National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 20
1977

BIOASSAY OF

DAPSONE

FOR POSSIBLE CARCINOGENICITY

CAS No. 80-08-0

NCI-CG-TR-20

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

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Carcinogen Bioassay and Program Resources Branch
Carcinogenesis Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

DHEW Publication No. (NIH) 77-820

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CONTRIBUTORS: This report presents the results of the bioassay of dapsone for possible carcinogenicity, conducted for the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. The bioassay was conducted by Southern Research Institute, Birmingham, Alabama, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI carcinogenesis bioassay program.

The experimental design and doses were determined by Drs. D. P. Griswold[1], J. D. Prejean[1], E. K. Weisburger[2], and J. H. Weisburger[2,3]. Ms. J. Belzer[1] and Mr. I. Brown[1] were responsible for the care and feeding of the laboratory animals. Data management and retrieval were performed by Ms. C. A. Dominick[1]. Histopathologic examinations were performed by Drs. S. D. Kosanke[1] and J. C. Peckham[1], and the diagnoses included in this report represent their interpretation. Pathologists at NCI and Tracor Jitco have reviewed selected slides and concur with the overall pathologic evaluation of the study.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[4]. The statistical analyses were performed by Dr. J. R. Joiner[5], using methods selected for the bioassay program by Dr. J. J. Gart[6]. Chemicals used in this bioassay were analyzed under the direction of Dr. E. Murrill[7], and the analytical results were reviewed by Dr. C. W. Jameson[5].

This report was prepared at Tracor Jitco under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr.

Marshall Steinberg[5], Director of the Bioassay Program; Drs. J. F. Robens[5] and R. W. Fogleman[5], toxicologists; Ms. L. A. Waitz[5], bioscience writer; and Dr. E. W. Gunberg[5], technical editor, assisted by Ms. Y. E. Presley[5] and Ms. P. J. Graboske[5].

The statistical analysis was reviewed by a member or members of the Mathematical Statistics and Applied Mathematics Section of NCI (Dr. John J. Gart, Mr. Jun-mo Nam, Dr. Hugh. M. Pettigrew, and Dr. Robert E. Tarone served as reviewers on an alternating basis).

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings:

Dr. Kenneth C. Chu
Dr. Cipriano Cueto, Jr.
Dr. J. Fielding Douglas
Dr. Dawn G. Goodman
Dr. Richard A. Griesemer
Dr. Thomas W. Orme
Dr. Robert A. Squire[8]
Dr. Jerrold M. Ward

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[1]Southern Research Institute, 2000 Ninth Avenue South, Birmingham, Alabama.

[2]Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

[3]Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammond House Road, Valhalla, New York.

[4]EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

[5]Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

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

[7]Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri.

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

SUMMARY

A bioassay of dapsone, 4,4′-sulfonyldianiline, for possible carcinogenicity was conducted by administering the test material in feed to Fischer 344 rats and B6C3F1 mice.

Groups of 35 rats and 35 mice of each sex were administered dapsone at one of two doses, either 600 or 1,200 ppm for rats and either 500 or 1,000 ppm for mice. The rats and mice were treated for 78 weeks; the rats were then observed for 26-28 weeks, the mice for 28-30 weeks. Matched controls consisted of groups of 15 untreated rats and 14 untreated mice of each sex; pooled controls, used for statistical evaluation, consisted of the matched controls combined with 30 male and 30 female untreated rats and 29 male and 29 female untreated mice from similarly performed bioassays of two other test chemicals. All surviving rats were killed at 104-106 weeks, all surviving mice at 106-108 weeks.

Treated rats and mice had lower mean body weights than the corresponding controls; when treatment was discontinued at week 78, both species showed some increase in body weight. Survival among rats was unaffected by treatment with dapsone; adequate numbers of animals survived for meaningful statistical analyses of the incidences of tumors. Dapsone did not adversely affect the survival of mice, as shown by the test for positive dose-related trend. Suppurative bronchopneumonia was found in some mice in all matched-control and treated groups. Several control males died early in the study, while survival of the other groups of mice was not affected until week 75.

Among rats, mesenchymal tumors of the abdominal organs or peritoneal tissues occurred in 13/35 low-dose males and 22/33 high-dose males. None occurred among control males or among control or treated females. The most commonly occurring tumors were fibroma, fibrosarcoma, or sarcoma, NOS (not otherwise specified), of the spleen and the peritoneum. In male rats, these mesenchymal tumors of the spleen occurred in a statistically significant incidence in both treated groups

(low-dose 6/34, P = 0.006; high-dose 14/32, P < 0.001) when compared with pooled controls. In the peritoneum, the incidences of these mesenchymal tumors were significant in both treated groups (low-dose 5/35, P = 0.014; high-dose 6/33, P = 0.005) when compared with the pooled controls. No tumors related to treatment were found in female rats.

Among the mice, there were no tumors that could clearly be related to treatment.

It is concluded that under the conditions of this bioassay, dapsone was not carcinogenic for female Fischer 344 rats or B6C3F1 mice of either sex. Dapsone was carcinogenic (sarcomagenic) for male Fischer 344 rats, causing mesenchymal tumors in the spleen and the peritoneum.

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I. INTRODUCTION

Dapsone (CAS 80-08-0; NCI C01718) is the parent chemical of the sulfone drugs, and the major therapeutic agent in this group for the treatment of leprosy (Weinstein, 1975). It is also administered to treat dermatitis herpetiformis and malaria, and is used in combination with radiotherapy in the treatment of gynecologic neoplasms (Graham et al., 1968; Graham et al., 1969; Rollo, 1975). The mechanism of action of the sulfones is not known, although some evidence suggests that they act similarly to the sulfonamides, which inhibit bacterial utilization of p-aminobenzoic acid (Weinstein, 1975). Dapsone is also sold for use as an accelerator in epoxy resins (RSA Corp., 1977). Dapsone was selected for screening by the carcinogenesis program in an attempt to evaluate the carcinogenicity of certain drugs that are used extensively and for prolonged periods in humans.

II. MATERIALS AND METHODS

A. Chemical

Dapsone is the generic name for 4,4′-sulfonyldianiline. It was obtained in a single batch (Lot No. 870-5) from the RSA Corporation, Ardsley, New York. This lot, according to the RSA Corporation, met USP grade specifications, indicating a purity of > 99%. Nonaqueous titration of the amine functions performed at the Midwest Research Institute indicated 100.0 $\pm$ 0.4%. The melting point was 177.5-179°C (literature: 178.5°C). Elemental analyses (C, H, N, S) were correct for $C_{12}H_{12}N_2O_2S$, the molecular formula of 4,4′-sulfonyldianiline. Identity was confirmed by nuclear magnetic resonance and infrared spectra, which were in agreement with the structure and matched the spectra found in the literature.

The chemical was stored at 5°C in plastic bottles enclosed in sealed plastic bags.

B. Dietary Preparation

Test diets were formulated every 2 weeks using finely ground Wayne® Lab Blox (Allied Mills, Inc., Chicago, Ill.) to which was added the required amount of dapsone for each dietary concentration. A given amount of the test chemical was first hand-

mixed with a small amount of feed. This mixture was then added to a larger quantity of feed to give the desired concentration of the chemical, and mixed mechanically in a twin-shell blender for not less than 10 minutes to assure homogeneity of the mixture. Formulated diets were stored in plastic bags at room temperature until used.

C. Animals

Fischer 344 rats and B6C3F1 mice, used in the chronic studies, were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. The rats were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts, and the mice were obtained in mixed shipments from A. R. Schmidt, Madison, Wisconsin, and from Charles River Laboratories. On arrival at the laboratory, all animals were quarantined for an acclimation period (rats for 5 days, mice for 4 days) and were then assigned to control and treated groups.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature range was 20-24°C and the relative humidity was maintained at 40-60%. Room air was changed 15 times per hour and passed through both incoming and exhaust fiberglass roughing filters. In addition to natural light,

illumination was provided by fluorescent light for 9 hours per day. Food and water were supplied daily and were available ad libitum.

Rats were housed five per cage and mice seven per cage in solid-bottom stainless steel cages (Hahn Roofing and Sheet Metal Co., Birmingham, Ala.). The bottoms of the rat cages were lined with Iso-Dri® hardwood chips (Carworth, Edison, N. J.), and cage tops were covered with disposable filter bonnets beginning at week 25; mouse cages were provided with Sterolit® clay bedding (Englehard Mineral and Chemical Co., New York, N. Y.). Bedding was replaced once per week; cages, water bottles, feeders, and racks were sanitized once per week.

