapyridine

Date Prepared	Target Concentration (mg/g)	Determined Concentration (mg/g)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies (EG&G Mason)			
24 March 1986	269.4	269.6	269 ± 1
23 June 1986	72.0	72.39	72.5 ± 0.3
2-Year Studies (Southern Research Institute)			
Rats			
6 December 1988	18.3	17.8	18.1 ± 0.4
6 June 1989	73.4	72.2	73.7 ± 0.8
Mice			
21 December 1988	146.9	148	143 ± 1
27 February 1990	293.8	294	292.1 ± 0.9

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard error)

APPENDIX J
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE J1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE J2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.23 ± 0.67	21.80 - 24.30	36
Crude fat (% by weight)	5.24 ± 0.19	4.60 - 5.60	36
Crude fiber (% by weight)	3.51 ± 0.40	2.60 - 4.30	36
Ash (% by weight)	6.45 ± 0.20	6.11 - 6.94	36
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 - 1.390	10
Cystine	0.306 ± 0.075	0.181 - 0.400	10
Glycine	1.160 ± 0.050	1.060 - 1.220	10
Histidine	0.580 ± 0.024	0.531 - 0.608	10
Isoleucine	0.917 ± 0.034	0.867 - 0.965	10
Leucine	1.972 ± 0.052	1.850 - 2.040	10
Lysine	1.273 ± 0.051	1.200 - 1.370	10
Methionine	0.437 ± 0.115	0.306 - 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 - 1.110	10
Threonine	0.896 ± 0.055	0.824 - 0.985	10
Tryptophan	0.223 ± 0.160	0.107 - 0.671	10
Tyrosine	0.677 ± 0.105	0.564 - 0.794	10
Valine	1.089 ± 0.057	0.962 - 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 - 2.570	9
Linolenic	0.277 ± 0.036	0.210 - 0.320	9
Vitamins			
Vitamin A (IU/kg)	6,808 ± 1,864	4,180 - 12,140	36
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 - 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 - 48.9	9
Thiamine (ppm)	18.67 ± 2.20	15.0 - 28.0	36
Riboflavin (ppm)	7.92 ± 0.93	6.10 - 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 - 150.0	9
Pantothenic acid (ppm)	30.30 ± 3.60	23.0 - 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 - 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 - 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 - 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 - 65.0	10
Choline (ppm)	3,068 ± 314	2,400 - 3,430	9
Minerals			
Calcium (%)	1.20 ± 0.10	1.00 - 1.54	36
Phosphorus (%)	0.94 ± 0.03	0.85 - 1.00	36
Potassium (%)	0.887 ± 0.067	0.772 - 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 - 0.635	8
Sodium (%)	0.315 ± 0.034	0.258 - 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 - 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 - 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 - 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 - 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 - 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 - 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 - 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 - 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 - 1.150	6

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.31 ± 0.19	0.06 - 0.70	36
Cadmium (ppm)	0.10 ± 0.05	0.05 - 0.2	36
Lead (ppm)	0.28 ± 0.21	0.10 - 1.00	36
Mercury (ppm)	0.03 ± 0.19	0.02 - 0.11	36
Selenium (ppm)	0.38 ± 0.22	0.05 - 1.21	36
Aflatoxins (ppb)[c]	<5.0		35
Nitrate nitrogen (ppm)[d]	14.50 ± 5.17	2.90 - 24.0	36
Nitrite nitrogen (ppm)[d]	0.19 ± 0.16	0.10 - 0.70	36
BHA (ppm)[e]	1.75 ± 1.64	1.00 - 10.0	36
BHT (ppm)[e]	1.50 ± 1.34	1.00 - 8.00	36
Aerobic plate count (CFU/g)	43,434 ± 28,288	4,100 - 120,000	35
Coliform (MPN/g)	4.08 ± 4.42	3.00 - 23.00	36
Escherichia coli (MPN/g)	3.00	<3.00	36
Salmonella (MPN/g)	Negative		36
Total nitrosoamines (ppb)[f]	7.57 ± 2.62	3.60 - 16.50	36
N-Nitrosodimethylamine (ppb)[f]	5.70 ± 2.28	2.60 - 13.00	36
N-Nitrosopyrrolidine (ppb)[f]	1.87 ± 1.02	1.00 - 4.30	36
Pesticides (ppm)			
α-BHC	<0.01		31
β-BHC	<0.02		31
γ-BHC	<0.01		31
δ-BHC	<0.01		31
Heptachlor	<0.01		31
Aldrin	<0.01		31
Heptachlor epoxide	<0.01		31
DDE	<0.01		31
DDD	<0.01		31
DDT	<0.01		31
HCB	<0.01		31
Mirex	<0.01		31
Methoxychlor	<0.05		31
Dieldrin	<0.01		31
Endrin	<0.01		31
Telodrin	<0.01		31
Chlordane	<0.05		31
Toxaphene	<0.1		31
Estimated PCBs	<0.2		31
Ronnel	<0.01		31
Ethion	<0.02		31
Trithion	<0.05		31
Diazinon	<0.1		31
Methyl parathion	<0.02		31
Ethyl parathion	<0.02		31
Malathion	0.25 ± 0.24	0.05 - 1.00	36
Endosulfan I	<0.01		31
Endosulfan II	<0.01		31
Endosulfan sulfate	<0.03		31

