National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 101
1978

BIOASSAY OF FORMULATED FENAMINOSULF FOR POSSIBLE CARCINOGENICITY

CAS No. 140-56-7

NCI-CG-TR-101

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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BIOASSAY OF

FORMULATED FENAMINOSULF

FOR POSSIBLE CARCINOGENICITY

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

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DHEW Publication No. (NIH) 78-1351

REPORT ON THE BIOASSAY OF FORMULATED FENAMINOSULF
FOR POSSIBLE CARCINOGENICITY

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

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

CONTRIBUTORS: This bioassay of formulated fenaminosulf was conducted by Mason Research Institute, Worcester, Massachusetts, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3). Chemical analysis was performed by Midwest Research Institute (4) and the analytical results were reviewed by Dr. N. Zimmerman (5).

Histopathologic examinations were performed by Dr. A. S. Krishna Murthy (3) and Dr. D. S. Wyand (3) at the Mason Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (6).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Mr. W. W. Belew (5) and Dr. J. R. Joiner (6) using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (8).

This report was prepared at METREK, a Division of The MITRE Corporation (5) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (5), task leader Dr. M. R. Kornreich (5), senior biologist Ms. P. Walker (5), biochemist Mr. S. C. Drill (5), and technical editor Ms. P. A. Miller (5). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,9), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay of formulated fenaminosulf for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. Fenaminosulf was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The time-weighted average high and low dietary concentrations of fenaminosulf were, respectively, 0.10 and 0.05 percent for rats, 0.19 and 0.10 percent for male mice, and 0.10 and 0.05 percent for female mice. After a 78-week period of compound administration, observation of the rats continued for up to an additional 31 weeks and observation of the mice continued for up to an additional 19 weeks.

Fifty male mice and 50 rats of each sex were placed on test as controls and fed only the basal diet. For female mice, 50 animals served as controls for the high dose group and 50 as controls for the low dose group.

For female rats there was no significant association between fenaminosulf dosage and mortality and, if the 21 male rats that died in the first two weeks of the bioassay were excluded from consideration, the same was true for male rats. For both male and female mice there was a significant positive association between dosage and mortality. In all groups of both species, however, adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors.

No convincing, statistically significant positive associations were demonstrated between chemical administration and the incidence of neoplasms in either sex of either species. An increased incidence of necrosis and mineralization of the tubular cells of the renal papilla occurred in treated rats and mice. These nonneoplastic lesions were not present in control animals of either species.

Under the conditions of this bioassay, dietary administration of formulated fenaminosulf was not carcinogenic in either Fischer 344 rats or B6C3F1 mice.

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I. INTRODUCTION

Fenaminosulf (NCI No. C03010), an aromatic diazo compound used exclusively as a fungicide, was selected for bioassay by the National Cancer Institute because of conflicting reports concerning its ability to induce hepatomas in rats (Herrmann and DuBois, 1949; Miller et al., 1957). The structural similarity of fenaminosulf to the carcinogenic aminoazo dyes, such as dimethylaminoazobenzene (Terayama, 1967) was an additional factor in its selection for testing.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is sodium 4-(dimethylamino)phenol diazenesulfonate.* It is also known as p-dimethylaminobenzenediazo sodium sulfonate; sodium 4-dimethylaminobenzenediazosulfonate; DAS; Dexon®; diazoben; and Bayer 22555.

Fenaminosulf is registered by the U.S. Environmental Protection Agency as a seed-treatment fungicide for beans, beets, corn, cotton, cucumbers, peas, sorghum, spinach, and sugar beets; and as the active ingredient in commercial fungicides for use on avocados, ornamentals, sugarcane, lawns, and turf (Carter et al., 1973; as cited in International Agency for Research on Cancer, 1975).

Specific production figures for fenaminosulf are not available; however, the inclusion of this compound in the 1977 Directory of Chemical Producers, U.S.A. (Stanford Research Institute, 1977) implies an

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*The CAS registry number is 140-56-7.

annual commercial production in excess of 1000 pounds or $1000 in value.

The potential for exposure to fenaminosulf is greatest for agricultural workers, although workers in fenaminosulf production facilities may also be exposed. The general population may be exposed via dermal contact to fenaminosulf on packaged seeds, in lawn and garden fungicides, and to residues in soils and turf. Ingestion is unlikely since fenaminosulf is apparently not sprayed directly on food crops. Persistence may not be a major problem because fenaminosulf is labile in the environment (Farm Chemicals Handbook, 1976).

II. MATERIALS AND METHODS

A. Chemicals

A fenaminosulf formulation manufactured by Chemagro Corporation (Kansas City, Missouri) under the trade name Dexon® was purchased by the NCI for Mason Research Institute. Chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. The composition of this formulation was estimated by the manufacturer to contain 35 percent fenaminosulf, 41 percent Kaolin clay, 12 percent synthetic silica, 5 percent sodium naphthalene sulfonate, and 6 percent sodium ligno-sulfate.

The results of elemental analysis were consistent with those which would be expected from this formulation. Direct current polarography indicated that the formulation was 30 to 35 percent pure fenaminosulf.

Throughout this report the term fenaminosulf is used to represent this mixture.

B. Dietary Preparation

The basal laboratory diet for both treated and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). Fenaminosulf was administered to the treated animals as a component of the diet. The chemical was hand-mixed with an aliquot of the ground feed until visual uniformity was attained. This premix was then placed into a 6 kg capacity Patterson-Kelley twin-shell stainless steel V-blender along with the remainder of the feed and blended

for 20 minutes. Prepared diets were placed in double plastic bags and stored in the dark at 4°C. Mixtures were prepared weekly and stored for not longer than 2 weeks.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. The animals were received in several separate shipments from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. All male mice to be assigned to treated groups and the female mice to be assigned to the high dose group were received approximately 5 weeks before the mice to be used as controls for these groups. Low dose female mice were received 3 months after the first shipment and the controls for this group were received 1 week later. Rats to be utilized for the high dose and control groups were received 12 weeks before the low dose rats.

Upon arrival, a sample of animals was examined for parasites and other signs of disease. The remaining animals were quarantined by species for 2 weeks prior to initiation of the test. Animals were assigned to groups and distributed among cages so that the average body weight per cage was approximately equal for a given sex and species.

D. Animal Maintenance

All animals were housed by species in rooms having a temperature range of 23° to 34°C. Incoming air was filtered through Tri-Dek®

15/40 denier Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex. During quarantine and for the first 16 months of study, high dose and control rats were housed in galvanized-steel wire-mesh cages suspended above newspapers. Low dose rats were housed in galvanized wire-mesh cages during quarantine and for the first 14 months of study. Newspapers under cages were replaced daily and cages and racks washed weekly. For the remainder of the study, rats were housed in suspended polycarbonate cages equipped with disposable nonwoven fiber filter sheets. Clean bedding and cages were provided twice weekly. Corncob bedding (SAN-I-CEL®, Paxton Processing Company, Paxton, Illinois) was used for the first 7 months that high dose and control rats were housed in polycarbonate cages and for the first 6 months that low dose rats were housed in polycarbonate cages. For the remainder of the study Aspen hardwood chip bedding (American Excelsior Company, Baltimore, Maryland) was provided in rat cages. Stainless steel cage racks were cleaned once every two weeks, and disposable filters were replaced at that time.

Mice were housed by sex in polycarbonate shoe box type cages fitted with perforated stainless steel lids (Lab Products, Inc., Garfield, New Jersey) and nonwoven fiber filter bonnets. All mice were housed ten per cage for the first part of the study. Low dose

treated and control females, treated males and high dose females, and control males and high dose control females were reduced to five per cage after 11, 14, and 13 months, respectively. Cages, lids, filters, and bedding were provided three times per week when the number of mice per cage was ten and twice per week when cage populations were five. Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products Company, Norway, Maine) was used for 2 months (control males and high dose control females) and 3 months (treated males and high dose females). Subsequently, SAN-I-CEL® was used for the next 12 months for these groups and for the first 12 months for low dose treated and control females. A second corncob bedding (Bed-o-Cobs®, The Andersons Cob Division, Maumee, Ohio) was used for the next 8 months. Aspen bedding was then provided for the remainder of the study. Reusable filter bonnets and pipe racks were sanitized every 2 weeks throughout the study.

Water was available ad libitum for both species from 250 ml water bottles equipped with rubber stoppers and stainless steel sipper tubes. Bottles were replaced twice weekly and, for rats only, refilled as needed between changes.

Wayne Lab-Blox® was supplied ad libitum throughout the entire test. Pelleted Wayne Lab-Blox® was supplied to treated and control male mice and high dose treated and control female mice during the final observation period. During the quarantine and dosing periods, all animals received Wayne Lab-Blox® meal. Alpine® aluminum feed

cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) containing stainless steel baffles were used to distribute powdered feed until the last 5 months of the study for rats, all control male mice, and high dose control female mice. This same apparatus was used until the last 4 months of the study for treated male mice and high dose female mice, and until the last 7 months of the study for low dose treated and control female mice. After these periods stainless steel gangstyle food hoppers (Scientific Cages, Inc., Bryan, Texas) were utilized.

During the final observation period, treated and control male mice and high dose female mice were fed pellets from a wire bar hopper incorporated into the cage lid, low dose treated and control females were fed meal from gangstyle hoppers, and rats were fed pellets on the cage floor. Food hoppers were changed on the same schedule as were cages. Food was replenished daily in Alpine® feed cups.

Treated and control rats were housed with rats being intubated with* m-cresidine (102-50-1); and with other rats receiving diets containing 2,5-dithiobiurea (142-46-1) and cupferron (135-20-6).

All treated male mice, high dose treated female mice, and low dose control female mice were housed with other mice receiving diets containing 2-methyl-1-nitroanthraquinone (129-15-7); acetylaminofluorene (53-96-3); p-cresidine (120-71-8); and 4-chloro-m-phenylenediamine (5131-60-2). Low dose treated female mice, high dose control

*CAS registry numbers are given in parentheses.

male mice, low dose control male mice, and high dose control female mice were housed with other mice receiving diets containing cupferron (135-20-6); 2,5-dithiobiurea (142-46-1); 4-chloro-o-phenylenediamine (95-83-0); o-anisidine hydrochloride (134-29-0); and p-anisidine hydrochloride (20265-97-8).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of fenaminosulf for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among five groups, each consisting of five males and five females. Fenaminosulf was incorporated into the basal laboratory diet and supplied ad libitum to four of the five rat groups and four of the five mouse groups in concentrations of 0.008, 0.015, 0.030, and 0.060 percent. The fifth group of each species served as a control group, receiving only the basal laboratory diet. The dosed dietary preparations were administered for a period of 7 weeks, followed by a 1-week observation period during which all animals were fed the untreated basal diet.

The highest concentration causing no deaths, no compound-related gross abnormalities, and no mean body weight depression in excess of 30 percent relative to controls was selected as the high concentration utilized for the rat and mouse chronic bioassays.

No deaths or gross abnormalities were observed in male or female rats treated with fenaminosulf. Mean body weight depression was

approximately 28 and 8 percent, respectively, in male and female rats receiving a dietary concentration of 0.060 percent. The initial high dose selected for use in the rat chronic bioassay was 0.10 percent for both sexes.