The rats and mice were housed in separate rooms. Control animals were housed with respective treated animals. Animals treated with dapsone were maintained in the same rooms as animals of the same species being treated with the following chemicals:

RATS

Feed Studies

4-acetyl-N-((cyclohexylamino)carbonyl)benzenesulfonamide
(acetohexamide) (CAS 968-81-0)
anthranilic acid (CAS 118-92-3)
1-butyl-3-(p-tolylsulfonyl)urea (tolbutamide) (CAS 64-77-7)
4-chloro-N-((propylamino)carbonyl)benzenesulfonamide
(chlorpropamide) (CAS 94-20-2)
5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine
(pyrimethamine) (CAS 58-14-0)

2,6-diamino-3-(phenylazo)pyridine hydrochloride (CAS 136-40-3)
L-tryptophan (CAS 73-22-3)
N-9H-fluoren-2-ylacetamide (CAS 53-96-3)
N-(p-toluenesulfonyl)-N′-hexamethyleniminourea
(tolazamide) (CAS 1156-19-0)
1-phenethylbiguanide hydrochloride (phenformin) (CAS 114-86-3)
pyrazinecarboxamide (pyrazinamide) (CAS 98-96-4)
4,4′-thiodianiline (CAS 139-65-1)
ethionamide (CAS 536-33-4)

MICE

Feed Studies

4-acetyl-N-((cyclohexylamino)carbonyl)benzenesulfonamide
(acetohexamide) (CAS 968-81-0)
anthranilic acid (CAS 118-92-3)
1-butyl-3-(p-tolylsulfonyl)urea (tolbutamide) (CAS 64-77-7)
4-chloro-N-((propylamino)carbonyl)benzenesulfonamide
(chlorpropamide) (CAS 94-20-2)
5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine
(pyrimethamine) (CAS 58-14-0)
2,6-diamino-3-(phenylazo)pyridine hydrochloride (CAS 136-40-3)
L-tryptophan (CAS 73-22-3)
N-9H-fluoren-2-ylacetamide (CAS 53-96-3)
N-(p-toluenesulfonyl)-N′-hexamethyleniminourea
(tolazamide) (CAS 1156-19-0)
1-phenethylbiguanide hydrochloride (phenformin) (CAS 114-86-3)
pyrazinecarboxamide (pyrazinamide) (CAS 98-96-4)
4,4′-thiodianiline (CAS 139-65-1)
ethionamide (CAS 536-33-4)

Gavage Studies

cholesterol (p-(bis(2-chloroethyl)amino)phenyl)acetate
(phenesterin) (CAS 3546-10-9)
estradiol bis((p-(bis(2-chloroethyl)amino)phenyl)acetate)
(estradiol mustard) (CAS 22966-79-6)

Intraperitoneal Injection Studies

4′-(9-acridinylamino)methansulfon-m-aniside monohydrochloride
(MAAM) (NSC 141549)
acronine (CAS 7008-42-6)
5-azacytidine (CAS 320-67-2)
beta-2′-deoxy-6-thioguanosine monohydrate (beta-TGDR)
(CAS 789-61-7)

1,4-butanediol dimethanesulfonate (busulfan) (CAS 55-98-1)
emetine dihydrochloride tetrahydrate (CAS 316-42-7)
3,3′-iminobis-1-propanol dimethanesulfonate (ester) hydrochloride (CAS 3458-22-8)
(±)-4,4′-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione (ICRF-159) (CAS 21416-87-5)
N,3-bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide (isophosphamide) (CAS 3778-73-2)
N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)benzylamine hydrochloride (phenoxybenzamine) (CAS 63-92-3)
N-(1-methylethyl)-4-((2-methylhydrazino)methyl)benzamide monohydrochloride (procarbazine) (CAS 366-70-1)
tris(1-aziridinyl)phosphine sulfide (thio-TEPA) (CAS 52-24-4)
2,4,6-tris(dimethylamino)-s-triazine (CAS 645-05-6)

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses of dapsone, on the basis of which low and high concentrations (hereinafter referred to as "low doses" and "high doses") were determined for administration in the chronic studies. In these subchronic studies, dapsone was added to the animal feed in concentrations of 1,200, 3,000, 6,000, 15,000, or 30,000 ppm for rats and 2,000, 5,000, 10,000, or 50,000 ppm for mice. The treated and control groups each consisted of five male animals. The chemical was provided in the feed to the treated groups 7 days per week for 45 days, followed by a 45-day period of observation.

All rats receiving 30,000 ppm died before termination of the study, as did 4/5 rats receiving 15,000 or 6,000 ppm, and 1/5 rats receiving 3,000 ppm. At 1,200 ppm there were no deaths;

weight gains in this group were depressed throughout both the treatment and the observation periods, but were within 15% of the control weights. The low and high doses for the chronic studies in rats were set at 600 and 1,200 ppm.

Because deaths occurred in all treated groups of mice, a second study was conducted using twofold increasing concentrations ranging from 120 to 2,000 ppm. In this study, one animal receiving 2,000 ppm died during week 2. Body weights of all treated animals, and particularly those of the high-dose groups, were depressed during the treatment period, but were similar to those of the controls by the end of the observation period. The low and high doses for the chronic studies in mice were set at 500 and 1,000 ppm.

F. Designs of Chronic Studies

The designs of the chronic studies are shown in tables 1 and 2.

Since the numbers of animals in the matched-control groups were small, pooled-control groups also were used for statistical comparisons. Matched controls from the current studies on dapsone were combined with matched controls from studies performed on anthranilic acid (CAS 118-92-3) and 4,4′-thiodianiline (CAS 139-65-1). The pooled controls for statistical tests using rats consisted of 45 males and 45 females; using

Table 1. Design of Dapsone Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals[a]	Dapsone in Diet (ppm)[b]	Time on Study	
			Treated (weeks)	Untreated (weeks)
Male				
Matched-Control	15	0	0	106
Low-Dose	35	600	78	27
High-Dose	35	1,200	78	26
Female				
Matched-Control	15	0	0	106
Low-Dose	35	600	78	27
High-Dose	35	1,200	78	27

[a]All animals were 34 days of age when placed on study.

[b]Animals were fed diets containing dapsone 5 days per week, and control diets 2 days per week.

Table 2. Design of Dapsone Chronic Feeding Studies in Mice

Sex and Treatment Group	Initial No. of Animals[a]	Dapsone in Diet (ppm)[b]	Time on Study	
			Treated (weeks)	Untreated (weeks)
Male				
Matched-Control	14	0	0	106
Low-Dose	35	500	78	29
High-Dose	35	1,000	78	29
Female				
Matched-Control	14	0	0	108
Low-Dose	35	500	78	30
High-Dose	35	1,000	78	29

[a]Male animals were 34 days of age and females 38 days of age when placed on study.

[b]Animals were fed diets containing dapsone 5 days per week, and control diets 2 days per week.

mice, 43 males and 43 females. The studies on chemicals other than dapsone were also conducted at Southern Research Institute and overlapped the dapsone study by at least 7 months for rats and at least 10 months for mice. The matched-control groups for the different test chemicals were of the same strain and from the same supplier, and they were examined by the same pathologists.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity, and palpated for masses at each weighing. Rats and mice were weighed individually each week for 8 weeks and every 2 weeks for the remainder of the study. Animals that were moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically: skin, muscle, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder and bile duct (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, brain and sensory organs. Peripheral blood smears were prepared

from each animal. Occasionally, additional tissues were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

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

H. Data Recording and Statistical Analyses

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

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

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

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling

(e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of 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) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relation-

ship. 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 treated 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% 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. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Among males, decreased body weight gains occurred in the high-dose animals after about 20 weeks on study; animals at the low dose also had depressed body weights as compared with the matched controls after approximately 40 weeks. Body weights in both high- and low-dose female rats were lower than those in the control group after aproximately 12 weeks. Following withdrawal of the chemical at week 78, the body weights of these groups increased (figure 1).

B. Survival (Rats)

Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed dapsone in the diet at the doses of this experiment, together with those of the controls, are shown in figure 2. In both sexes, the Tarone test results are not significant at the 0.05 level for positive dose-related trend in mortality over the period. In male rats, 51% of both treated groups and 73% of the controls lived to the end of the study. The overall survival rate was higher in females than in males, with more than 80% of the treated and control female rats living to termination of the study. Sufficient animals of both sexes