[a] CFU=colony forming units (excludes the high value of 710,000 obtained on batches produced on 2 October 1991), MPN=most probable number, BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] No aflatoxin measurement was recorded for the lot milled 2 October 1989.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

APPENDIX K
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
ELISA	
Mycoplasma arthritidis	6 months, study termination (males)
Mycoplasma pulmonis	6 months, study termination (males)
PVM (pneumonia virus of mice)	6, 12, 14, 15, and 18 months, study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	6, 12, 14, 15, and 18 months, study termination
Sendai	6, 12, 14, 15, and 18 months, study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	6, 12, 14, 15, and 18 months, study termination
KRV (Kilham rat virus)	6, 12, 14, 15, and 18 months, study termination
MICE	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	18 months, study termination
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months, study termination
MVM (minute virus of mice)	6 months
Mouse adenoma virus	6 and 12 months
Mouse adenoma virus - FL	18 months, study termination (males)
MHV (mouse hepatitis virus)	6, 12, 18, and 23 months, study termination
M. arthritidis	6 months
M. pulmonis	6 months
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, 18, and 23 months, study termination
Sendai	6, 12, 18, and 23 months, study termination

MICE (continued)

Immunofluorescence Assay	
EDIM	6 and 12 months
GDVII	18 months
MVM	12 and 18 months
Mouse adenoma virus - FL	Study termination
MHV	Study termination
Reovirus 3	23 months, study termination (males)
Hemagglutination Inhibition	
K (papovavirus)	6, 12, and 18 months, study termination
MVM	Study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Studies of Salicylazosulfapyridine

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Rats		
6 Months	1/10	*M. arthritidis*[a]
12 Months	0/10	None positive
14 Months	0/1	None positive
15 Months	0/1	None positive
18 Months	0/8	None positive
Study termination	0/10	None positive
Mice		
6 Months	0/10	None positive
12 Months	0/8	None positive
18 Months	0/11	None positive
23 Months	10/10	MHV
Study termination	9/10	MHV (ELISA)
	8/10	MHV (Immunofluorescence assay)

[a] Further evaluation of the sample positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titer may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only one sample was positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in the animal with the positive titer. Accordingly, the *M. arthritidis*-positive titer was considered to be a false positive.

APPENDIX L
CHEMICAL DISPOSITION OF SALICYLAZOSULFAPYRIDINE IN F344 RATS AND B6C3F$_1$ MICE

Excerpted from:
National Toxicology Program (NTP) (1994a). Chemical Disposition in Mammals: Toxicokinetics of Salicylazosulfapyridine and Sulfapyridine in B6C3F$_1$ Mice and Fischer 344 Rats. Final Report. NIEHS Contract NO1-ES-85230.

CHEMICAL DISPOSITION OF SALICYLAZOSULFAPYRIDINE IN F344 RATS AND B6C3F$_1$ MICE

OBJECTIVE

The primary objective of these studies was to investigate the pharmacokinetics of salicylazosulfapyridine in male F344 rats and B6C3F$_1$ mice following intravenous administration of salicylazosulfapyridine (5 mg/kg) and in male and female B6C3F$_1$ mice following gavage dosing (67.5, 675, 1,350, or 2,700 mg/kg). To determine if male and female mice form the same metabolites of salicylazosulfapyridine, the metabolites were identified in plasma collected following gavage administration.

CHEMICALS

Chemicals were obtained from the following sources: salicylazosulfapyridine (2-hydroxy-5-[[4-[(2-pyridyl-amino) sulfonyl] phenyl] azo] benzoic acid, CAS No. 599-79-1) from the NTP Chemical Repository (Research Triangle Park, NC); sulfapyridine from Sigma (St. Louis, MO); and sodium phosphate (dibasic or monobasic) and methanol from Fisher Scientific Co. (Fair Lawn, NJ). *N*-Acetylsulfapyridine standard was synthesized by acetylation of sulfapyridine with acetic anhydride and purified by recrystallization. The structure was confirmed by mass spectrometry. All reagents used in this experiment were analytical grade, high-performance liquid chromatography (HPLC) grade, or the best available pharmaceutical grade.