One of the five male and one of the five female mice receiving dietary concentrations of 0.060 percent fenaminosulf died. No mean body weight depression was observed among male mice. There was, however, slight spleen enlargement in all males treated with 0.060 percent. Mean body weight depression was approximately 14 percent in female mice treated with 0.060 percent. The initial high doses selected for use in the mouse chronic bioassay were 0.20 and 0.10 percent for males and females, respectively.

F. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, actual concentrations administered, duration of treated and untreated observation periods, and the time-weighted average concentrations) are summarized in Tables 1 and 2.

The rat groups receiving an initial concentration of 0.20 percent had a lower time-weighted average dose at the end of the study, than the rat groups receiving an initial concentration of 0.10 percent, and thus will be referred to as the low dose groups throughout this report, while the latter groups will be referred to as the high dose groups. At the time of inclusion in the study, high dose and control male and female rats were approximately 6 weeks old. Low

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
FENAMINOSULF FEEDING EXPERIMENT

	INITIAL GROUP SIZE	FENAMINOSULF CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	50	0	0	110	0
LOW DOSE[c]	50	0.20 0.05 0	1 77	 27	0.05
HIGH DOSE[c]	50	0.10 0.05 0.10 0	1 6 71	 31	0.10
FEMALE					
CONTROL	50	0	0	110	0
LOW DOSE[c]	50	0.20 0.05 0	1 77	 27	0.05
HIGH DOSE[c]	50	0.10 0.05 0.10 0	1 6 71	 31	0.10

[a] Concentrations given in percentages in feed.

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

[c] Group designations were determined by time-weighted average concentrations.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
FENAMINOSULF FEEDING EXPERIMENT

	INITIAL GROUP SIZE	FENAMINOSULF CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	50	0	0	97	0
LOW DOSE	50	0.10 0.05 0.10 0	1 6 71	 17	0.10
HIGH DOSE	50	0.20 0.10 0.20 0	1 6 71	 17	0.19
FEMALE					
LOW DOSE CONTROL	50	0	0	97	0
HIGH DOSE CONTROL	50	0	0	98	0
LOW DOSE[c]	50	0.20 0.05 0	1 77	 19	0.05
HIGH DOSE[c]	49	0.10 0.05 0.10 0	1 6 71	 17	0.10

[a]Concentrations given in percentages in feed.

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

[c]Group designations were determined by time-weighted average concentrations.

dose male and female rats were also approximately 6 weeks old; however, they were started on test 12 weeks later than the other groups. The high and low concentrations utilized for both sexes for the first week were 0.20 and 0.10 percent. The dietary concentrations of fenaminosulf for all treated rats were reduced to 0.05 percent in week 2 and in week 8 the concentration administered to the high dose male and female rats was increased to 0.10 percent. These concentrations were maintained for the remainder of the fenaminosulf administration period. Subsequent to chemical exposure was an untreated observation period of up to 31 weeks.

As the female mouse group receiving an initial concentration of 0.20 percent had the lower time-weighted average dose at the end of the bioassay, this female mouse group will be referred as the low dose group throughout this report; the female mouse group receiving an initial concentration of 0.10 percent, on the other hand, will be referred to as the high dose group. For males the initial concentrations utilized were 0.20 and 0.10 percent and the males receiving the former concentration will be referred to as the high dose group while those receiving the latter will be referred to as the low dose group. At the time of inclusion in the study all mice were approximately 6 to 7 weeks old. High and low dose males and high dose females were approximately 5 weeks older than their controls. The low dose females were 12 weeks younger than the other treated mice and the low dose control females were 1 week younger than the low dose treated

females. The high and low dose male mice received initial dietary concentrations of 0.20 and 0.10 percent, respectively. After 1 week the concentrations were decreased to 0.10 and 0.05 percent for high and low dose male mice, respectively. Six weeks later concentrations were increased to original levels and these were maintained for the remainder of the fenaminosulf administration period. Subsequently, the male mice were observed for an untreated period of up to 17 weeks. The high and low dose females received initial dietary concentrations of 0.10 and 0.20 percent, respectively. After 1 week the concentration administered to both groups was decreased to 0.05 percent. Six weeks later the concentration administered to the high dose groups was increased to 0.10 percent. These concentrations were maintained for the remainder of the fenaminosulf administration period. An untreated observation period of up to 19 weeks followed.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights were recorded twice weekly for the first 12 weeks of the study and at monthly intervals thereafter. From the first day, all animals were inspected twice daily for mortality. Food consumption, for two cages from each group, was monitored for seven consecutive days once a month for the first nine months of the bioassay and for three consecutive days each month thereafter. The presence of tissue masses and lesions was determined by monthly observation and palpation of each animal.

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

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

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, uterus, mammary gland, and ovary.

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

H. Data Recording and Statistical Analyses

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

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

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

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

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

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

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing

these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

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

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it

can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

No distinct mean body weight depression was associated with compound administration in either males or females (Figure 1). Although the low dose male groups experienced high early mortality, the mean body weight for this group was consistently higher than that for the other male groups.

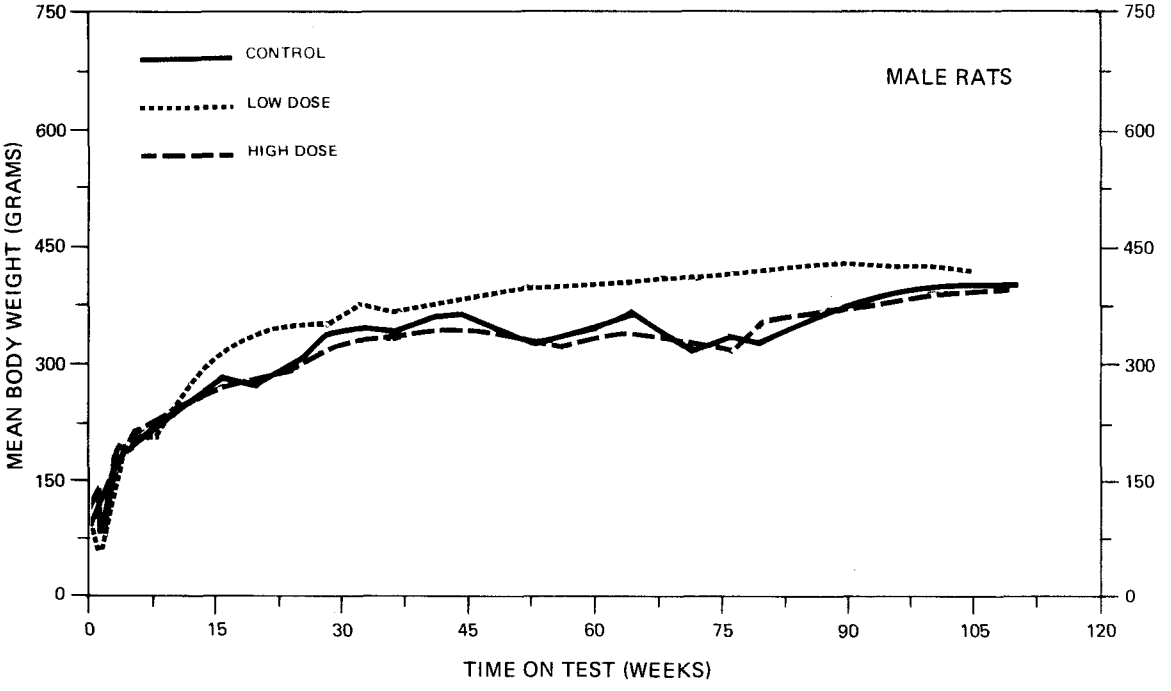
Two high dose females developed subcutaneous masses, one high dose female had a cutaneous growth, and one control male developed a crusted cutaneous lesion. One high dose female and one low dose male exhibited discoloration of the eye and there was brown exudate from the eyes of one low dose female.

B. Survival

The estimated probabilities of survival for male and female rats in the control and fenaminosulf-dosed groups are shown in Figure 2.

Twenty-one of the original high dose male rats died in weeks 1 or 2 from toxic effects--at which point the dosage was lowered and the original high dose group was renamed as the low dose group. These 21 animals were excluded for test purposes; the Tarone test did not indicate a positive association between dosage and mortality.

Five animals were sacrificed from the high dose treated group and five from the control group in week 78. Adequate numbers of males were at risk from late-developing tumors as 78 percent (39/50)



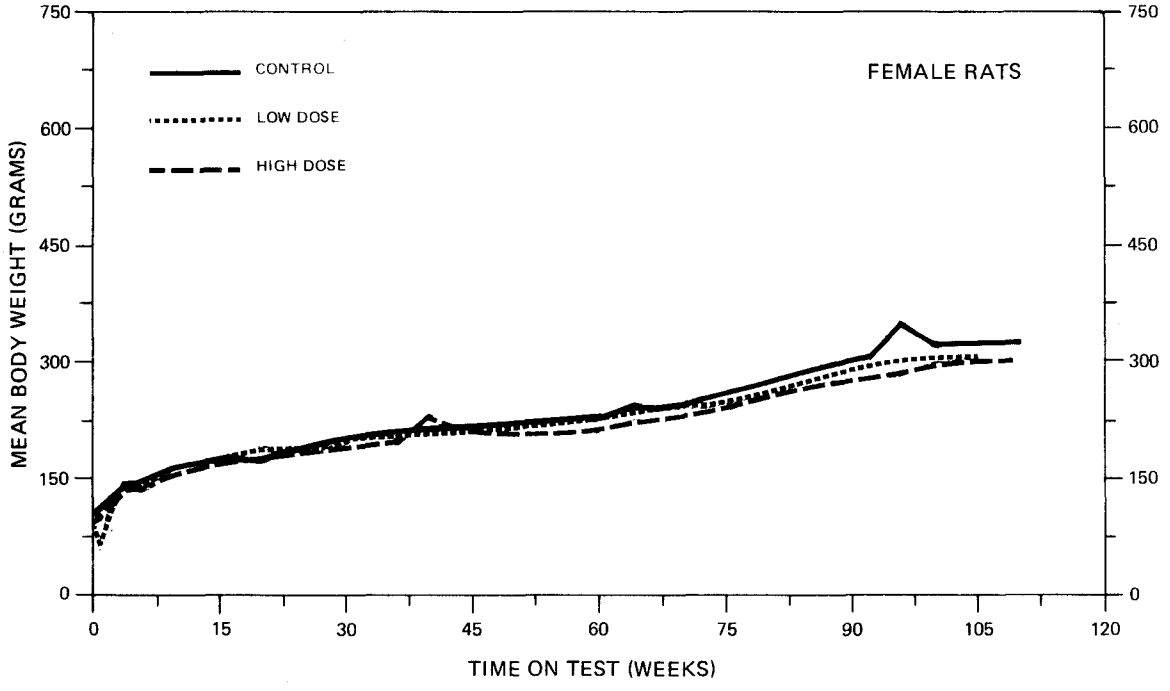
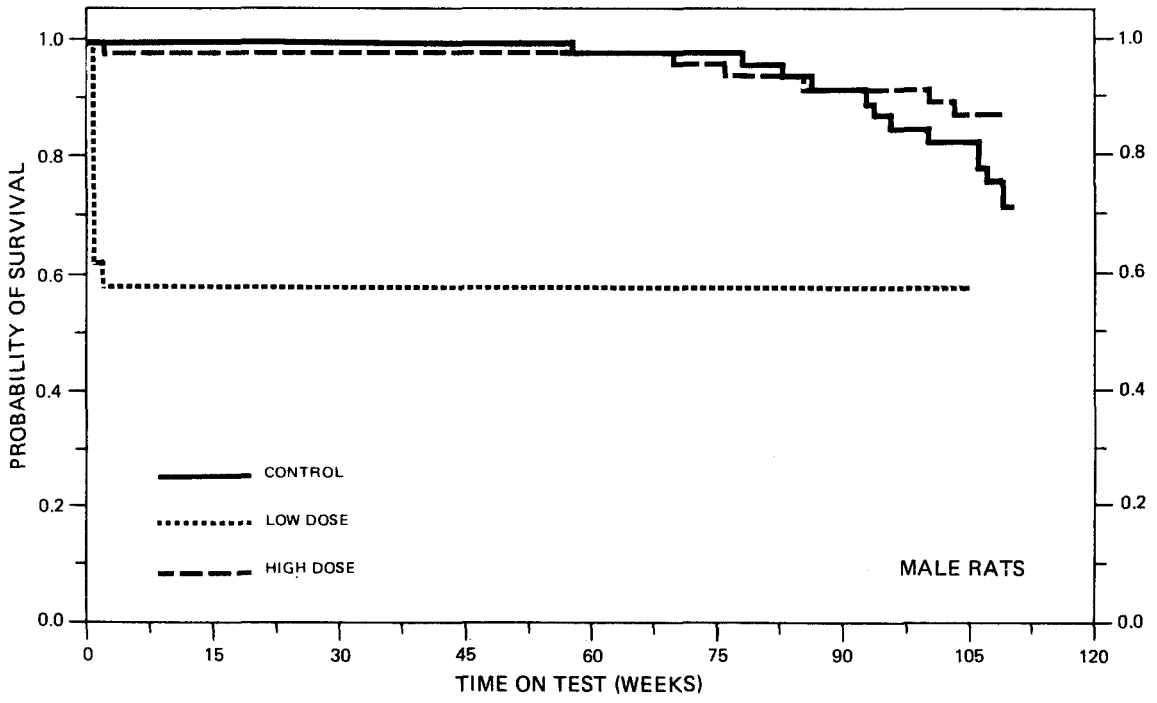