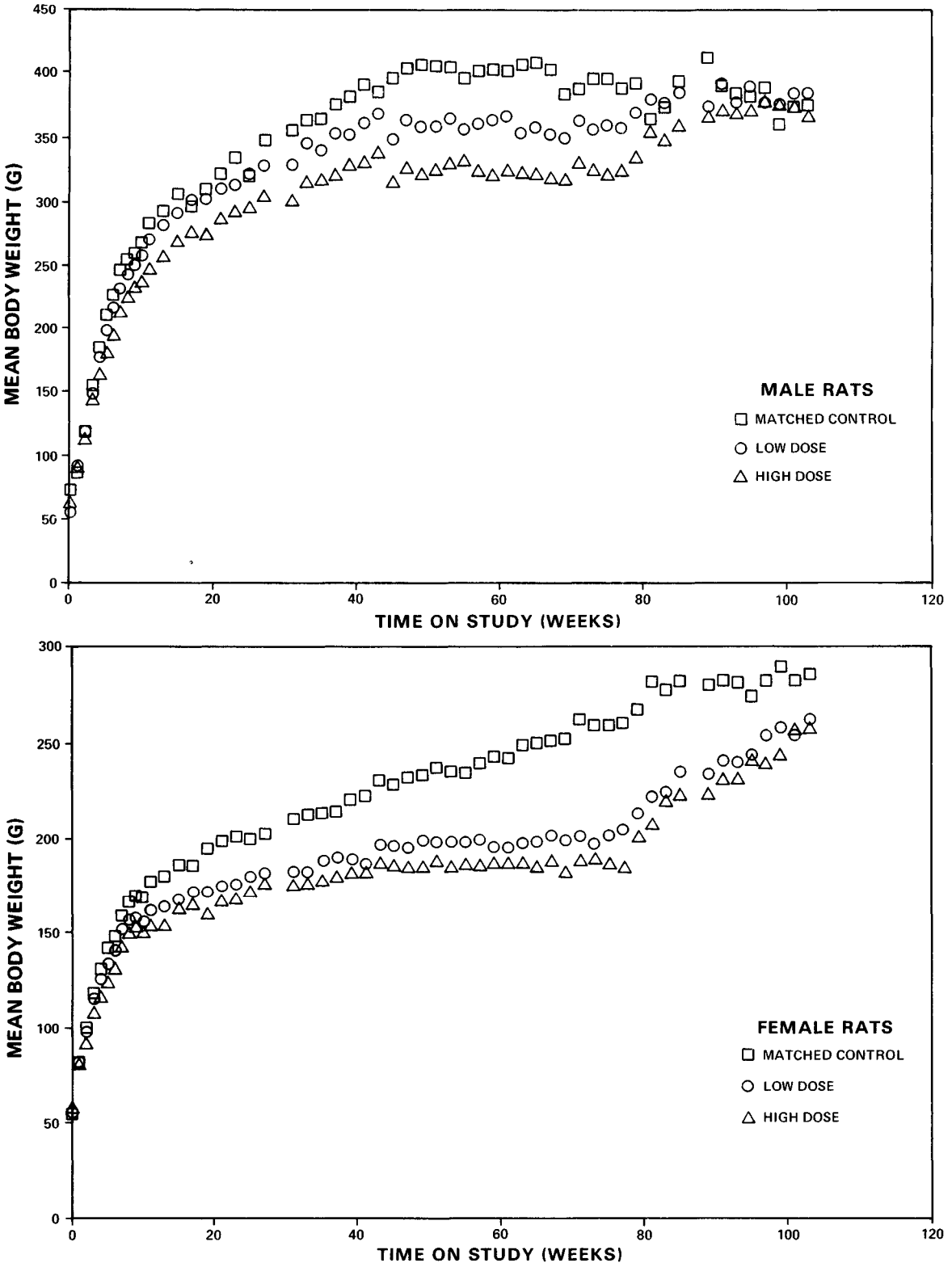

Figure 1. Growth Curves for Rats Fed Dapsone in the Diet

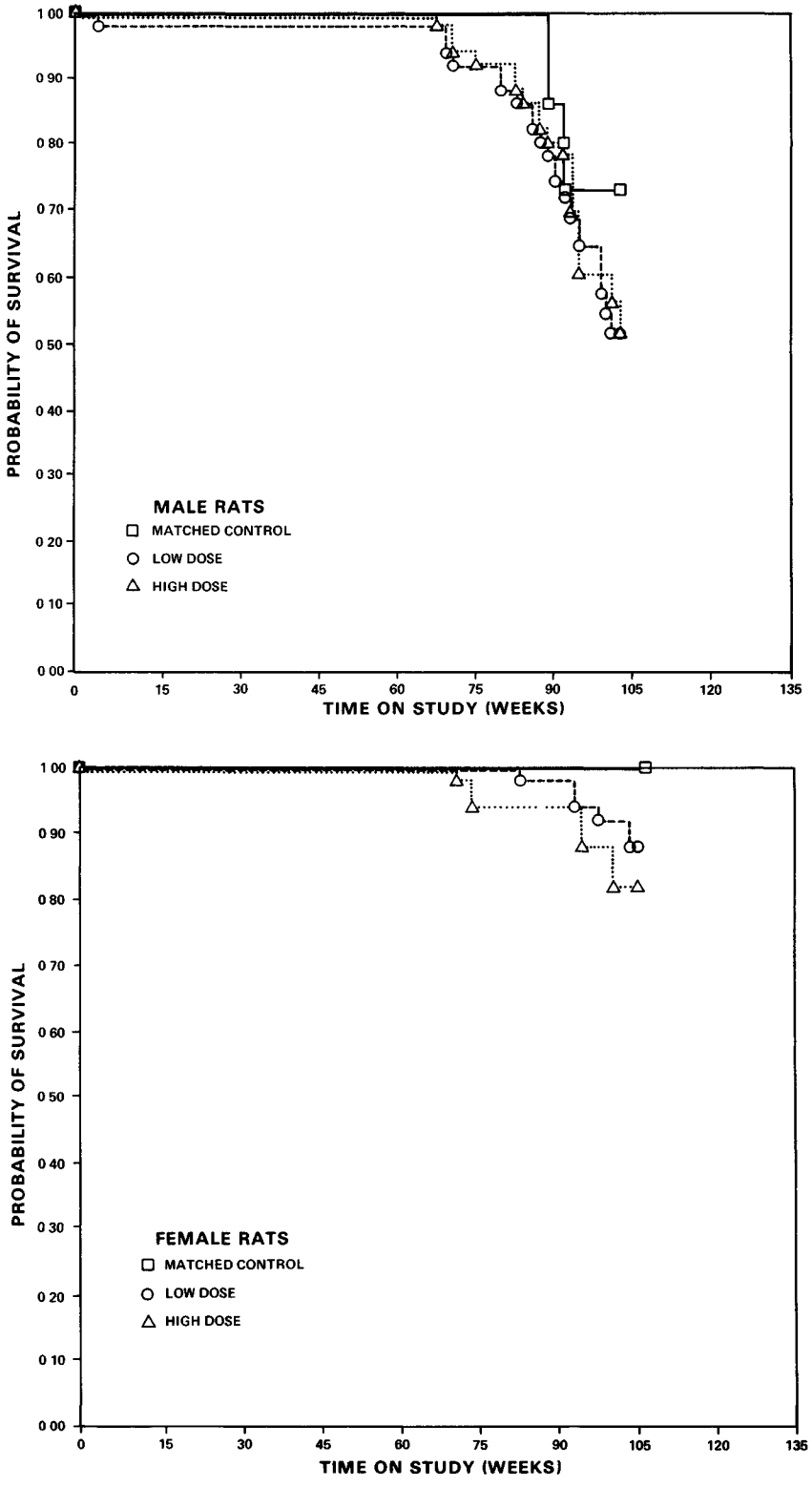

Figure 2. Survival Curves for Rats Fed Dapsone in the Diet

were available for meaningful statistical analyses of the incidences of late-developing tumors.

C. Pathology (Rats)

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

A variety of neoplasms occurred in both the control and treated groups. With the exception of malignant lymphomas and mesenchymal tumors of the abdominal cavity and viscera in treated male rats, the neoplasms listed in Appendix A either occurred with approximately equal frequency in treated and matched-control rats, or occurred in insufficient numbers for accurate evaluation of dose relationships.

Of the low-dose male rats, 4/35 (11%) had lesions classified as malignant lymphomas of the histiocytic type. Similar lymphoreticular neoplasms have been observed previously in the Fischer 344 rat independent of any treatment. In some areas, the histiocytes of the lymphomas had marked pleomorphism including spindle-cell shapes with various degrees of invasion into adjacent tissues and the peritoneal cavity. In these areas, the malignant histiocytes could not be differentiated from spindle cells of mesenchymal tumors arising from the spleen and peritoneum.

Mesenchymal lesions which occurred only in chemical-treated male rats had the following tissue distribution and incidences:

Tissue-Lesion	Matched Control	Low Dose	High Dose
Spleen	14	34	32
sarcoma, NOS*			3 (9%)
fibroma		6 (18%)	10 (31%)
fibrosarcoma			3 (9%)
fibrosis		3 (9%)	3 (9%)
metaplasia, osseous			6 (19%)
Pancreas	14	33	32
fibroma		1 (3%)	
metaplasia, osseous			1 (3%)
Abdominal cavity	14	35	33
fibroma		1 (3%)	
Peritoneum	14	35	33
sarcoma, NOS		4 (11%)	3 (9%)
fibroma		1 (3%)	
fibrosarcoma		1 (3%)	3 (9%)
fibrosis		2 (6%)	
metaplasia, osseous		2 (6%)	1 (3%)
Peritoneal cavity	14	35	33
metaplasia, osseous		1 (3%)	
Mesentery	14	35	33
metaplasia, osseous		1 (3%)	
Multiple organs	14	35	33
sarcoma, NOS			1 (3%)
fibrosarcoma			1 (3%)
metaplasia, osseous		1 (3%)	
Number of Rats Examined	14	35	33

*Not otherwise specified.

The group frequencies for animals with lesions of the abdominal organs or peritoneal tissues were as follows: mesenchymal tumors, low-dose males 13/35 (37%) and high-dose males 22/33 (67%); splenic and peritoneal fibrosis, low-dose males 4/35 (11%) and high-dose males 3/33 (9%); and osseous metaplasia, low-dose males 3/35 (9%) and high-dose males 7/33 (21%).

The mesenchymal tumors were classified as fibromas, fibrosarcomas, and sarcomas, NOS. They were spindle-cell neoplasms which varied in morphology and differentiation and had various degrees of collagen formation. The fibromas had well-differentiated fibroblasts with ample collagen, whereas the fibrosarcomas were more pleomorphic, more anaplastic, and more variable in the amount of collagen deposited. The poorly differentiated spindle-cell tumors with little or no collagen production were classified as sarcomas, NOS. Nonneoplastic proliferation of the connective tissues, either fibrosis or fibroplasia, showed mature collagen formation. Osseous metaplasia was associated with proliferation of connective tissues, and was most often seen in rats with neoplastic lesions. These osseous lesions were well-differentiated, localized, and noninvasive. They did not metastasize.

In addition to the neoplastic and nonneoplastic proliferative lesions of the connective tissues of the abdomen, a number of

other degenerative, proliferative, and inflammatory changes were also encountered in animals of the treated and control groups. These nonneoplastic lesions are commonly seen in aged rats.

The spleen appeared to be a primary site affected by dapsone. Both neoplastic and nonneoplastic proliferative lesions were often present in the same spleen. These proliferative mesenchymal lesions ranged from focal areas of fibrosis, fibroplasia, and fibromas with deposits of mature collagen to poorly differentiated fibrosarcomas and sarcomas of unspecified type. In some rats, lesions became disseminated throughout the peritoneal cavity. The formation of well-differentiated membranous bone and osseous metaplasia are believed to be secondary to the neoplastic proliferation of the connective tissues caused by chemical treatment.