ANIMALS

Rats: Male, jugular-vein cannulated F344 rats were supplied by Hilltop Lab Animals, Inc. (Scottdale, PA). The weight range of the animals at the start of the study was 188 ± 5.89 g. Upon receipt, the rats were housed in a temperature-controlled, 12-hour light/dark cycle facility and were acclimated for 1 week prior the start of the study. Rats were given tap water and feed (Teklad 4% Mouse/Rat Diet, Harlan Teklad, Madison, WI) *ad libitum*.

Mice: Male and female B6C3F$_1$ mice (24 ± 3 g) were supplied by the NIEHS (Research Triangle Park, NC). At the start of the study they were 8 to 10 weeks old. Upon receipt, the mice were kept in a temperature-controlled, 12-hour light/dark cycle facility and were acclimated for 1 week prior to the start of the study. Mice were given tap water and feed (Teklad 4% Mouse/Rat Diet, Harlan Teklad, Madison, WI) *ad libitum*. Mice were fasted for 12 hours prior to gavage administration of salicylazosulfapyridine.

ADMINISTRATION OF TEST COMPOUNDS

Rats: Salicylazosulfapyridine (5 mg/kg) was dissolved in distilled, deionized water (pH 9-10, adjusted with 5 N NaOH) and administered intravenously to four male F344 rats.

Mice: Salicylazosulfapyridine was dissolved in corn oil and administered by gavage to groups of male and female mice at doses of 67.5, 675, 1,350, and 2,700 mg/kg. For the intravenous administration, salicylazosulfapyridine was dissolved in distilled, deionized water (pH 9-10, adjusted with 5 N NaOH) and administered via the tail vein at a dose of 5 mg/kg (0.2 to 0.3 mL/mouse) over approximately 5 to 10 seconds.

COLLECTION OF BLOOD SAMPLES

Rats: Blood samples were collected from the cannulated jugular vein into heparinized syringes at 0.03, 0.08, 0.17, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 hours following intravenous administration. Four rats were evaluated at each time point. The blood was centrifuged at 5,000 × g for 5 minutes, and the plasma was transferred to an Eppendorf tube and stored at -20° C until analyzed. The samples were usually processed within 3 days.

Mice: Mice were anesthetized with carbon dioxide, and blood samples were collected from the inferior vena cava into heparinized syringes prior to (0 hours) and at 0.25, 0.5, 1, 3, 4, 6, 8, and 12 hours following intravenous administration and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours following gavage administration. Four to seven mice were evaluated at each time point. The blood was centrifuged at 5,000× g for 5 minutes, and the plasma was transferred to an Eppendorf tube and stored at -20°C until analyzed. The samples were usually processed within 3 days.

SAMPLE ANALYSIS

Wavelength scanning of salicylazosulfapyridine in methanol/0.025 M (pH 2.5) phosphate buffer (64:36, v:v) showed two absorption peaks at 364 nm and 244 nm in the ultraviolet range. Since 360 nm specifically represents the integrity of azo linkage, 360 nm was used for the detection of the parent compound.

The plasma samples were mixed with two volumes of methanol and were allowed to stand in an ice bath for 15 minutes to precipitate protein. After centrifugation at 13,000 × g at 4° C for 15 minutes, an aliquot of the supernatant was analyzed using HPLC. Salicylazosulfapyridine and its metabolites were separated and quantitated on a Phenomax 250 × 4.6 mm Ultracarb C_{18} reverse-phase column (7 μm) coupled to a Spectra-Physics Model 100 UV detector. Mobile phase system 1 consisted of methanol and 0.025 M (pH 2.5) phosphate buffer (64:36, v:v) and was used for salicylazosulfapyridine analysis. Separations were performed at room temperature at a rate of 1 mL/minute. Mobile phase system 2 was composed of methanol and 0.02 M (pH 7.0) phosphate buffer (20:80, v:v) and was used for sulfapyridine and *N*-acetylsulfapyridine analyses. The metabolites were separated at room temperature at a flow rate of 2 mL/minute. A Spectra-Physics Model 100 UV detector was used for detection of salicylazosulfapyridine and its metabolites (360 nm for salicylazosulfapyridine and 254 nm for the metabolites, respectively). The detection limits in plasma were 0.32 nmol/mL for salicylazosulfapyridine, 0.5 nmol/mL for sulfapyridine, and 1.0 nmol/mL for *N*-acetylsulfapyridine.

The results of these studies are presented in Tables L1 through L3.