FIGURE 1
GROWTH CURVES FOR FENAMINOSULF CHRONIC STUDY RATS



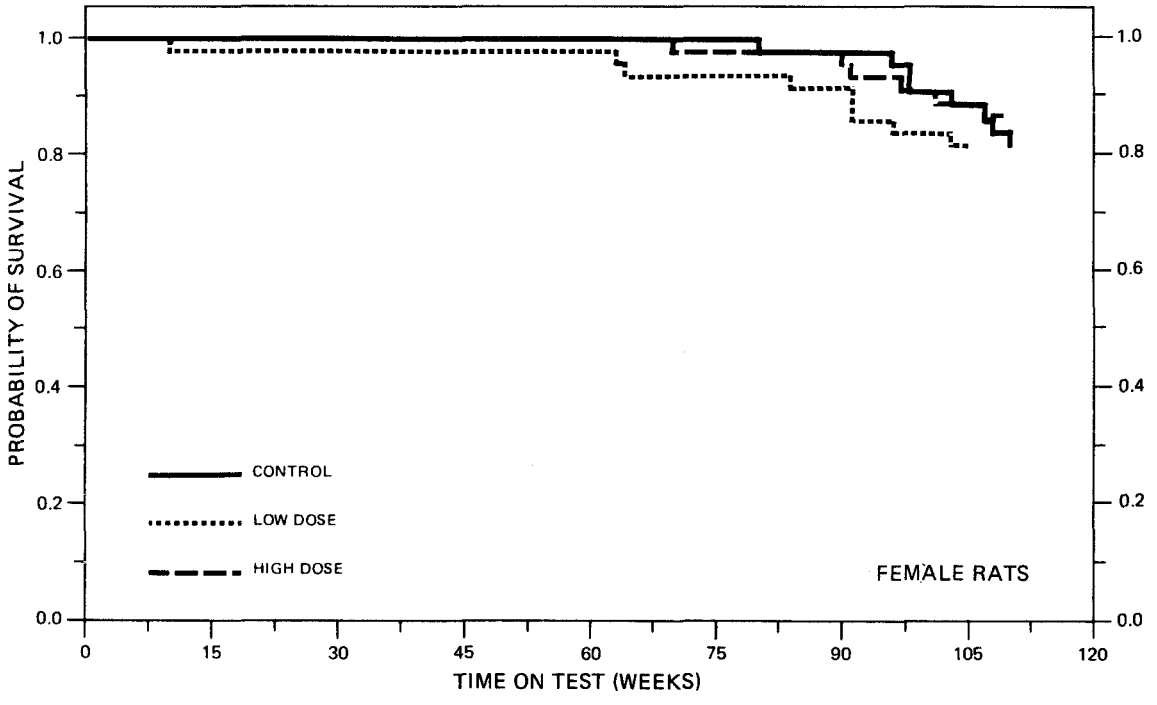


FIGURE 2
SURVIVAL COMPARISONS OF FENAMINOSULF CHRONIC STUDY RATS

high dose, 58 percent (29/50) low dose, and 64 percent (32/50) control rats survived on test until the termination of the study.

For female rats, the Tarone test for association between dosage and mortality was not significant. Five animals were sacrificed from the high dose and five from the control group in week 78. With 78 percent (39/50) high dose, 82 percent (41/50) low dose and 72 percent (36/50) control rats alive on test until the end of the study, adequate numbers of females were at risk from late-developing tumors.

C. Pathology

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

A variety of neoplasms was observed with approximately equal frequency in the treated and control rats. The most frequently observed neoplasms in the male rats were interstitial-cell adenomas of the testis. In the female rats, the most commonly observed neoplasms were adenomas of the pituitary gland, fibroadenomas of the mammary gland, and endometrial stromal polyps of the uterus. A high spontaneous incidence of these tumors is characteristic of aged Fischer 344 rats. A neoplasm which was observed in the treated female rats was endometrial stromal sarcoma. This neoplasm was seen in 3/48 (6 percent) low dose females and 1/47 (2 percent) high dose females but in none of the control females.

There were instances in this study, as noted in the summary tables, where neoplasms occurred only in treated animals, or with increased frequency when compared to the control animals. The nature and incidence of these lesions were similar to those known to occur spontaneously in aged Fischer 344 rats.

A high incidence of necrosis and mineralization of the tubules of the renal papilla was present in the treated rats. These lesions were not observed in control rats. Mineralization of tubules was present in 21/41 (51 percent) low dose and 32/48 (67 percent) high dose male rats and 34/48 (71 percent) low dose and 12/49 (24 percent) high dose female rats. The severity of the papillary necrosis and mineralization was quite variable and was superimposed on chronic renal disease (nephrosis, nephropathy) commonly seen in aged Fischer 344 rats. Several other nonneoplastic lesions commonly seen in aged Fischer 344 rats were observed with approximately equal frequency in the treated and control animals.

Under the conditions of this study, the administration of fenaminosulf did not appear to induce neoplastic lesions in Fischer 344 rats. Although endometrial stromal sarcomas were present only in treated female rats, the low incidence observed in this study does not provide conclusive evidence that these neoplasms were induced by the compound. The concentrations of the compound administered did have a toxic effect on the kidney, producing tubular necrosis and mineralization of the renal papilla.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or fenaminosulf-dosed groups and where such tumors were observed in at least 5 percent of the group. Because of high early mortality noted in rats of both sexes, the analyses for males were based on those rats surviving at least 52 weeks.

In male rats the Fisher exact test indicated a significantly ($P = 0.021$) higher incidence of interstitial-cell tumors of the testis in the low dose treated group than in the control. The high dose comparison and the Cochran-Armitage test, however, were not significant.

For both male and female rats the possibility of a negative association between chemical administration and the incidence of leukemia or of malignant lymphomas was observed. For females, however, none of the Fisher exact tests were significant under the Bonferroni criterion.

No other statistical tests for any site indicated a significant association between compound administration and incidence. Based upon these results there was no convincing statistical evidence of the carcinogenicity of fenaminosulf in rats.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH FENAMINOSULF
SURVIVING AT LEAST 52 WEEKS[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Skin and Subcutaneous Tissue: Fibroma[b]	2/50(0.04)	2/29(0.07)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.724	1.531
Lower Limit	---	0.130	0.183
Upper Limit	---	22.468	17.671
Weeks to First Observed Tumor	86	105	108
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	10/50(0.20)	1/29(0.03)	1/49(0.02)
P Values[c]	P = 0.002(N)	P = 0.037(N)	P = 0.004(N)
Relative Risk (Control)[d]	---	0.172	0.102
Lower Limit	---	0.004	0.002
Upper Limit	---	1.109	0.675
Weeks to First Observed Tumor	78	105	108
Pituitary: Adenoma NOS, Chromophobe Adenoma, or Acidophil Adenoma[b]	7/45(0.16)	7/26(0.27)	9/42(0.21)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.731	1.378
Lower Limit	---	0.577	0.502
Upper Limit	---	5.029	3.955
Weeks to First Observed Tumor	78	105	78

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma[b]	3/50(0.06)	6/29(0.21)	3/47(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.448	1.064
Lower Limit	---	0.796	0.149
Upper Limit	---	19.588	7.571
Weeks to First Observed Tumor	78	105	103
Thyroid: C-Cell Carcinoma[b]	2/37(0.05)	1/26(0.04)	2/44(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.712	0.841
Lower Limit	---	0.012	0.064
Upper Limit	---	12.845	11.135
Weeks to First Observed Tumor	109	105	108
Thyroid: C-Cell Carcinoma or C-Cell Adenoma[b]	3/37(0.08)	5/26(0.19)	3/44(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.372	0.841
Lower Limit	---	0.505	0.120
Upper Limit	---	13.893	5.944
Weeks to First Observed Tumor	109	105	108

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pancreatic Islets: Islet-Cell Carcinoma or Islet-Cell Adenoma[b]	1/47(0.22)	3/29(0.10)	2/47(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	4.862	2.000
Lower Limit	---	0.411	0.108
Upper Limit	---	245.698	115.483
Weeks to First Observed Tumor	110	105	108
Testis: Interstitial-Cell Tumor[b]	42/50(0.84)	29/29(1.00)	40/47(0.85)
P Values[c]	N.S.	P = 0.021	N.S.
Departure from Linear Trend[e]	P = 0.025	---	---
Relative Risk (Control)[d]	---	1.190	1.013
Lower Limit	---	1.007	0.842
Upper Limit	---	1.190	1.208
Weeks to First Observed Tumor	78	105	100

[a]Treated groups received time-weighted average doses of 0.05 or 0.10 percent in feed.