In the judgment of the pathologists, a dose-related increase occurred in the number and malignancy of abdominal tumors found in male Fischer 344 rats. Under the conditions of this study, dapsone was carcinogenic (sarcomagenic) for male but not female Fischer 344 rats.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those specific primary tumors that were

observed in at least 5% of one or more treated groups of either sex.

In male rats, the Cochran-Armitage test results for positive dose-related trend in proportions of fibroma of the spleen are significant when the pooled-control group ($P < 0.001$) or the matched-control group ($P = 0.012$) is used. The Fisher exact test shows that the incidence in the high-dose group is significantly higher than that in either the pooled controls ($P < 0.001$) or the matched controls ($P = 0.016$), and the incidence in the low-dose group is significantly higher than that in the pooled controls ($P = 0.006$). The lower limits of the 95% confidence interval of these relative risks have values greater than one. The statistical conclusion is that the occurrence of fibroma of the spleen in male rats is associated with dapsone at the doses of this experiment. No such tumor was observed in female rats.

Fibrosarcomas of the spleen were found exclusively in the high-dose males. The Cochran-Armitage test shows probability levels of 0.023 when the pooled controls are used. The Fisher exact test results are not significant. The spontaneous rate of this tumor in the male Fischer 344 historical-control rats compiled to date by this laboratory is 0/235. No such tumor was observed in female rats.

The analyses of the incidence of sarcoma, NOS, of the spleen in male rats show significant Cochran-Armitage test results (P = 0.023) when the pooled-control group is used. The Fisher exact test results are not significant. The incidence observed in the male historical-control rats compiled to date by this laboratory is 0/235. No such tumor was observed in females. When the incidences of fibroma, fibrosarcoma, and sarcoma, NOS, of the spleen in male rats are grouped for statistical analyses, all test results are significant ($P \leq 0.006$), indicating a dose association of this combination of tumors with the chemical.

Malignant lymphomas were observed exclusively in the low-dose male rats. The Cochran-Armitage test results for linearity are not significant, but an indicated departure from linear trend is observed when the pooled-control group (P = 0.003) or the matched-control group (P = 0.022) is used, since the proportion in the low-dose group is greater than that in the high-dose group. The Fisher exact test results show a P value of 0.035 when the incidence in the low-dose group is compared with that in the pooled-control group, but this is above the 0.025 level required by the Bonferroni inequality criterion for significance. No such tumors were observed in female rats.

In male rats, the Cochran-Armitage tests on the proportions of sarcoma, NOS, of the peritoneum are not significant. The Fisher

exact test shows a P value of 0.035 when the incidence in the low-dose group is compared with that in the pooled-control group, and the lower limit of the 95% confidence interval for the relative risk of the low-dose group versus the pooled-control group has a value greater than one. This positive finding is accentuated by the zero incidence of this tumor in the 235 Fischer 344 male historical-control rats from similar bioassays conducted by this laboratory. However, the probability level of 0.035 is above the Bonferroni criterion of 0.025, and therefore, the significance of the result of the analysis of this specific tumor is questionable. No such tumors were observed in female rats.

Fibrosarcomas of the peritoneum of male rats were observed in both treated groups, and the incidence in the high-dose group was three times that in the low-dose group. The Cochran-Armitage test shows a probability level of 0.037 when the pooled-control group is used, but the Fisher exact test shows that the incidences in the treated groups are not significantly higher than the incidence in either of the control groups. This tumor did not occur in any of the 235 Fischer 344 male historical-control rats used by this laboratory. When the incidences of fibrosarcoma or of sarcoma, NOS, of the peritoneum in male rats are grouped for statistical analysis, increased significance ($P \leq$

0.014) is observed for both Fisher exact test results and for the test of linear trend using the pooled controls. The statistical conclusion is that the combination of these tumors and the chemical are dose related.

Negative results are observed in the incidence of mammary tumors in female rats, where the incidence in the pooled controls exceeds the incidences in the treated groups. There is no other incidence of tumors at any specific site in either male or female rats for which the statistical test results are significant in the positive direction.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of both high- and low-dose male mice were lower than those of the matched controls from initiation of the study to about week 70 (figure 3). Among the females, the mean body weights of the matched controls were unusually high, approaching 50g, and it is difficult to assess the significance of the lower mean body weights among the treated animals.

When treatment was stopped at week 78, body weights increased. At this time, mean body weights of the controls decreased to less than those of the male treated groups, and were equal to those of the female treated groups.

B. Survival (Mice)

Kaplan and Meier curves estimating the probabilities of survival for male and female mice fed dapsone in the diet at the doses of this experiment, together with those of the controls, are shown in figure 4. In both sexes, the Tarone test results for positive dose-related trend in mortality over the period are not significant. In male mice, 73% of the high-dose mice and 67% of the low-dose mice, but only 8% of the controls, survived to the end of the study. Early deaths in the male controls were not tumor