TABLE L1
Pharmacokinetic Parameters Following Intravenous Administration of 5 mg/kg Salicylazosulfapyridine in Male F344 Rats

	k[a] (hr^{-1})	$t_{1/2}$[b] (hr)	AUC[c] ($\mu M \cdot hr$)	CLs[d] (L/kg·hr)	MRT[e] (hr)	V_d[f] (L/kg)
Rat A	1.558	0.445	15.36	0.82	0.37	0.52
Rat B	2.126	0.326	17.85	0.70	0.29	0.33
Rat C	0.845	0.820	19.88	0.63	0.36	0.75
Rat D	1.329	0.521	28.19	0.45	0.37	0.33
Mean	1.465	0.528	20.32	0.65	0.35	0.48
SEM	0.266	0.105	2.78	0.08	0.02	0.099

[a] k=Elimination rate constant
[b] $t_{1/2}$=Elimination half-life
[c] AUC=Area under the concentration-time curve
[d] CLs=Clearance
[e] MRT=Mean residence time
[f] V_d=Volume of distribution

TABLE L2
Comparison of Pharmacokinetic Parameters Following Intravenous Administration of 5 mg/kg Salicylazosulfapyridine in Male F344 Rats and B6C3F$_1$ Mice[a]

	k[b] (hr^{-1})	$t_{1/2}$[c] (hr)	AUC[d] ($\mu M \cdot hr$)	CLs[e] (L/kg·hr)	MRT[f] (hr)	V_d[g] (L/kg)
Rats	1.47	0.53	20.32	0.65	0.35	0.48
Mice	1.28	0.54	9.21	1.36	0.45	1.07

[a] The data were calculated from the plasma concentration-time curves where each point represents the mean of four to six animals from the mouse intravenous study and of four animals from the rat study.
[b] k=Elimination rate constant
[c] $t_{1/2}$=Elimination half-life
[d] AUC=Area under the concentration-time curve
[e] CLs=Clearance
[f] MRT=Mean residence time
[g] V_d=Volume of distribution

TABLE L3
Toxicokinetic Parameters of Salicylazosulfapyridine, Sulfapyridine, and *N*-Acetylsulfapyridine Following Single Gavage Doses of Salicylazosulfapyridine in B6C3F$_1$ Mice[a]

Dose (mg/kg)	Compound Analyzed	C_{max}[b] (μM)	$t_{1/2}$[c] (hr)	k[d] (hr^{-1})	AUC[e] ($\mu M \cdot hr$)	MRT[f] (hr)	F[g] (%)
Male							
67.5	Salicylazosulfapyridine	15.6	0.9	0.802	21	0.4	16.6
	Sulfapyridine	91.4	2.2	0.318	430		
	N-Acetylsulfapyridine	11.9	1.6	0.440	44		
675	Salicylazosulfapyridine	31.0	1.7	0.402	97	2.0	7.82
	Sulfapyridine	240.6	11.1	0.063	3,134		
	N-Acetylsulfapyridine	21.5	5.8	0.119	239		
1,350	Salicylazosulfapyridine	40.1	2.3	0.304	135	2.8	5.44
	Sulfapyridine	237.7	7.4	0.094	2,995		
	N-Acetylsulfapyridine	19.8	6.2	0.112	260		
2,700	Salicylazosulfapyridine	42.3	1.8	0.379	127	2.4	2.56
	Sulfapyridine	258.6	7.3	0.094	2,811		
	N-Acetylsulfapyridine	18.2	10.1	0.068	271		
Female							
67.5	Salicylazosulfapyridine	39.5	1.3	0.520	52	0.73	18.2
	Sulfapyridine	111.0	3.3	0.210	540		
	N-Acetylsulfapyridine	4.2	3.4	0.206	17		
675	Salicylazosulfapyridine	127.0	1.0	0.672	250	0.72	8.66
	Sulfapyridine	483.7	7.9	0.088	6,261		
	N-Acetylsulfapyridine	20.5	8.7	0.080	234		
1,350	Salicylazosulfapyridine	167.5	1.4	0.483	385	1.2	6.67
	Sulfapyridine	320.3	8.3	0.084	3,464		
	N-Acetylsulfapyridine	20.5	8.7	0.080	234		
2,700	Salicylazosulfapyridine	212.5	1.7	0.401	845	2.03	7.32
	Sulfapyridine	237.0	9.8	0.071	4,082		
	N-Acetylsulfapyridine	22.9	8.3	0.083	224		

[a] Five to seven mice were evaluated per time point.
[b] C_{max}=Maximum observed concentration
[c] $t_{1/2}$=Elimination half-life
[d] k=Elimination rate constant
[e] AUC=Area under the concentration-time curve
[f] MRT=Mean residence time
[g] F=Bioavailability

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
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Central Data Management
P.O. Box 12233, MD E1-02
Research Triangle Park, NC 27709

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