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

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

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

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

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	7/49(0.14)	1/48(0.02)	1/50(0.02)
P Values[c]	P = 0.010(N)	P = 0.032(N)	P = 0.028(N)
Relative Risk (Control)[d]	---	0.146	0.140
Lower Limit	---	0.003	0.003
Upper Limit	---	1.072	1.030
Weeks to First Observed Tumor	96	91	109
Pituitary: Adenoma NOS, Chromophobe Adenoma, or Acidophil Adenoma[b]	17/39(0.44)	18/40(0.45)	17/41(0.41)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.032	0.951
Lower Limit	---	0.598	0.542
Upper Limit	---	1.791	1.678
Weeks to First Observed Tumor	78	84	101
Adrenal: Pheochromocytoma[b]	3/49(0.06)	2/46(0.04)	2/46(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.710	0.710
Lower Limit	---	0.062	0.062
Upper Limit	---	5.914	5.914
Weeks to First Observed Tumor	110	63	70

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma[b]	2/45(0.04)	2/46(0.04)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.978	1.378
Lower Limit	---	0.074	0.166
Upper Limit	---	12.993	15.892
Weeks to First Observed Tumor	110	105	109
Thyroid: C-Cell Carcinoma or C-Cell Adenoma[b]	2/45(0.04)	2/46(0.04)	7/49(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.978	3.214
Lower Limit	---	0.074	0.654
Upper Limit	---	12.993	30.445
Weeks to First Observed Tumor	110	105	91
Mammary Gland: Fibroadenoma[b]	12/49(0.24)	8/48(0.17)	8/50(0.16)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.681	0.653
Lower Limit	---	0.265	0.254
Upper Limit	---	1.642	1.581
Weeks to First Observed Tumor	103	105	70

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	5/46(0.11)	7/48(0.15)	4/47(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.342	0.783
Lower Limit	---	0.396	0.165
Upper Limit	---	4.998	3.409
Weeks to First Observed Tumor	110	105	109
Uterus: Endometrial Stromal Sarcoma[b]	0/46(0.00)	3/48(0.06)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.578	0.053
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	91

[a]Treated groups received time-weighted average doses of 0.05 or 0.10 percent in feed.

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

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

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

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by fenaminosulf that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

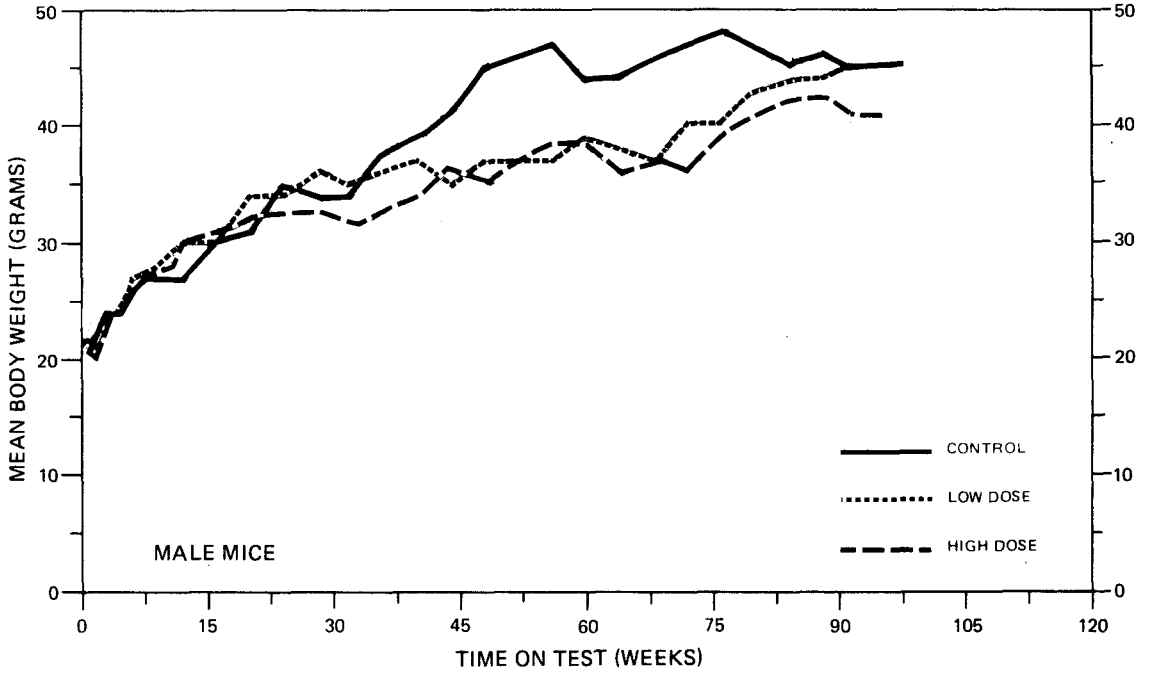
There was no significant mean body weight depression in treated male mice when compared to controls until approximately week 32, at which time the mean body weight of the treated male mice was consistently lower than that of control mice (Figure 3). Slight mean body weight depression was noted when low dose female mice were compared to their controls. Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

No clinical abnormalities were observed in treated or control mice of either sex.

B. Survival

The estimated probabilities of survival for male and female mice in the control and fenaminosulf-dosed groups are shown in Figure 4.

Nineteen of the 50 high dose male mice died in weeks 1 or 2 from toxic reactions. After excluding these mice, the Tarone test still indicated a significant positive association between dose and mortality. Twelve high dose male mice died in weeks 42 and 43, nine of which were autolyzed. With only 13 of the high dose male mice surviving on test beyond week 52, five of which were sacrificed in week 78, inadequate numbers of high dose male mice were at risk from late-developing tumors. Five control male mice were sacrificed in week 79. Survival was adequate in the low dose and control groups



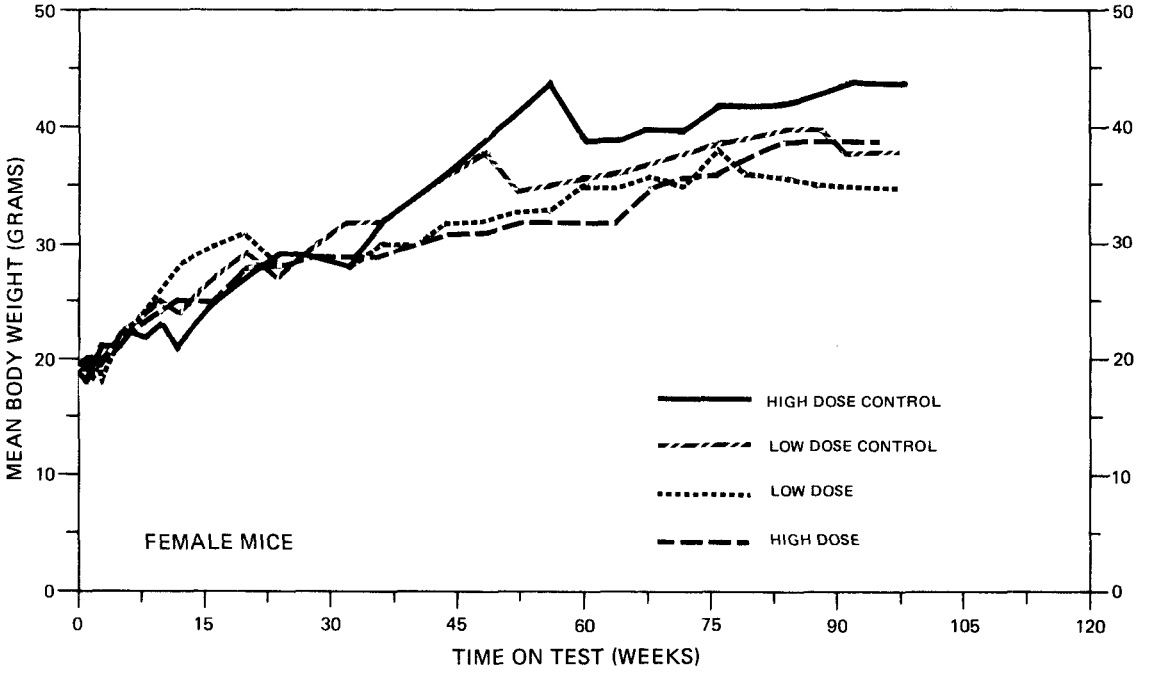
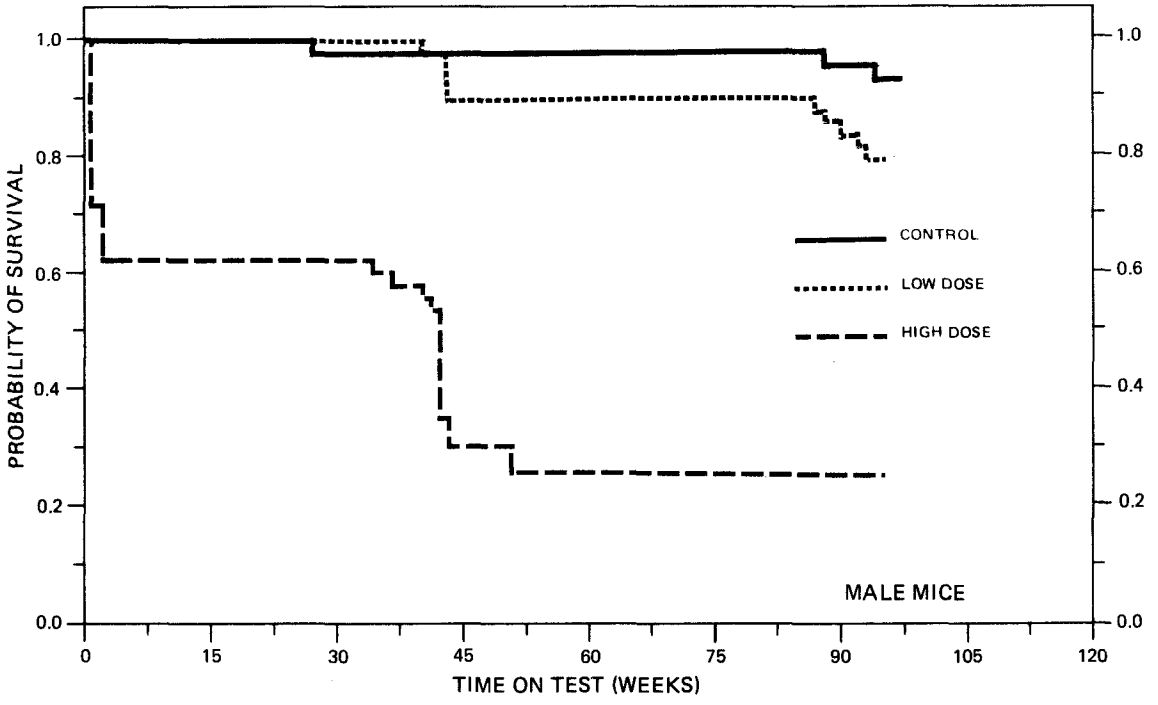