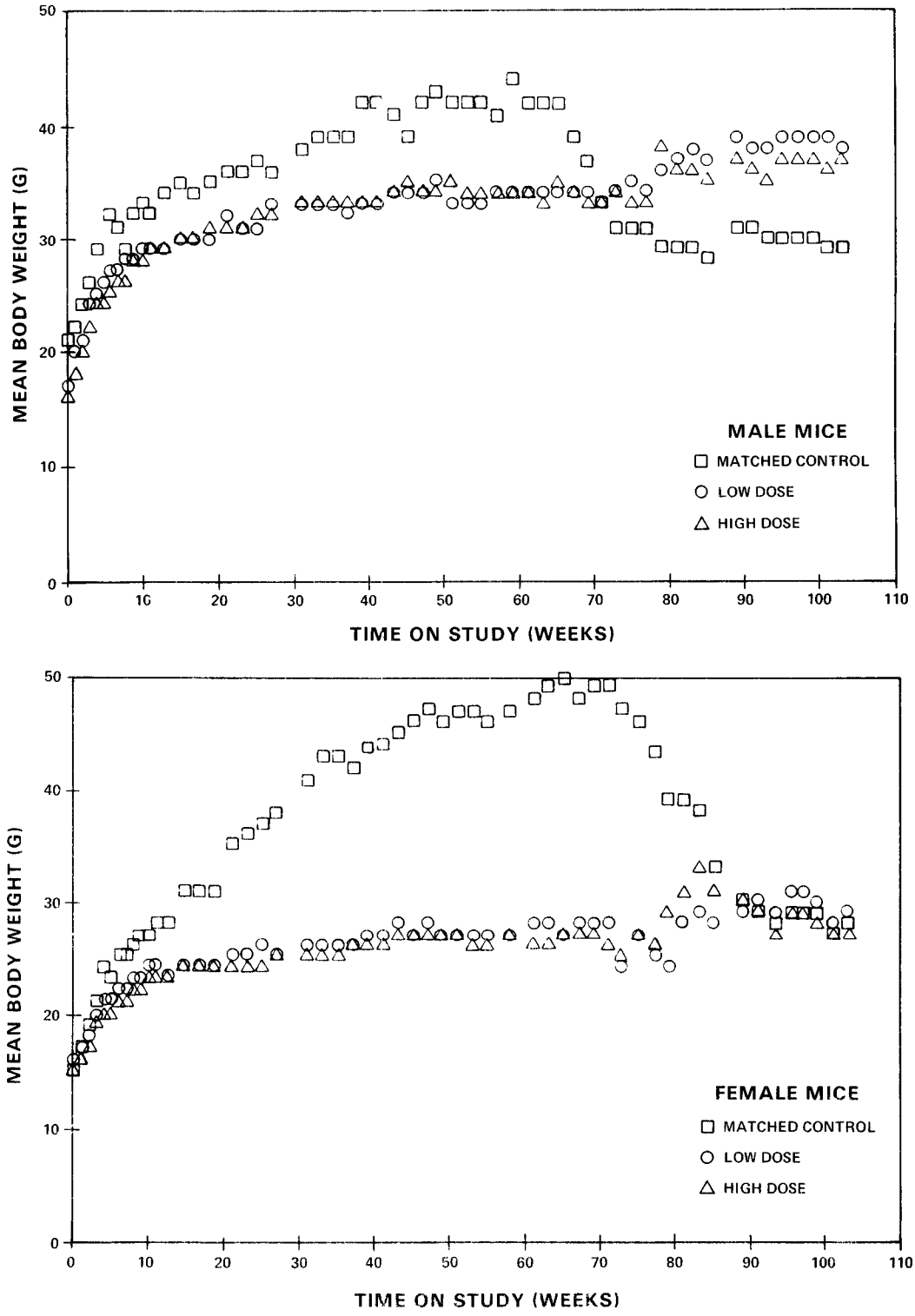

Figure 3. Growth Curves for Mice Fed Dapsone in the Diet

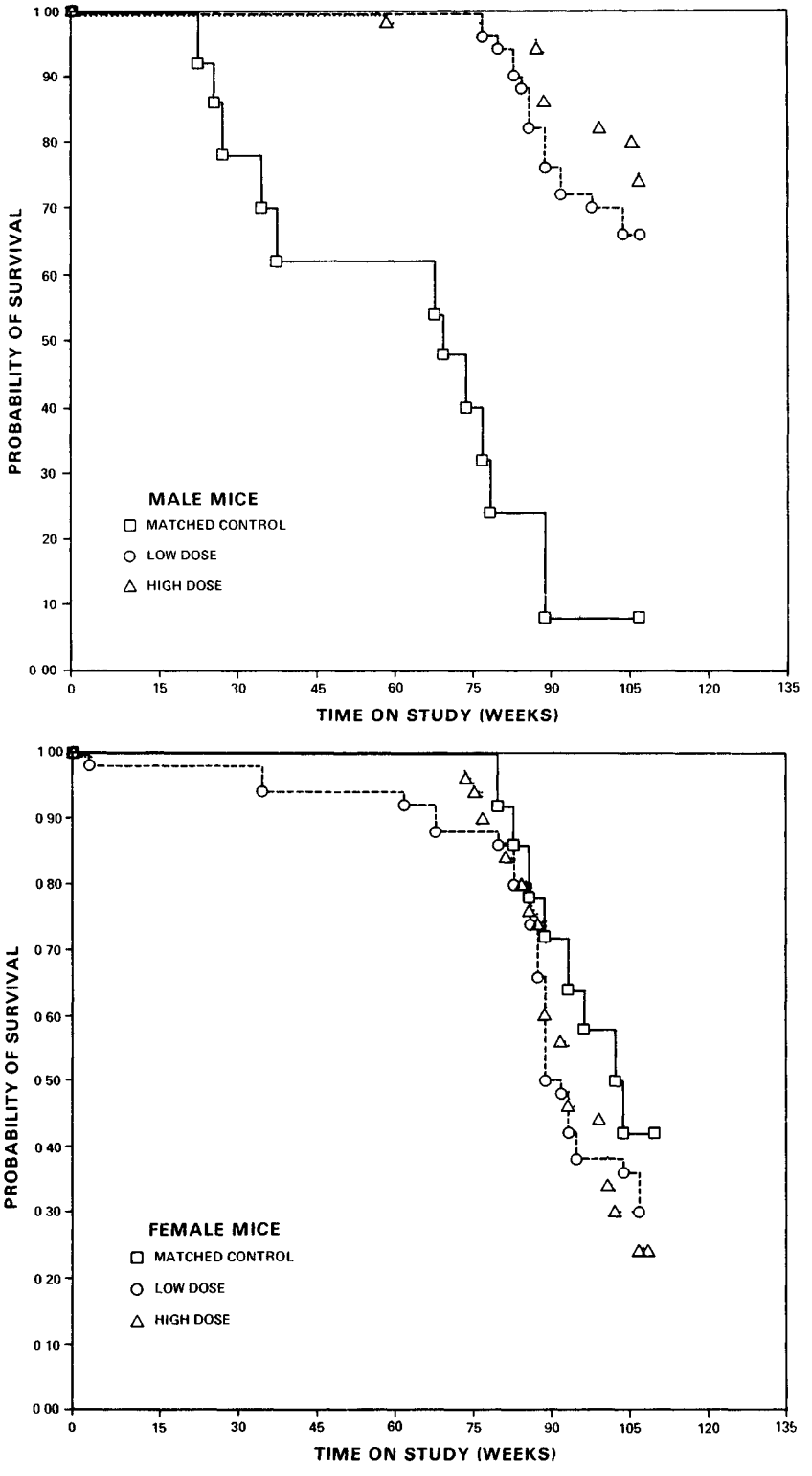

Figure 4. Survival Curves for Mice Fed Dapsone in the Diet

associated, since there was no incidence of tumors in this group. The median time on study was 69 weeks in the controls. Fewer females than males survived, with only 23% of the high-dose group, 31% of the low-dose group, and 43% of the controls living to termination of the study. The median time on study was 92 weeks in the treated groups and 102 weeks in the controls. The severe early mortality rate in the female mice may have suppressed the incidence of late-developing tumors.

C. Pathology (Mice)

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

A variety of neoplasms occurred in both matched-control and treated groups. The neoplasms listed in Appendix B occurred with approximately equal frequency in treated and control mice, or appeared in insignificant numbers. No malignant tumors occurred in male mice of this study, and more neoplasms occurred in control females than in treated females. No tumor metastases were recorded in these mice.

In addition to the neoplastic lesions, a number of degenerative, proliferative, and inflammatory changes were encountered in

animals of both the treated and control groups (Appendix D). These nonneoplastic lesions are commonly seen in aged mice; however, the suppurative lesions involving the lungs were associated with increased mortalities or decreased life spans in the treated and control groups of mice. The incidence of suppurative bronchopneumonia in the male mice was as follows: matched controls 6/11 (55%), low-dose group 5/33 (15%), and high-dose group 9/32 (29%). In the female mice the incidence was as follows: matched controls 9/13 (69%), low-dose group 22/30 (73%), and high-dose group 21/35 (60%). The reduction in life spans was caused by respiratory disease.

In the judgment of the pathologists, feeding the mice dapsone in the diet for 18 months resulted in no increase in the incidence of tumors. Under the conditions of this study, dapsone was not carcinogenic for B6C3F1 mice.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

In male mice, although the results of the Cochran-Armitage test

for positive dose-related linear trend in the incidence of alveolar/bronchiolar adenoma of the lung are not significant, the Fisher exact test shows a P value of 0.031 when the incidence in the low-dose group is compared with that in the pooled-control group. This probability level, however, is below the Bonferroni criterion of 0.025 required by the multiple comparisons. Therefore, association between this incidence of tumors and dapsone is not confirmed, since the incidence in the high-dose group is not statistically significant. No such tumor was observed in female mice.

There is no other incidence of tumors at any specific site in either male or female mice for which the statistical test results are significant in the positive direction. When lymphoma and leukemia in female mice were combined for analysis, the incidence of leukemia was not included in table F2, since the proportion in each of the treated groups is less than 5%. A list of the incidences of each type of tumor is provided in Appendix B, tables B1 and B2.

In all but one of the 95% confidence intervals, shown in the tables, the lower limit has a value less than one; this indicates the negative aspects of the results. It should also be noted that each of these intervals has an upper limit greater than one,

indicating the theoretical possibility of the induction of tumors by dapsone, which could not be detected under the conditions of this test.

V. DISCUSSION

In this bioassay, dapsone was toxic to both the treated rats and treated mice, since the mean body weights of these animals were lower than those of the corresponding matched controls throughout most of the study. However, the body weights of control female mice were unusually high. When the drug was discontinued at week 78, treated animals of both species showed varying increases in body weight.

Dapsone did not affect survival of rats; adequate numbers of animals survived for meaningful statistical analyses of the incidences of tumors. Dapsone also did not affect the survival of mice, as shown by the test for positive dose-related trend, but suppurative bronchopneumonia was found in some animals in all matched-control and treated groups. Several control males died early in the study, while survival of the other groups of mice was not affected until week 75.

Among rats, mesenchymal tumors of the abdominal organs or peritoneal tissues occurred in 13/35 low-dose males and 22/33 high-dose males. None occurred among control males or among control or treated females. The most commonly occurring tumors were fibroma, fibrosarcoma, or sarcoma, NOS, of the spleen and the peritoneum. In male rats, these mesenchymal tumors of the

spleen occurred in a statistically significant incidence in both treated groups (low-dose 6/34, $P = 0.006$; high-dose 14/32, $P < 0.001$) when compared with pooled controls. In the peritoneum, the incidences of these mesenchymal tumors were significant in both treated groups (low-dose 5/35, $P = 0.014$; high-dose 6/33, $P = 0.005$) when compared with the pooled controls. No tumors related to treatment were found in female rats.

Among the mice, there were no tumors that could clearly be related to treatment. In the males, alveolar/bronchiolar adenoma was observed in 5/33 low-dose animals. Although significant ($P = 0.031$) when compared with pooled controls, the tumors cannot clearly be associated with treatment, because of the low incidence in the low-dose group, and because only one tumor was found in the high-dose group. Similar tumors were not observed in female mice.

In studies of the toxicity of dapsone in animals, Dhar and Mukherji (1971) administered daily intraperitoneal injections at a dose of 20 mg/kg/week (chosen to simulate the human dose) for 22 weeks. In this study, there were minor changes in hematological values, but none in the histology of the liver or spleen. Higher doses for shorter periods of time caused anemia and enlargement and degeneration of the spleen and liver.

Bergel (1973) reported that in a feeding study with Wistar rats, tumors were found in 8/15 animals living more than 17 months, but none were found in the 15 controls. Five of the eight animals had tumors similar to those found in significant incidences in rats in the present bioassay; i.e., mesenchymal tumors of the peritoneum and organs of the abdominal cavity.

Dapsone inhibits the oxidation of pyruvate in the citric acid cycle in rats and mice, and this is believed to be related to the toxicity of the chemical (Wu and Dubois, 1970). It is metabolized to the monohydroxylamine by N-oxidation; this occurs to a greater extent in man than in rats (Israili et al., 1973). The monohydroxylamine metabolite is excreted in the urine in the form of various conjugates.

It is concluded that under the conditions of this bioassay, dapsone was not carcinogenic for female Fischer 344 rats or B6C3F1 mice of either sex. Dapsone was carcinogenic (sarcomagenic) for male Fischer 344 rats, causing mesenchymal tumors in the spleen and the peritoneum.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, John Wiley & Sons, Inc., New York, 1971, pp. 362-365.

Berenblum, I., ed., Carcinogenicity Testing: A Report of the Panel of Carcinogenicity of the Cancer Research Commission of the UICC, Vol. 2, International Union Against Cancer, Geneva, 1969.

Cox, D. R., Regression models and life tables. J. R. Statist. Soc. B 34:187-220, 1972.

Cox, D. R., Analysis of Binary Data, Methuen & Co., Ltd., London, 1970, pp. 48-52.

Dhar, D. C. and Mukherji, A., Effect of long-term administration of 4,4′-diamino diphenyl sulphone (DDS) in white rats. Indian J. Exp. Biol. 9:388-390, 1971.

Gart, J. J., The comparison of proportions: a review of significance tests, confidence limits and adjustments for stratification. Rev. Int. Stat. Inst. 39:148-169, 1971.

Graham, J. and Graham, R., Cancer treatment with sulfones. Surg. Gynec. Obstet. 127:103-107, 1969.

Graham, J., Graham, R., and Hirabayashi, K., Recurrent cancer of the cervix uteri. Surg. Gynec. Obstet. 126:799-804, 1968.

Israili, Z. H., Cucinell, S. A., Vaught, J., Davis, E., Lesser, J. M., and Dayton, P. G., Studies of the metabolism of dapsone in man and experimental animals: formation of N-hydroxy metabolites. J. Pharmacol. Expertl. Therap. 187 (1):138-151, 1973.

Kaplan, E. L. and Meier, P., Nonparametric estimation from incomplete observations. J. Amer. Statist. Assoc. 53: 457-481, 1958.

Linhart, M. S., Cooper, J. A., Martin, R. L., Page, N. P., and Peters, J. A., Carcinogenesis bioassay data system. Comp. and Biomed. Res. 7:230-248, 1974.

Miller, R. G., Jr., Simultaneous Statistical Inference, McGraw-Hill Book Co., New York, 1966, pp. 6-10.

Rollo, I. M., Drugs used in the chemotherapy of malaria, chapter 52 in Goodman, L. S. and Gilman, A., eds., The Pharmacological Basis of Therapeutics, Macmillan Publishing Co., Inc., New York, 1975, pp. 1045-1069.

RSA Corporation, personal communication, Ardsley, N. Y., 1977.

Saffiotti, U., Montesano, R., Sellakumar, A. R., Cefis, F., and Kaufman, D. G., Respiratory tract carcinogenesis in hamsters induced by different numbers of administrations of benzo (a) pyrene and ferric oxide. Cancer Res. 32:1073-1081, 1972.

Tarone, R. E., Tests for trend in life table analysis. Biometrika 62:679-682, 1975.

Weinstein, L., antimicrobial agents, drugs used in the chemotherapy of tuberculosis and leprosy, chapter 60 in Goodman, L. S. and Gilman, A. eds., The Pharmacological Basis of Therapeutics, Macmillan Publishing Co., Inc., New York, 1975, pp. 1201-1223.

Wu, D. L. and Dubois, K. P., Effect of DDS on endogenous respiration and the oxidation of several substrates by rat diaphragm. Arch. int. Pharmacodyn. 183:36-45, 1970.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED DAPSONE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DAPSONE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	35
ANIMALS NECROPSIED	14	35	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	14	35	33
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(14)	(35)	(33)
BASAL-CELL CARCINOMA			1 (3%)
RESPIRATORY SYSTEM			
#LUNG	(14)	(34)	(31)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (3%)	
OSTEOSARCOMA, METASTATIC	1 (7%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(14)	(35)	(33)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		4 (11%)	
UNDIFFERENTIATED LEUKEMIA	1 (7%)		
#SPLEEN	(14)	(34)	(32)
SARCOMA, NOS			3 (9%)
FIBROMA		6 (18%)	10 (31%)
FIBROSARCOMA			3 (9%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(14)	(35)	(32)
HEMANGIOSARCOMA			1 (3%)
#PANCREAS	(14)	(33)	(32)
FIBROMA		1 (3%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(14)	(28)	(28)
CHROMOPHOBE ADENOMA	1 (7%)	2 (7%)	2 (7%)
CHROMOPHOBE CARCINOMA			2 (7%)
#THYROID	(14)	(33)	(28)
FOLLICULAR-CELL CARCINOMA		1 (3%)	
C-CELL ADENOMA		1 (3%)	
C-CELL CARCINOMA	1 (7%)	1 (3%)	1 (4%)
#PANCREATIC ISLETS	(14)	(33)	(32)
ISLET-CELL ADENOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
#TESTIS	(14)	(35)	(31)
INTERSTITIAL-CELL TUMOR	14 (100%)	29 (83%)	28 (90%)
NERVOUS SYSTEM			
#BRAIN	(14)	(32)	(32)
SARCOMA, NOS	2 (14%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(14)	(35)	(33)
FIBROMA		1 (3%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*PERITONEUM	(14)	(35)	(33)
SARCOMA, NOS		4 (11%)	3 (9%)
FIBROMA		1 (3%)	
FIBROSARCOMA		1 (3%)	3 (9%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(14)	(35)	(33)
SARCOMA, NOS			1 (3%)
FIBROSARCOMA			1 (3%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	15	35	35
NATURAL DEATH@	2	10	10
MORIBUND SACRIFICE	2	7	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	11	18	18
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	32	32
TOTAL PRIMARY TUMORS	19	54	59
TOTAL ANIMALS WITH BENIGN TUMORS	14	31	30
TOTAL BENIGN TUMORS	15	42	40
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	12	16
TOTAL MALIGNANT TUMORS	4	12	19
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED DAPSONE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	35
ANIMALS NECROPSIED	15	34	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	34	35
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(15)	(34)	(35)
SQUAMOUS CELL PAPILLOMA		1 (3%)	
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
NONE			
URINARY SYSTEM			
#KIDNEY	(15)	(34)	(34)
ADENOCARCINOMA, NOS		1 (3%)	
#URINARY BLADDER	(15)	(31)	(33)
TRANSITIONAL-CELL CARCINOMA		1 (3%)	
ENDOCRINE SYSTEM			
#PITUITARY	(15)	(24)	(30)
CHROMOPHOBE ADENOMA	6 (40%)	5 (21%)	11 (37%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(15)	(32)	(34)
ADENOCARCINOMA, NOS			1 (3%)
C-CELL ADENOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(15)	(34)	(35)
ADENOMA, NOS		1 (3%)	
FIBRCADENOMA	1 (7%)	2 (6%)	1 (3%)
#UTERUS	(14)	(33)	(34)
ADENOCARCINOMA, NOS	1 (7%)		
ENDOMETRIAL STROMAL POLYP	3 (21%)	8 (24%)	2 (6%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	15	35	35
NATURAL DEATH@		4	2
MORIBUND SACRIFICE			4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	15	31	29
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	8	15	14
TOTAL PRIMARY TUMORS	11	20	15
TOTAL ANIMALS WITH BENIGN TUMORS	7	14	13
TOTAL BENIGN TUMORS	10	18	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	2	1
TOTAL MALIGNANT TUMORS	1	2	1
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* 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 FED DAPSONE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DAPSONE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	14	35	34
ANIMALS MISSING	1	1	1
ANIMALS NECROPSIED	11	33	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	11	33	32
INTEGUMENTARY SYSTEM			
*SKIN	(11)	(33)	(33)
FIBROMA			1 (3%)
RESPIRATORY SYSTEM			
#LUNG	(11)	(33)	(32)
ALVEOLAR/BRONCHIOLAR ADENOMA		5 (15%)	1 (3%)
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(11)	(33)	(31)
HEPATOCELLULAR ADENOMA		6 (18%)	2 (6%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(7)	(28)	(16)
CHROMOPHOBE ADENOMA			1 (6%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(8)	(30)	(24)
FOLLICULAR-CELL ADENOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(11)	(33)	(33)
ADENOMA, NOS		1 (3%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	14	35	34
NATURAL DEATH@	12	6	4
MORIBUND SACRIFICE		3	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED		1	
TERMINAL SACRIFICE	1	24	22
ANIMAL MISSING	1	1	1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*		11	5
TOTAL PRIMARY TUMORS		13	5
TOTAL ANIMALS WITH BENIGN TUMORS		11	5
TOTAL BENIGN TUMORS		13	5
TOTAL ANIMALS WITH MALIGNANT TUMORS			
TOTAL MALIGNANT TUMORS			
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED DAPSONE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	14	35	36
ANIMALS MISSING		3	
ANIMALS NECROPSIED	13	31	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	13	31	35
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(13)	(31)	(35)
FIBROMA	1 (8%)		
FIBROSARCOMA	1 (8%)	1 (3%)	
RESPIRATORY SYSTEM			
#LUNG	(13)	(30)	(35)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (8%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(13)	(31)	(35)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (8%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)
#PANCREATIC L.NODE		(6)	(1)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (17%)	
#LIVER	(13)	(30)	(35)
GRANULOCYTIC LEUKEMIA	1 (8%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
NONE			
URINARY SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(25)	(27)
ACIDOPHIL CARCINOMA		1 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(13)	(31)	(35)
ADENOCARCINOMA, NOS	1 (8%)		
#UTERUS	(13)	(31)	(35)
ENDOMETRIAL STROMAL POLYP		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(13)	(31)	(35)
SARCOMA, NOS			1 (3%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(13)	(31)	(35)
MESOTHELIOMA, MALIGNANT	1 (8%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	14	35	36
NATURAL DEATH@	4	14	8
MORIBUND SACRIFICE	4	9	17
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED		2	
TERMINAL SACRIFICE	6	7	11
ANIMAL MISSING		3	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	6	4	2
TOTAL PRIMARY TUMORS	7	4	2
TOTAL ANIMALS WITH BENIGN TUMORS	1	1	
TOTAL BENIGN TUMORS	1	1	
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	3	2
TOTAL MALIGNANT TUMORS	6	3	2
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED DAPSONE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DAPSONE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	35
ANIMALS NECROPSIED	14	35	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	14	35	33
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(14)	(35)	(31)
INFLAMMATION, SUPPURATIVE	1 (7%)		7 (23%)
INFLAMMATION, ACUTE/CHRONIC			1 (3%)
INFLAMMATION, CHRONIC	1 (7%)	1 (3%)	1 (3%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (7%)	6 (17%)	1 (3%)
#LUNG/BRONCHIOLE	(14)	(34)	(31)
HYPERPLASIA, LYMPHOID	1 (7%)	1 (3%)	2 (6%)
#LUNG	(14)	(34)	(31)
INFLAMMATION, INTERSTITIAL			1 (3%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	
BRONCHOPNEUMONIA CHRONIC SUPPURA			1 (3%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(13)	(32)	(28)
ATROPHY, NOS	5 (38%)	3 (9%)	2 (7%)
#SPLEEN	(14)	(34)	(32)
CONGESTION, NOS		1 (3%)	
HEMORRHAGE		3 (9%)	3 (9%)
FIBROSIS		3 (9%)	3 (9%)
NECROSIS, NOS			1 (3%)
DEPOSIT, NOS		1 (3%)	3 (9%)
ATROPHY, NOS		1 (3%)	
METAPLASIA, OSSEOUS			6 (19%)
HEMATOPOIESIS		1 (3%)	2 (6%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(14)	(35)	(32)
NECROSIS, FOCAL			1 (3%)
CYTOPLASMIC VACUOLIZATION			1 (3%)
HEMATOPOIESIS			1 (3%)
#LIVER/CENTRILOBULAR	(14)	(35)	(32)
NECROSIS, NOS		2 (6%)	1 (3%)
NECROSIS, DIFFUSE			1 (3%)
*BILE DUCT	(14)	(35)	(33)
HYPERPLASIA, NOS			1 (3%)
#PANCREAS	(14)	(33)	(32)
METAPLASIA, OSSEOUS			1 (3%)
#PANCREATIC ACINUS	(14)	(33)	(32)
ATROPHY, NOS	1 (7%)		
URINARY SYSTEM			
#KIDNEY	(14)	(35)	(32)
INFLAMMATION, INTERSTITIAL			5 (16%)
INFLAMMATION, CHRONIC	14 (100%)	22 (63%)	15 (47%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(14)	(35)	(32)
HYPERPLASIA, NOS		1 (3%)	
#THYROID	(14)	(33)	(28)
HYPERPLASIA, FOLLICULAR-CELL			1 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(14)	(35)	(33)
CYST, NOS			1 (3%)
#PROSTATE	(13)	(31)	(27)
INFLAMMATION, SUPPURATIVE			1 (4%)
*SEMINAL VESICLE	(14)	(35)	(33)
INFLAMMATION, SUPPURATIVE			1 (3%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#TESTIS	(14)	(35)	(31)
LYMPHOCYTIC INFILTRATE		1 (3%)	2 (6%)
NECROSIS, FAT	1 (7%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/CRYSTALLINE LENS	(14)	(35)	(33)
MINERALIZATION	1 (7%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(14)	(35)	(33)
INFLAMMATION, CHRONIC		1 (3%)	
FIBROSIS		2 (6%)	
METAPLASIA, OSSEOUS		2 (6%)	1 (3%)
*PERITONEAL CAVITY	(14)	(35)	(33)
METAPLASIA, OSSEOUS		1 (3%)	
*MESENTERY	(14)	(35)	(33)
METAPLASIA, OSSEOUS		1 (3%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(14)	(35)	(33)
METAPLASIA, OSSEOUS			1 (3%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		2	
AUTOLYSIS/NO NECROPSY	1		2