FIGURE 3
GROWTH CURVES FOR FENAMINOSULF CHRONIC STUDY MICE



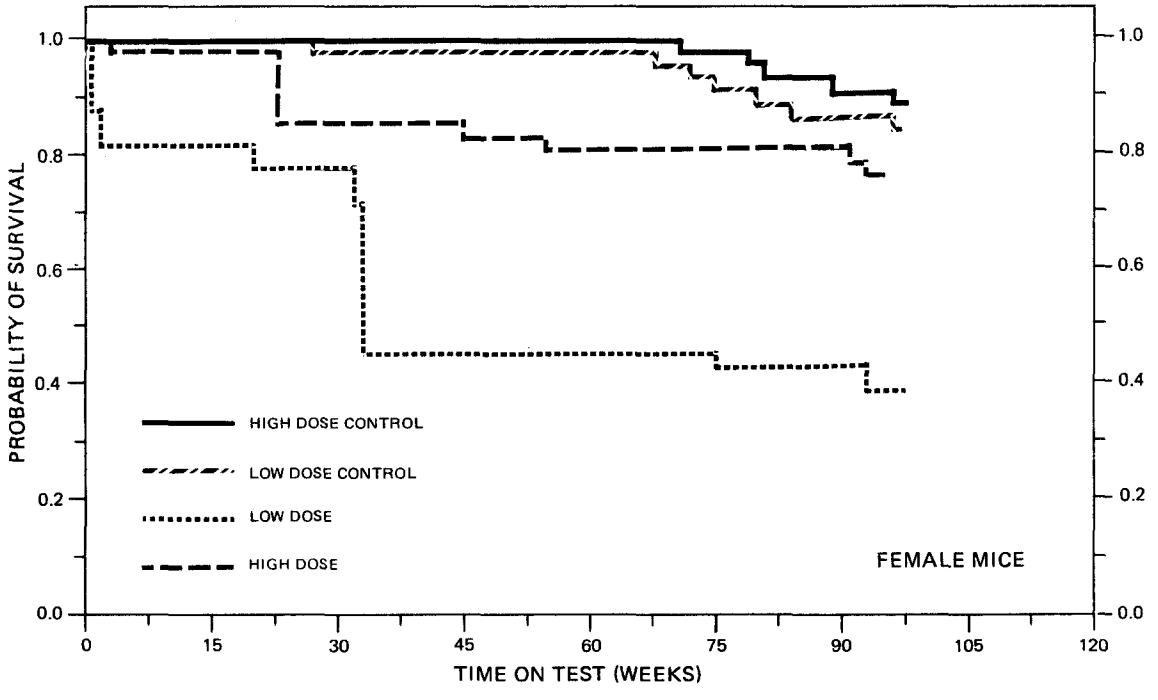


FIGURE 4
SURVIVAL COMPARISONS OF FENAMINOSULF CHRONIC STUDY MICE

with 78 percent (39/50) of the low dose and 84 percent (42/50) of the controls surviving on test until the end of the study.

For female mice the Cox tests also showed significant positive differences between each of the dosed groups and its respective control; for the low dose those females that died in weeks 1 and 2 were excluded for this Cox test. The departure from linear trend was also significant, primarily because survival was poorer in the low dose group than in the high dose group. Five females from the high dose treated group, five from the low dose control, and five from the high dose control group were sacrificed in week 79. Adequate numbers of female mice were at risk from late-developing tumors with 64 percent (32/50) of the high dose, 72 percent (36/50) of the low dose control, and 80 percent (40/50) of the high dose control mice alive on test until the end of the study. In the low dose group, 18/21 of those mice surviving at least 52 weeks were alive on test until the end of the study. Since no tumors were observed in females that died before week 78, there was no evidence that early mortality was tumor-related.

C. Pathology

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

A variety of neoplasms occurred with approximately equal frequency in the treated and control mice. Occasionally, as shown in

the summary tables, neoplasms occurred only in the treated mice or with an increased frequency when compared with the control animals. The nature and incidence of these neoplasms were similar to spontaneously occurring neoplasms in B6C3F1 mice. An unusual tumor was a teratoma of the ovary in 1/37 (3 percent) of the high dose mice.

The treated mice had a variety of nonneoplastic lesions. The incidence and severity of the lesions were approximately equal in the treated and control groups, with the exception of 13/16 low dose female mice that died in weeks 32 and 33 having either kidney nephropathy, kidney tubule mineralization, or both.

The results of this microscopic examination indicate that the administration of fenaminosulf was not carcinogenic to B6C3F1 mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or fenaminosulf-dosed groups and where such tumors were observed in at least 5 percent of the group. Because of high early mortality noted in mice of both sexes, these analyses were based on those mice surviving at least 52 weeks. No Cochran-Armitage tests were used in the analyses of the female mice because the high dose group and its control were started at a different time from the low dose group and its control.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH FENAMINOSULF SURVIVING AT LEAST 52 WEEKS[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	3/47(0.06)	3/42(0.07)	0/13(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.119	0.000
Lower Limit	---	0.158	0.000
Upper Limit	---	7.921	5.581
Weeks to First Observed Tumor	97	90	---
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	7/47(0.15)	7/42(0.17)	1/13(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.119	0.516
Lower Limit	---	0.365	0.012
Upper Limit	---	3.421	3.391
Weeks to First Observed Tumor	97	90	95
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	1/49(0.02)	7/43(0.16)	0/13(0.00)
P Values[c]	N.S.	P = 0.019	N.S.
Departure from Linear Trend[e]	P = 0.009	---	---
Relative Risk (Control)[d]	---	7.977	0.000
Lower Limit	---	1.088	0.000
Upper Limit	---	349.807	66.474
Weeks to First Observed Tumor	97	87	---

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	15/49(0.31)	7/43(0.16)	2/13(0.15)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.532	0.503
Lower Limit	---	0.202	0.060
Upper Limit	---	1.243	1.752
Weeks to First Observed Tumor	94	88	95
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	15/49(0.31)	9/43(0.21)	2/13(0.15)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.684	0.503
Lower Limit	---	0.294	0.060
Upper Limit	---	1.485	1.752
Weeks to First Observed Tumor	94	88	95

[a]Treated groups received time-weighted doses of 0.10 or 0.19 percent in feed.

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

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

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

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

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH FENAMINOSULF SURVIVING AT LEAST 52 WEEKS[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	3/45(0.07)	3/50(0.06)	0/20(0.00)	1/39(0.03)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.427
Lower Limit	---	---	0.000	0.008
Upper Limit	---	---	3.598	5.060
Weeks to First Observed Tumor	97	79	---	93
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	4/45(0.09)	4/50(0.08)	3/20(0.15)	4/39(0.10)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.687	1.282
Lower Limit	---	---	0.265	0.253
Upper Limit	---	---	8.837	6.438
Weeks to First Observed Tumor	97	79	93	93
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	6/46(0.13)	6/50(0.12)	3/20(0.15)	5/39(0.13)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.150	1.068
Lower Limit	---	---	0.200	0.277
Upper Limit	---	---	4.701	3.872
Weeks to First Observed Tumor	68	98	93	91

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	0/45(0.00)	2/49(0.04)	2/19(0.11)	3/37(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	1.986
Lower Limit	---	---	0.706	0.239
Upper Limit	---	---	Infinite	22.690
Weeks to First Observed Tumor	---	98	97	78
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	0/45(0.00)	2/49(0.04)	4/19(0.21)	3/37(0.08)
P Values[c]	---	---	P = 0.006	N.S.
Relative Risk (Control)[d]	---	---	Infinite	1.986
Lower Limit	---	---	2.228	0.239
Upper Limit	---	---	Infinite	22.690
Weeks to First Observed Tumor	---	98	93	78
Pituitary: Adenoma NOS[b]	1/32(0.03)	0/42(0.00)	3/16(0.19)	3/32(0.09)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	6.000	Infinite
Lower Limit	---	---	0.523	0.796
Upper Limit	---	---	291.426	Infinite
Weeks to First Observed Tumor	80	---	97	95

TABLE 6 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 0.05 or 0.10 percent in feed.

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

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

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

In male mice the incidence of leukemia or malignant lymphoma was increased in the low dose treated group. The Fisher exact test showed a significantly (P = 0.019) greater incidence in the low dose than in the control group. However, in historical data compiled by this laboratory for the NCI Carcinogenesis Testing Program 29/275 (11 percent) of the untreated male B6C3F1 mice had a malignant lymphoma or leukemia, compared to the 7/43 (16 percent) observed in the low dose group.

In female mice the combined incidence of hepatocellular adenomas or hepatocellular carcinomas was increased in the treated groups compared to their respective controls. The results of the Fisher exact test comparing the low dose treated group to its control was significant (P = 0.006). This was not supported, however, by significant high dose Fisher exact test results.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by fenaminosulf that could not be established under the conditions of this test.

V. DISCUSSION

It is recognized that the results reported in this study are not for pure or technical-grade fenaminosulf, but for the commercially available formulated product containing fenaminosulf.

There was no significant association for female rats between fenaminosulf dosage and mortality; this was also true for male rats if the 21 males that died in the first two weeks of the bioassay are excluded from consideration. For both male and female mice there was a significant positive association between dosage and mortality. In all groups of both species, except for high dose male and low dose female mice, adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors.

No convincing statistical evidence was provided for a significant positive association between compound administration and the incidence of any tumor in male or female rats. Endometrial stromal sarcomas were observed only in treated female rats (i.e., 3/48 [6 percent] low dose and 1/47 [2 percent] high dose). These incidences did not, however, prove to be statistically significant when compared to controls.

There were increased incidences of necrosis and mineralization of the renal papillary tubules in treated rats and mice when compared to controls. The severity of these lesions was variable and they were observed in addition to the chronic renal disease often seen in aging rodents.

When those female mice having either hepatocellular carcinomas or hepatocellular adenomas were combined and the resulting tumor incidences statistically analyzed, the low dose group had an incidence significantly higher than that of the low dose control group. This finding was not, however, supported by similar results for the high dose females. In addition, the historical incidence for this combination of tumors in control female mice at Mason Research Institute during the NCI Carcinogenesis Testing Program was 19/275 (7 percent), in contrast to the 0/46 observed in the low dose controls during this chronic study. The importance of the significant Fisher exact comparison for hepatocellular neoplasms in low dose female mice, therefore, appears questionable and is considered as insufficient evidence of carcinogenicity.

When those male mice having leukemia or malignant lymphoma were combined and the resulting tumor incidences statistically analyzed, the Fisher exact test indicated a significantly greater incidence of these neoplasms in the low dose group when compared with controls. However, the incidence of these neoplasms in the historical control untreated male B6C3F1 mice compiled by this laboratory for the Carcinogenesis Testing Program is 29/275 (11 percent) as compared to 7/43 (16 percent) observed in the low dose male mice in this bioassay, not a convincing difference.

No unusual tumors were observed among mice of either sex and no convincing statistical evidence was provided for a significant

positive association between compound administration and the incidence of any tumor in either sex.