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED DAPSONE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	35
ANIMALS NECROPSIED	15	34	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	34	35
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(15)	(34)	(34)
LYMPHOCYTIC INFILTRATE			1 (3%)
INFLAMMATION, SUPPURATIVE		1 (3%)	2 (6%)
INFLAMMATION, CHRONIC			1 (3%)
INFLAMMATION, CHRONIC SUPPURATIV	2 (13%)	3 (9%)	
#LUNG/BRONCHIOLE	(15)	(33)	(35)
HYPERPLASIA, LYMPHOID	2 (13%)	1 (3%)	2 (6%)
#LUNG	(15)	(33)	(35)
INFLAMMATION, INTERSTITIAL			4 (11%)
BRONCHOPNEUMONIA CHRONIC SUPPURA			1 (3%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(14)	(33)	(35)
ATROPHY, NOS	8 (57%)	20 (61%)	22 (63%)
#SPLEEN	(15)	(33)	(34)
HEMATOPOIESIS	1 (7%)	1 (3%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER/PERIPORTAL	(15)	(34)	(34)
HYPERPLASIA, LYMPHOID	1 (7%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ACINUS	(15)	(33)	(34)
ATROPHY, NOS	1 (7%)		1 (3%)
URINARY SYSTEM			
#KIDNEY	(15)	(34)	(34)
INFLAMMATION, CHRONIC	13 (87%)	16 (47%)	4 (12%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)
ENDOCRINE SYSTEM			
#ADRENAL	(15)	(34)	(34)
ANGIECTASIS		1 (3%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(15)	(34)	(35)
CYST, NOS		6 (18%)	
#UTERUS	(14)	(33)	(34)
EDEMA, NOS			2 (6%)
PYOMETRA			1 (3%)
#UTERUS/ENDOMETRIUM	(14)	(33)	(34)
INFLAMMATION, SUPPURATIVE	7 (50%)	11 (33%)	7 (21%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (7%)		4 (12%)
HYPERPLASIA, NOS	6 (43%)		
HYPERPLASIA, CYSTIC		2 (6%)	
#OVARY/OVIDUCT	(14)	(33)	(34)
INFLAMMATION, SUPPURATIVE			1 (3%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)
#OVARY	(14)	(33)	(34)
CYST, NOS		3 (9%)	
INFLAMMATION, SUPPURATIVE		1 (3%)	
#OVARY/MEDULLA	(14)	(33)	(34)
HYPERPLASIA, NOS	1 (7%)		
NERVOUS SYSTEM			
#BRAIN	(15)	(31)	(34)
MALACIA			1 (3%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/CRYSTALLINE LENS	(15)	(34)	(35)
MINERALIZATION		1 (3%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(15)	(34)	(35)
INFLAMMATION, CHRONIC			1 (3%)
*MESENTERY	(15)	(34)	(35)
NECROSIS, FAT		1 (3%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		4	4
AUTOLYSIS/NO NECROPSY		1	

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED DAPSONE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DAPSONE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	14	35	34
ANIMALS MISSING	1	1	1
ANIMALS NECROPSIED	11	33	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	11	33	32
INTEGUMENTARY SYSTEM			
*SKIN	(11)	(33)	(33)
INFLAMMATION, SUPPURATIVE			1 (3%)
FIBROSIS			1 (3%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(11)	(33)	(32)
HYPERPLASIA, PLASMA CELL		1 (3%)	
HYPERPLASIA, LYMPHOID			2 (6%)
#LUNG	(11)	(33)	(32)
INFLAMMATION, INTERSTITIAL			4 (13%)
INFLAMMATION, SUPPURATIVE		1 (3%)	
BRONCHOPNEUMONIA SUPPURATIVE		5 (15%)	4 (13%)
ABSCESS, NOS	2 (18%)		
BRONCHOPNEUMONIA CHRONIC SUPPURA	6 (55%)		5 (16%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(9)	(33)	(32)
CONTRACTURE		1 (3%)	
HEMORRHAGE			2 (6%)
HYPERPLASIA, LYMPHOID		1 (3%)	1 (3%)
HEMATOPOIESIS		2 (6%)	2 (6%)
#MESENTERIC L. NODE	(1)	(7)	(6)
CONGESTION, NOS		1 (14%)	3 (50%)
HEMORRHAGE			1 (17%)
HYPERPLASIA, LYMPHOID		2 (29%)	1 (17%)
HEMATOPOIESIS		1 (14%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(11)	(33)	(32)
INFLAMMATION, INTERSTITIAL		1 (3%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC		1 (3%)	
FIBROSIS, DIFFUSE		1 (3%)	
DIGESTIVE SYSTEM			
#LIVER	(11)	(33)	(31)
FIBROSIS, FOCAL			1 (3%)
NECROSIS, NOS			1 (3%)
HYPERPLASIA, NODULAR			2 (6%)
ANGIECTASIS			1 (3%)
HYPERPLASIA, LYMPHOID			1 (3%)
#LIVER/CENTRILOBULAR	(11)	(33)	(31)
NECROSIS, NOS		1 (3%)	1 (3%)
*BILE DUCT	(11)	(33)	(33)
CYST, NOS			1 (3%)
#ESOPHAGUS	(6)	(33)	(30)
ABSCESS, NOS		1 (3%)	
#DUODENUM	(6)	(33)	(32)
HYPERPLASIA, ADENOMATOUS			1 (3%)
URINARY SYSTEM			
#URINARY BLADDER	(9)	(32)	(32)
MUCOCELE		1 (3%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	13	10
ANIMAL MISSING/NO NECROPSY	1	1	1
ACCIDENTAL DEATH		1	
NECROPSY PERF/NO HISTO PERFORMED			1
AUTOLYSIS/NO NECROPSY	2		