Contradictory carcinogenicity data have been obtained in two other studies with fenaminosulf. An unspecified number of Sprague-Dawley rats fed fenaminosulf at a concentration of 1000 mg/kg of diet developed "hepatomas resembling those produced by dimethylaminoazobenzene" after 12 months (Herrmann and DuBois, 1949); however, no liver tumors were found in 2 groups of 20 Holtzmann rats 15 months after administration of a diet containing 1.35 or 4.0 millimoles of fenaminosulf per kg of feed (339.12 or 1004.8 mg/kg) (Miller et al., 1957).

Under the conditions of this bioassay, dietary administration of formulated fenaminosulf was not carcinogenic in either Fischer 344 rats or B6C3F1 mice.

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

April 26, 1978

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

The primary reviewer said that the compound was not carcinogenic in rats or mice under the conditions of test. He noted that only 35% of the tested compound was estimated to be Fenaminosulf, the remainder being clay, silica, sodium naphthalene sulfonate, and sodium ligno-sulfate. Despite certain experimental shortcomings, he said that the study was adequate to conclude that Formulated Fenaminosulf was not carcinogenic under the conditions of test.

Although the secondary reviewer agreed that the study was "essentially negative," he pointed out the elevated incidence of hepatocellular carcinomas in low dose treated female mice and hematopoietic system tumors in low dose treated male mice. The meaningfulness of these increases was obscured by excessive early mortality due to toxicity. If Formulated Fenaminosulf is still a major environmental hazard, he suggested that it be retested, at least in mice.

A motion was made that the report on the bioassay of Formulated Fenaminosulf be accepted as written. The motion was seconded and approved unanimously.

Members present were:

Michael Shimkin (Acting Chairman), University of California at San Diego
Joseph Highland, Environmental Defense Fund
George Roush, Jr., Monsanto Company
Louise Strong, University of Texas Health Sciences Center
John Weisburger, American Health Foundation
(David Clayson, Eppley Institute for Cancer Research, submitted a written review)

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

☆U.S. GOVERNMENT PRINTING OFFICE: 1978-260-899/3205

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH FENAMINOSULF

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

	CONTROL (UNTR) 01-0160	LOW DOSE 01-R150	HIGH DOSE 01-0140
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	43	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	41	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(43)	(49)
FIBROMA	1 (2%)		
FIBROSARCOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(43)	(49)
SARCOMA, NOS	1 (2%)	1 (2%)	
FIBROMA	1 (2%)	2 (5%)	3 (6%)
FIBROSARCOMA	1 (2%)		
LEIOMYOSARCOMA			1 (2%)
FIBROADENOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(41)	(48)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		1 (2%)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(43)	(49)
LEUKEMIA,NOS	1 (2%)		
MYELOMONOCYTIC LEUKEMIA	9 (18%)		
#SPLEEN	(50)	(41)	(48)
MYELOMONOCYTIC LEUKEMIA		1 (2%)	1 (2%)
#THYMUS	(24)	(23)	(34)
C-CELL CARCINOMA, METASTATIC		1 (4%)	
CIRCULATORY SYSTEM			
#HEART	(48)	(40)	(48)
SARCOMA, NOS, METASTATIC	1 (2%)		

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0160	LOW DOSE 01-R150	HIGH DOSE 01-0140
DIGESTIVE SYSTEM			
#LIVER	(49)	(41)	(48)
NEOPLASTIC NODULE		1 (2%)	
#JEJUNUM	(49)	(36)	(47)
SARCOMA, NOS		1 (3%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(30)	(42)
ADENOMA, NOS	5 (11%)	4 (13%)	5 (12%)
CHROMOPHOBE ADENOMA	2 (4%)	3 (10%)	2 (5%)
ACIDOPHIL ADENOMA			2 (5%)
#ADRENAL	(50)	(41)	(47)
CORTICAL ADENOMA		1 (2%)	1 (2%)
PHEOCHROMOCYTOMA	3 (6%)	6 (15%)	3 (6%)
#THYROID	(37)	(31)	(44)
FOLLICULAR-CELL CARCINOMA	1 (3%)		1 (2%)
C-CELL ADENOMA	1 (3%)	4 (13%)	1 (2%)
C-CELL CARCINOMA	2 (5%)	1 (3%)	2 (5%)
#PARATHYROID	(20)	(17)	(24)
ADENOMA, NOS		1 (6%)	
#PANCREATIC ISLETS	(47)	(40)	(47)
ISLET-CELL ADENOMA	1 (2%)	2 (5%)	2 (4%)
ISLET-CELL CARCINOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(43)	(49)
CARCINOMA,NOS	2 (4%)		
#TESTIS	(50)	(41)	(47)
INTERSTITIAL-CELL TUMOR	42 (84%)	29 (71%)	40 (85%)

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0160	LOW DOSE 01-R150	HIGH DOSE 01-0140
NERVOUS SYSTEM			
#CEREBRAL CORTEX	(50)	(39)	(47)
GLIOMA, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(43)	(49)
SEBACEOUS ADENOCARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*BODY CAVITIES	(50)	(43)	(49)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	5	21	3
MORIBUND SACRIFICE	8		3
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	29	39
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-0160	LOW DOSE 01-R150	HIGH DOSE 01-0140
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	29	42
TOTAL PRIMARY TUMORS	76	60	66
TOTAL ANIMALS WITH BENIGN TUMORS	46	29	41
TOTAL BENIGN TUMORS	56	52	60
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	6	6
TOTAL MALIGNANT TUMORS	20	6	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	
TOTAL SECONDARY TUMORS	1	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH FENAMINOSULF

	CONTROL(UNTR) 02-0160	LOW DOSE 02-R150	HIGH DOSE 02-0140
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	48	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(49)	(48)	(50)
FIBROMA	2 (4%)	1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(49)	(48)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(48)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
LEUKEMIA,NOS	1 (2%)		
MYELOMONOCYTIC LEUKEMIA	6 (12%)		
#SPLEEN	(47)	(48)	(49)
MYELOMONOCYTIC LEUKEMIA			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(48)	(48)	(50)
HEPATOCELLULAR CARCINOMA	1 (2%)	1 (2%)	
#COLON	(49)	(45)	(42)
ADENOMATOUS POLYP, NOS		1 (2%)	
URINARY SYSTEM			
NONE			

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 02-0160	LOW DOSE 02-R150	HIGH DOSE 02-0140
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(40)	(41)
NEOPLASM, NOS			1 (2%)
ADENOMA, NOS	15 (38%)	16 (40%)	16 (39%)
CHROMOPHOBE ADENOMA	2 (5%)	2 (5%)	
ACIDOPHIL ADENOMA			1 (2%)
#ADRENAL	(49)	(46)	(46)
CORTICAL CARCINOMA			1 (2%)
PHEOCHROMOCYTOMA	3 (6%)	2 (4%)	2 (4%)
#THYROID	(45)	(46)	(49)
C-CELL ADENOMA			4 (8%)
C-CELL CARCINOMA	2 (4%)	2 (4%)	3 (6%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(48)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
PAPILLARY ADENOCARCINOMA			1 (2%)
FIBROADENOMA	12 (24%)	8 (17%)	8 (16%)
*CLITORAL GLAND	(49)	(48)	(50)
ADENOMA, NOS	1 (2%)		1 (2%)
#UTERUS	(46)	(48)	(47)
NEOPLASM, NOS			1 (2%)
ENDOMETRIAL STROMAL POLYP	5 (11%)	7 (15%)	4 (9%)
ENDOMETRIAL STROMAL SARCOMA		3 (6%)	1 (2%)
#OVARY	(47)	(48)	(49)
GRANULOSA-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(48)	(50)
ASTROCYTOMA	1 (2%)		1 (2%)
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(49)	(48)	(50)
CERUMINOUS CARCINOMA	1 (2%)		

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 02-0160	LOW DOSE 02-R150	HIGH DOSE 02-0140
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2	6	3
MORIBUND SACRIFICE	6	3	3
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	41	39
ANIMAL MISSING	1		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	31	33	30
TOTAL PRIMARY TUMORS	52	47	47
TOTAL ANIMALS WITH BENIGN TUMORS	27	30	25
TOTAL BENIGN TUMORS	40	38	36
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	8	8
TOTAL MALIGNANT TUMORS	12	8	9
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		1	2
TOTAL UNCERTAIN TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH FENAMINOSULF

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

	CONTROL (UNTR) 05-0160	LOW DOSE 05-0140	HIGH DOSE 05-0150
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	44	22
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	44	22
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(47)	(43)	(22)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (9%)	4 (9%)	1 (5%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	3 (7%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(44)	(22)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#SPLEEN	(49)	(43)	(20)
HEMANGIOMA			
HEMANGIOSARCOMA	1 (2%)	1 (2%)	
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#LYMPH NODE	(40)	(40)	(14)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
#MESENTERIC L. NODE	(40)	(40)	(14)
MALIGNANT LYMPHOMA, NOS			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
#LIVER	(49)	(44)	(22)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			
#PEYERS PATCH	(49)	(42)	(19)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 05-0160	LOW DOSE 05-0140	HIGH DOSE 05-0150
#THYMUS	(30)	(24)	(7)
MALIGNANT LYMPHOMA, NOS		1 (4%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(49)	(44)	(22)
HEPATOCELLULAR ADENOMA		2 (5%)	
HEPATOCELLULAR CARCINOMA	15 (31%)	7 (16%)	2 (9%)
#STOMACH	(49)	(41)	(19)
ADENOMATOUS POLYP, NOS	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(42)	(39)	(14)
FOLLICULAR-CELL ADENOMA			
FOLLICULAR-CELL CARCINOMA			
REPRODUCTIVE SYSTEM			
#TESTIS	(49)	(44)	(22)
INTERSTITIAL-CELL TUMOR	1 (2%)		
EMBRYONAL CARCINOMA			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(44)	(22)
CYSTADENOMA, NOS			

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 05-0160	LOW DOSE 05-0140	HIGH DOSE 05-0150
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	9	36
MORIBUND SACRIFICE		1	1
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	42	39	8
ANIMAL MISSING		1	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	20	3
TOTAL PRIMARY TUMORS	26	24	3
TOTAL ANIMALS WITH BENIGN TUMORS	6	6	1
TOTAL BENIGN TUMORS	6	6	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	15	2
TOTAL MALIGNANT TUMORS	20	18	2
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		
TOTAL SECONDARY TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

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

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
ANIMALS INITIALLY IN STUDY	50	50	50	@50
ANIMALS MISSING		2	2	1
ANIMALS NECROPSIED	50	47	43	42
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	47	38	39
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(47)	(43)	(42)
KERATOACANTHOMA		1 (2%)		
*SUBCUT TISSUE	(50)	(47)	(43)	(42)
FIBROSARCOMA	1 (2%)			
HEMANGIOSARCOMA	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG	(50)	(46)	(39)	(39)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)	3 (8%)	3 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	3 (7%)		1 (3%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(47)	(43)	(42)
MALIGNANT LYMPHOMA, NOS	3 (6%)	1 (2%)	2 (5%)	2 (5%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		3 (6%)		
#BONE MARROW	(49)	(39)	(35)	(32)
HEMANGIOSARCOMA				1 (3%)
#SPLEEN	(49)	(45)	(38)	(38)
HEMANGIOSARCOMA	1 (2%)			1 (3%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	2 (4%)		1 (3%)
#MANDIBULAR L. NODE	(40)	(38)	(29)	(35)
MALIGNANT LYMPHOMA, NOS	1 (3%)			
#MESENTERIC L. NODE	(40)	(38)	(29)	(35)
MALIGNANT LYMPHOMA, NOS				1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMALS WERE INITIALLY IN THE STUDY BUT ONE ANIMAL WAS FOUND TO BE A MALE IN A FEMALE GROUP.

TABLE B2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
#PEYERS PATCH	(49)	(44)	(34)	(37)
MALIGNANT LYMPHOMA, NOS	1 (2%)		1 (3%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (3%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(49)	(46)	(36)	(37)
HEPATOCELLULAR ADENOMA			2 (6%)	
HEPATOCELLULAR CARCINOMA	2 (4%)		2 (6%)	3 (8%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(33)	(25)	(32)
ADENOMA, NOS		1 (3%)	3 (12%)	3 (9%)
#ADRENAL/CAPSULE	(47)	(40)	(37)	(39)
ADENOMA, NOS		1 (3%)		
#THYROID	(41)	(29)	(27)	(31)
FOLLICULAR-CELL ADENOMA		1 (3%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(47)	(43)	(42)
ADENOCARCINOMA, NOS			1 (2%)	
#OVARY	(48)	(40)	(32)	(37)
PAPILLARY ADENOMA		1 (3%)		
PAPILLARY CYSTADENOMA, NOS			1 (3%)	
TERATOMA, BENIGN				1 (3%)
NERVOUS SYSTEM				
NONE				

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

TABLE B2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(47)	(43)	(42)
CYSTADENOMA, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	3	4	23	10
MORIBUND SACRIFICE	2	3	7	1
SCHEDULED SACRIFICE	5	5		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	40	36	18	32
ANIMAL MISSING		2	2	1
ANIMAL DELETED (WRONG SEX)				1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	14	10	16
TOTAL PRIMARY TUMORS	15	15	15	19
TOTAL ANIMALS WITH BENIGN TUMORS	1	5	7	8
TOTAL BENIGN TUMORS	1	6	9	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	9	5	10
TOTAL MALIGNANT TUMORS	14	9	6	11
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			
TOTAL SECONDARY TUMORS	1			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MAIIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

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

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

	CONTROL (UNTR) 01-0160	LOW DOSE 01-R150	HIGH DOSE 01-0140
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	43	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	41	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(43)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(41)	(48)
CONGESTION, CHRONIC PASSIVE	1 (2%)		
INFLAMMATION, INTERSTITIAL	4 (8%)	2 (5%)	1 (2%)
FIBROSIS, DIFFUSE	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL		2 (5%)	1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
#LUNG/ALVEOLI	(49)	(41)	(48)
HEMORRHAGE	1 (2%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(41)	(48)
FIBROSIS	1 (2%)		
HEMOSIDEROSIS	2 (4%)		2 (4%)
HEMATOPOIESIS			1 (2%)
#LYMPH NODE	(49)	(34)	(47)
INFLAMMATION, NOS			1 (2%)
#MANDIBULAR L. NODE	(49)	(34)	(47)
HYPERPLASIA, PLASMA CELL	1 (2%)		
#MESENTERIC L. NODE	(49)	(34)	(47)
HYPERPLASIA, PLASMA CELL	1 (2%)		

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0160	LOW DOSE 01-R150	HIGH DOSE 01-0140
CIRCULATORY SYSTEM			
#MYOCARDIUM	(48)	(40)	(48)
INFLAMMATION, INTERSTITIAL	1 (2%)		
FIBROSIS	2 (4%)		
DEGENERATION, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(38)	(46)
HYPERTROPHY, FOCAL		1 (3%)	
HYPERPLASIA, INTRADUCTAL	1 (2%)		
#LIVER	(49)	(41)	(48)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NECROSIS, FOCAL	3 (6%)	1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	2 (4%)
HYPERPLASIA, FOCAL	1 (2%)	4 (10%)	5 (10%)
#LIVER/CENTRILOBULAR	(49)	(41)	(48)
CONGESTION, PASSIVE	1 (2%)		
*BILE DUCT	(50)	(43)	(49)
HYPERPLASIA, NOS	2 (4%)		2 (4%)
#PANCREAS	(47)	(40)	(47)
INFLAMMATION, NOS	2 (4%)		2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#PANCREATIC ACINUS	(47)	(40)	(47)
ATROPHY, NOS			1 (2%)
#STOMACH	(49)	(40)	(46)
HYPERKERATOSIS	1 (2%)		
ACANTHOSIS	1 (2%)	1 (3%)	
#PEYERS PATCH	(49)	(36)	(47)
HYPERPLASIA, NOS	1 (2%)		2 (4%)
#JEJUNUM	(49)	(36)	(47)
METAPLASIA, OSSEOUS		1 (3%)	
#COLON	(48)	(30)	(43)
PARASITISM			2 (5%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0160	LOW DOSE 01-R150	HIGH DOSE 01-0140
URINARY SYSTEM			
#KIDNEY	(50)	(41)	(48)
HYDRONEPHROSIS			1 (2%)
CONGESTION, NOS	1 (2%)		
GLOMERULONEPHRITIS, NOS	4 (8%)		5 (10%)
NEPHROPATHY		39 (95%)	42 (88%)
DEGENERATION, CYSTIC		1 (2%)	
NEPHROSIS, NOS	35 (70%)		
HYPERPLASIA, EPITHELIAL		1 (2%)	
#KIDNEY/TUBULE	(50)	(41)	(48)
MINERALIZATION		21 (51%)	32 (67%)
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(30)	(42)
CYST, NOS		1 (3%)	
CONGESTION, NOS	1 (2%)		
HYPERPLASIA, NOS		1 (3%)	2 (5%)
#ADRENAL MEDULLA	(50)	(41)	(47)
HYPERPLASIA, NOS		2 (5%)	1 (2%)
HYPERPLASIA, FOCAL		2 (5%)	5 (11%)
#THYROID	(37)	(31)	(44)
CYSTIC FOLLICLES	1 (3%)		
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, PAPILLARY			1 (2%)
HYPERPLASIA, C-CELL	2 (5%)		1 (2%)
#PARATHYROID	(20)	(17)	(24)
HYPERPLASIA, NOS			1 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(43)	(49)
HYPERPLASIA, NOS			2 (4%)
#PROSTATE	(48)	(26)	(39)
INFLAMMATION, NOS	3 (6%)		
ABSCESS, NOS			1 (3%)
HYPERPLASIA, FOCAL		1 (4%)	

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-0160	LOW DOSE 01-R150	HIGH DOSE 01-0140
#TESTIS	(50)	(41)	(47)
PERIVASCULITIS	1 (2%)		
CALCIFICATION, NOS	3 (6%)		
CALCIFICATION, FOCAL	1 (2%)		
ATROPHY, NOS	11 (22%)	4 (10%)	9 (19%)
HYPERPLASIA, INTERSTITIAL CELL	4 (8%)		5 (11%)
#TESTIS/TUBULE	(50)	(41)	(47)
MINERALIZATION		3 (7%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/RETINA	(50)	(43)	(49)
DEGENERATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(50)	(43)	(49)
FIBROSIS, DIFFUSE	1 (2%)		
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT		1	1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
AUTO/NECROPSY/NO HISTO		2	1
AUTOLYSIS/NO NECROPSY		7	1

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

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

	CONTROL(UNTR) 02-0160	LOW DOSE 02-R150	HIGH DOSE 02-0140
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	48	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(49)	(48)	(49)
CONGESTION, ACUTE PASSIVE	1 (2%)		
INFLAMMATION, INTERSTITIAL			3 (6%)
PNEUMONIA, CHRONIC MURINE			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(47)	(48)	(49)
HEMOSIDEROSIS	3 (6%)	5 (10%)	6 (12%)
HYPERPLASIA, HEMATOPOIETIC			2 (4%)
HYPERPLASIA, ERYTHROID			2 (4%)
HEMATOPOIESIS		8 (17%)	6 (12%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(48)	(48)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(48)	(48)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NECROSIS, FOCAL	1 (2%)		

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0160	LOW DOSE 02-R150	HIGH DOSE 02-0140
NECROSIS, COAGULATIVE		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	3 (6%)	2 (4%)
BASOPHILIC CYTO CHANGE	2 (4%)	9 (19%)	17 (34%)
HYPERPLASIA, FOCAL	1 (2%)	4 (8%)	10 (20%)
ANGIECTASIS			2 (4%)
HEMATOPOIESIS			1 (2%)
*BILE DUCT	(49)	(48)	(50)
HYPERPLASIA, NOS	2 (4%)		2 (4%)
HYPERPLASIA, FOCAL	1 (2%)		
#PANCREAS	(48)	(46)	(47)
INFLAMMATION, NOS			1 (2%)
#STOMACH	(49)	(45)	(47)
INFLAMMATION, NOS	1 (2%)		
ACANTHOSIS		1 (2%)	1 (2%)
#GASTRIC SUBMUCOSA	(49)	(45)	(47)
EDEMA, NOS	1 (2%)		
#PEYERS PATCH	(49)	(46)	(48)
HYPERPLASIA, NOS	2 (4%)		3 (6%)
#COLON	(49)	(45)	(42)
PARASITISM	1 (2%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(48)	(48)	(49)
HYDRONEPHROSIS		1 (2%)	
CYST, NOS			1 (2%)
GLOMERULONEPHRITIS, NOS	4 (8%)		3 (6%)
NEPHROPATHY		44 (92%)	35 (71%)
NEPHROSIS, NOS	29 (60%)		
#KIDNEY/CORTEX	(48)	(48)	(49)
METAMORPHOSIS FATTY	1 (2%)		
#KIDNEY/TUBULE	(48)	(48)	(49)
MINERALIZATION		34 (71%)	12 (24%)
ENDOCRINE SYSTEM			
#ADRENAL MEDULLA	(49)	(46)	(46)
HYPERPLASIA, FOCAL		4 (9%)	1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0160	LOW DOSE 02-R150	HIGH DOSE 02-0140
#THYROID	(45)	(46)	(49)
HYPERPLASIA, C-CELL	2 (4%)	2 (4%)	3 (6%)
#PARATHYROID	(27)	(21)	(35)
HYPERPLASIA, NOS		1 (5%)	
#PANCREATIC ISLETS	(48)	(46)	(47)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(48)	(50)
DILATATION/DUCTS	1 (2%)		
GALACTOCELE		3 (6%)	5 (10%)
HYPERPLASIA, NOS			1 (2%)
*MAMMARY DUCT	(49)	(48)	(50)
HYPERPLASIA, CYSTIC	1 (2%)		
#UTERUS	(46)	(48)	(47)
HYDROMETRA	1 (2%)		
HEMATOMA, NOS	1 (2%)		
ABSCESS, NOS		1 (2%)	
POLYP, INFLAMMATORY	1 (2%)		
#OVARY	(47)	(48)	(49)
INFLAMMATION, CHRONIC	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*LENS CAPSULE	(49)	(48)	(50)
CALCIFICATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 02-0160	LOW DOSE 02-R150	HIGH DOSE 02-0140
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, NOS			1
CRANIOBUCCAL POUCH			
CYST, NOS			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	1	1
ANIMAL MISSING/NO NECROPSY	1		
AUTOLYSIS/NO NECROPSY		2	

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

APPENDIX D

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

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

	CONTROL (UNTR) 05-0160	LOW DOSE 05-0140	HIGH DOSE 05-0150
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	44	22
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	44	22
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(44)	(22)
HEMATOMA, NOS	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
ABSCESS, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(47)	(43)	(22)
INFLAMMATION, NOS		1 (2%)	
#LUNG	(47)	(43)	(22)
INFLAMMATION, INTERSTITIAL			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(49)	(43)	(20)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HEMATOPOIESIS			
ERYTHROPOIESIS	2 (4%)		
#MESENTERIC L. NODE	(40)	(40)	(14)
INFLAMMATION, NOS		2 (5%)	
HEMATOPOIESIS			
#RENAL LYMPH NODE	(40)	(40)	(14)
HYPERPLASIA, NOS	2 (5%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0160	LOW DOSE 05-0140	HIGH DOSE 05-0150
DIGESTIVE SYSTEM			
#LIVER	(49)	(44)	(22)
ABSCESS, NOS			
NECROSIS, FOCAL		1 (2%)	
NECROSIS, COAGULATIVE			
METAMORPHOSIS FATTY	1 (2%)		
HYPERPLASTIC NODULE		1 (2%)	
HYPERPLASIA, FOCAL			1 (5%)
ANGIECTASIS	1 (2%)		
HEMATOPOIESIS			
#LIVER/KUPFFER CELL	(49)	(44)	(22)
HYPERPLASIA, NOS	1 (2%)		
*GALLBLADDER	(50)	(44)	(22)
INFLAMMATION, NOS		2 (5%)	
#PANCREAS	(46)	(42)	(18)
CYSTIC DUCTS	1 (2%)		
INFLAMMATION, NOS			1 (6%)
PERIVASCULITIS	1 (2%)		
DEGENERATION, CYSTIC			1 (6%)
NECROSIS, FAT	1 (2%)		
#PANCREATIC ACINUS	(46)	(42)	(18)
DEGENERATION, NOS		1 (2%)	
ATROPHY, NOS			
HYPERTROPHY, NOS			
HYPERTROPHY, FOCAL			
#STOMACH	(49)	(41)	(19)
INFLAMMATION, NOS			
ACANTHOSIS			
#PEYERS PATCH	(49)	(42)	(19)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
#COLON	(48)	(40)	(18)
PARASITISM		1 (3%)	
URINARY SYSTEM			
*KIDNEY	(49)	(44)	(21)
HYDRONEPHROSIS	2 (4%)		

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0160	LOW DOSE 05-0140	HIGH DOSE 05-0150
INFLAMMATION, NOS			2 (10%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
NEPHROPATHY			3 (14%)
#KIDNEY/TUBULE	(49)	(44)	(21)
MINERALIZATION			1 (5%)
ENDOCRINE SYSTEM			
#ADRENAL	(47)	(38)	(21)
NECROSIS, NOS			
CALCIFICATION, NOS			
#THYROID	(42)	(39)	(14)
INFLAMMATION, NOS		1 (3%)	
INFLAMMATION, FOCAL		1 (3%)	
HYPERPLASIA, FOCAL	1 (2%)		
#PANCREATIC ISLETS	(46)	(42)	(18)
INFLAMMATION, NOS			
HYPERPLASIA, ADENOMATOUS			
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(44)	(22)
DILATATION, NOS	1 (2%)		
INFLAMMATION, NOS		1 (2%)	
#TESTIS	(49)	(44)	(22)
MINERALIZATION			1 (5%)
DEGENERATION, NOS		1 (2%)	
ATROPHY, NOS			
#TESTIS/TUBULE	(49)	(44)	(22)
MINERALIZATION			
NECROSIS, FOCAL	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 05-0160	LOW DOSE 05-0140	HIGH DOSE 05-0150
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(44)	(22)
ADHESION, NOS	1 (2%)		
*MESENTERY	(50)	(44)	(22)
STEATITIS	1 (2%)		
ABSCESS, NOS	1 (2%)		
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
STEATITIS	1		
NECROSIS, FAT	2		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	17	18	9
ANIMAL MISSING/NO NECROPSY		1	
NO NECROPSY PERFORMED			19
AUTO/NECROPSY/HISTO PERF	1		2
AUTO/NECROPSY/NO HISTO	1		
AUTOLYSIS/NO NECROPSY		5	9

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

TABLE D2

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH FENAMINOSULF

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
ANIMALS INITIALLY IN STUDY	50	50	50	@50
ANIMALS MISSING		2	2	1
ANIMALS NECROPSIED	50	47	43	42
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	47	38	39
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(47)	(43)	(42)
MINERALIZATION				1 (2%)
INFLAMMATION, NOS		1 (2%)		
NECROSIS, NOS				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(50)	(46)	(39)	(39)
INFLAMMATION, INTERSTITIAL			1 (3%)	
HEMATOPOIETIC SYSTEM				
#SPLEEN	(49)	(45)	(38)	(38)
HYPERPLASIA, LYMPHOID	1 (2%)			
HEMATOPOIESIS		1 (2%)	7 (18%)	5 (13%)
ERYTHROPOIESIS	1 (2%)			
#MANDIBULAR L. NODE	(40)	(38)	(29)	(35)
HYPERPLASIA, PLASMA CELL	1 (3%)			
#MEDIASTINAL L.NODE	(40)	(38)	(29)	(35)
HYPERPLASIA, NOS	1 (3%)			
#LUMBAR LYMPH NODE	(40)	(38)	(29)	(35)
HYPERPLASIA, NOS	1 (3%)			
#MESENTERIC L. NODE	(40)	(38)	(29)	(35)
INFLAMMATION, NOS				1 (3%)
HEMATOPOIESIS			1 (3%)	
#RENAL LYMPH NODE	(40)	(38)	(29)	(35)
HYPERPLASIA, NOS	1 (3%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMALS WERE INITIALLY IN THE STUDY BUT ONE ANIMAL WAS FOUND TO BE A MALE IN A FEMALE GROUP.

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
HYPERPLASIA, PLASMA CELL	1 (3%)			
CIRCULATORY SYSTEM				
*CARDIOVASCULAR SYSTE	(50)	(47)	(43)	(42)
PERIVASCULITIS			1 (2%)	
#MYOCARDIUM	(50)	(45)	(39)	(39)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
DIGESTIVE SYSTEM				
#LIVER	(49)	(46)	(36)	(37)
NECROSIS, NOS	1 (2%)			
NECROSIS, FOCAL	1 (2%)		1 (3%)	
INFARCT, NOS	1 (2%)			
METAMORPHOSIS FATTY		1 (2%)		
HYPERPLASIA, FOCAL			2 (6%)	1 (3%)
HEMATOPOIESIS			1 (3%)	1 (3%)
*BILE DUCT	(50)	(47)	(43)	(42)
INFLAMMATION, CHRONIC FOCAL	2 (4%)			
#PANCREAS	(47)	(45)	(34)	(38)
DILATATION/DUCTS				1 (3%)
#PANCREATIC ACINUS	(47)	(45)	(34)	(38)
HYPERTROPHY, FOCAL			1 (3%)	
#STOMACH	(49)	(46)	(34)	(36)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, CHRONIC	1 (2%)			
#PEYERS PATCH	(49)	(44)	(34)	(37)
HYPERPLASIA, LYMPHOID	1 (2%)			
#COLON	(50)	(42)	(27)	(35)
NEMATODIASIS	1 (2%)			
URINARY SYSTEM				
#KIDNEY	(49)	(46)	(39)	(39)
GLOMERULONEPHRITIS, NOS		1 (2%)	2 (5%)	1 (3%)

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
INFLAMMATION, CHRONIC	2 (4%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
NEPHROPATHY			15 (38%)	
GLOMERULOSCLEROSIS, NOS	1 (2%)			1 (3%)
#KIDNEY/TUBULE	(49)	(46)	(39)	(39)
MINERALIZATION			8 (21%)	
#URINARY BLADDER	(50)	(45)	(36)	(36)
INFLAMMATION, NOS				1 (3%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
HYPERPLASIA, EPITHELIAL				2 (6%)
#U.BLADDER/SUBMUCOSA	(50)	(45)	(36)	(36)
INFLAMMATION, CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	16 (32%)			
PERIVASCULITIS	1 (2%)			
#U.BLADDER/MUSCULARIS	(50)	(45)	(36)	(36)
CALCIUM DEPOSIT	1 (2%)			
ENDOCRINE SYSTEM				
#ADRENAL/CAPSULE	(47)	(40)	(37)	(39)
HYPERPLASIA, NOS			4 (11%)	2 (5%)
#THYROID	(41)	(29)	(27)	(31)
FOLLICULAR CYST, NOS			1 (4%)	
NECROSIS, FOCAL				1 (3%)
HYPERPLASIA, C-CELL	2 (5%)			
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(47)	(43)	(42)
HYPERPLASIA, NOS		1 (2%)		
METAPLASIA, SQUAMOUS			1 (2%)	
#UTERUS	(49)	(45)	(36)	(37)
HYDROMETRA	5 (10%)			1 (3%)
PYOMETRA				2 (5%)
ABSCESS, NOS				1 (3%)
NECROSIS, FAT	1 (2%)			

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
CALCIFICATION, NOS	1 (2%)			
METAPLASIA, SQUAMOUS			2 (6%)	
#UTERUS/ENDOMETRIUM	(49)	(45)	(36)	(37)
INFLAMMATION, SUPPURATIVE	2 (4%)			
HYPERPLASIA, NOS			9 (25%)	1 (3%)
HYPERPLASIA, CYSTIC	32 (65%)		4 (11%)	3 (8%)
#OVARY/OVIDUCT	(49)	(45)	(36)	(37)
INFLAMMATION, NOS				1 (3%)
DEGENERATION, NOS		1 (2%)		
#OVARY	(48)	(40)	(32)	(37)
CYST, NOS	6 (13%)			
INFLAMMATION, NOS			3 (9%)	
INFLAMMATION, SUPPURATIVE	1 (2%)			1 (3%)
ABSCESS, NOS			5 (16%)	1 (3%)
INFLAMMATION, CHRONIC	1 (2%)			1 (3%)
DEGENERATION, NOS			2 (6%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(50)	(47)	(43)	(42)
INFLAMMATION, NOS				1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(47)	(43)	(42)
AMYLOIDOSIS	1 (2%)			

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

TABLE D2. (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 06-0160	LOW DOSE CONTROL (UNTR) 06-0220	LOW DOSE 06-R151	HIGH DOSE 06-0140
OMENTUM				
PERIVASCULITIS	1			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	2	30	2	11
ANIMAL MISSING/NO NECROPSY		2	2	1
NECROPSY PERF/NO HISTO PERFORMED			2	
AUTO/NECROPSY/HISTO PERF	2	1		
AUTO/NECROPSY/NO HISTO			3	3
AUTOLYSIS/NO NECROPSY		1	5	6

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
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DHEW Publication No. (NIH) 78-1351