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED DAPSONE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	14	35	36
ANIMALS MISSING		3	
ANIMALS NECROPSIED	13	31	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	13	31	35
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(13)	(30)	(35)
INFLAMMATION, SUPPURATIVE	1 (8%)	1 (3%)	3 (9%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)
#LUNG	(13)	(30)	(35)
INFLAMMATION, INTERSTITIAL			1 (3%)
PNEUMONIA, LIPID			1 (3%)
BRONCHOPNEUMONIA SUPPURATIVE	9 (69%)	16 (53%)	16 (46%)
ABSCESS, NOS		2 (7%)	
BRONCHOPNEUMONIA CHRONIC SUPPURA		6 (20%)	5 (14%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (3%)	
CHOLESTEROL DEPOSIT			1 (3%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(13)	(28)	(34)
HYPERPLASIA, LYMPHOID		2 (7%)	
HEMATOPOIESIS	3 (23%)	5 (18%)	3 (9%)
#PULMONARY LYMPH NODE		(6)	(1)
INFLAMMATION, SUPPURATIVE		1 (17%)	
#ABDOMINAL LYMPH NODE		(6)	(1)
HEMATOPOIESIS		1 (17%)	
#PANCREATIC L.NODE		(6)	(1)
HYPERPLASIA, LYMPHOID		2 (33%)	
#MESENTERIC L. NODE		(6)	(1)
HYPERPLASIA, LYMPHOID		1 (17%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(13)	(30)	(35)
ANGIECTASIS		1 (3%)	
HEMATOPOIESIS		2 (7%)	
#LIVER/CENTRILOBULAR	(13)	(30)	(35)
NECROSIS, NOS	1 (8%)	1 (3%)	
*BILE DUCT	(13)	(31)	(35)
CYST, NOS	1 (8%)		
#PANCREATIC ACINUS	(13)	(29)	(34)
ATROPHY, NOS	1 (8%)		
URINARY SYSTEM			
#KIDNEY	(13)	(31)	(35)
AMYLOIDOSIS	1 (8%)		
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS	(13)	(31)	(35)
ABSCESS, NOS		1 (3%)	
#UTERUS/ENDOMETRIUM	(13)	(31)	(35)
INFLAMMATION, SUPPURATIVE	3 (23%)	3 (10%)	2 (6%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	
HYPERPLASIA, CYSTIC	5 (38%)	16 (52%)	17 (49%)
#OVARY	(13)	(30)	(35)
ABSCESS, NOS	1 (8%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (8%)		
NERVOUS SYSTEM			
NONE			

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(13)	(31)	(35)
MINERALIZATION	1 (8%)		
NECROSIS, NOS	1 (8%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		3	5
ANIMAL MISSING/NO NECROPSY		3	
ACCIDENTAL DEATH		1	
AUTOLYSIS/NO NECROPSY	1		1

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED DAPSONE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Hematopoietic System:				
Malignant Lymphoma[b]	0/14 (0.00)	0/44 (0.00)	4/35 (0.11)	0/33 (0.00)
P Values[c,d]	N.S.	N.S.	P = 0.035**	N.S.
Departure from Linear Trend[e]	P = 0.022	P = 0.003		
Relative Risk (Matched Control)[f]			Infinite	
Lower Limit			0.400	
Upper Limit			Infinite	
Relative Risk (Pooled Control)[f]			Infinite	
Lower Limit			1.170	
Upper Limit			Infinite	
Weeks to First Observed Tumor	--	--	71	--

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Hematopoietic System:				
Lymphoma or Leukemia[b]	1/14 (0.07)	1/44 (0.02)	4/35 (0.11)	0/33 (0.00)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]		P = 0.015		
Relative Risk (Matched Control)[f]			1.600	0.000
Lower Limit			0.183	0.000
Upper Limit			76.389	7.860
Relative Risk (Pooled Control)[f]			5.029	0.000
Lower Limit			0.525	0.000
Upper Limit			239.834	24.636
Weeks to First Observed Tumor	106	--	71	--

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Spleen: Fibroma[b]	0/14 (0.00)	0/43 (0.00)	6/34 (0.18)	10/32 (0.31)
P Values[c,d]	P = 0.012	P < 0.001	P = 0.006**	P < 0.001** P = 0.016*
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.710	1.406
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			2.041	4.044
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	69	91
Spleen: Fibrosarcoma[b]	0/14 (0.00)	0/43 (0.00)	0/34 (0.00)	3/32 (0.09)
P Values[c,d]	N.S.	P = 0.023	N.S.	N.S.
Relative Risk (Matched Control)[f]				Infinite
Lower Limit				0.281
Upper Limit				Infinite
Relative Risk (Pooled Control)[f]				Infinite
Lower Limit				0.815
Upper Limit				Infinite
Weeks to First Observed Tumor	--	--	--	95

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Spleen: Sarcoma, NOS[b]	0/14 (0.00)	0/43 (0.00)	0/34 (0.00)	3/32 (0.09)
P Values[c,d]	N.S.	P = 0.023	N.S.	N.S.
Relative Risk (Matched Control)[f]				Infinite
Lower Limit				0.281
Upper Limit				Infinite
Relative Risk (Pooled Control)[f]				Infinite
Lower Limit				0.815
Upper Limit				Infinite
Weeks to First Observed Tumor	--	--	--	94
Spleen: Fibroma, Fibrosarcoma, or Sarcoma, NOS[b]	0/14 (0.00)	0/43 (0.00)	6/34 (0.18)	14/32 (0.44)
P Values[c,d]	P = 0.001	P < 0.001	P = 0.006**	P < 0.001** P = 0.002*
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.710	2.067
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			2.041	5.948
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	69	91

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	1/14 (0.07)	2/38 (0.05)	2/28 (0.07)	2/28 (0.07)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			1.000	1.000
Lower Limit			0.059	0.059
Upper Limit			56.851	56.851
Relative Risk (Pooled Control)[f]			1.357	1.357
Lower Limit			0.104	0.104
Upper Limit			17.616	17.616
Weeks to First Observed Tumor	106	--	93	104
Pituitary: Chromophobe Carcinoma[b]	0/14 (0.00)	1/38 (0.03)	0/28 (0.00)	2/28 (0.07)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]				Infinite
Lower Limit				0.157
Upper Limit				Infinite
Relative Risk (Pooled Control)[f]			0.000	2.714
Lower Limit			0.000	0.148
Upper Limit			24.944	154.152
Weeks to First Observed Tumor	--	--	--	95

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	1/14 (0.07)	3/38 (0.08)	2/28 (0.07)	4/28 (0.14)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			1.000	2.000
Lower Limit			0.059	0.229
Upper Limit			56.851	94.585
Relative Risk (Pooled Control)[f]			0.905	1.810
Lower Limit			0.079	0.329
Upper Limit			7.325	11.364
Weeks to First Observed Tumor	106	--	93	95
Thyroid: C-cell Carcinoma[b]	1/14 (0.07)	2/44 (0.05)	1/33 (0.03)	1/28 (0.04)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.424	0.500
Lower Limit			0.006	0.007
Upper Limit			32.328	37.877
Relative Risk (Pooled Control)[f]			0.667	0.786
Lower Limit			0.012	0.014
Upper Limit			12.197	14.261
Weeks to First Observed Tumor	106	--	105	104

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Thyroid: C-cell Adenoma or Carcinoma[b]	1/14 (0.07)	3/44 (0.07)	2/33 (0.06)	1/28 (0.04)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.848	0.500
Lower Limit			0.049	0.007
Upper Limit			48.540	37.877
Relative Risk (Pooled Control)[f]			0.889	0.524
Lower Limit			0.077	0.010
Upper Limit			7.282	6.092
Weeks to First Observed Tumor	106	--	105	104
Testis: Interstitial-cell Tumor[b]	14/14 (1.00)	38/44 (0.86)	29/35 (0.83)	28/31 (0.90)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.829	0.903
Lower Limit			0.000	0.000
Upper Limit			1.122	1.133
Relative Risk (Pooled Control)[f]			0.959	1.046
Lower Limit			0.784	0.858
Upper Limit			1.169	1.204
Weeks to First Observed Tumor	89	--	71	75

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Peritoneum: Sarcoma, NOS[b]	0/14 (0.00)	0/44 (0.00)	4/35 (0.11)	3/33 (0.09)
P Values[c,d]	N.S.	N.S.	P = 0.035**	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.400	0.273
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			1.170	0.808
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	80	95
Peritoneum: Fibrosarcoma[b]	0/14 (0.00)	0/44 (0.00)	1/35 (0.03)	3/33 (0.09)
P Values[c,d]	N.S.	P = 0.037	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.022	0.273
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.068	0.808
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	105	84

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Peritoneum: Fibrosarcoma or Sarcoma, NOS[b]	0/14 (0.00)	0/44 (0.00)	5/35 (0.14)	6/33 (0.18)
P Values[c,d]	N.S.	P = 0.006	P = 0.014**	P = 0.005**
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.543	0.732
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			1.599	2.151
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	80	84

[a]Treated groups received doses of 600 or 1,200 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dapsone in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	6/15 (0.40)	9/39 (0.23)	5/24 (0.21)	11/30 (0.37)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.521	0.917
Lower Limit			0.161	0.409
Upper Limit			1.713	2.499
Relative Risk (Pooled Control)[f]			0.903	1.589
Lower Limit			0.265	0.686
Upper Limit			2.587	3.702
Weeks to First Observed Tumor	106	--	105	101
Thyroid: C-cell Adenoma[b]	0/15 (0.00)	0/41 (0.00)	1/32 (0.03)	0/34 (0.00)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	
Lower Limit			0.026	
Upper Limit			Infinite	
Relative Risk (Pooled Control)[f]			Infinite	
Lower Limit			0.069	
Upper Limit			Infinite	
Weeks to First Observed Tumor	--	--	105	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma or Adenoma, NOS[b]	1/15 (0.07)	9/44 (0.20)	2/34 (0.06)	1/35 (0.03)
P Values[c,d]	N.S.	P = 0.008(N)	N.S.	P = 0.019**(N)
Relative Risk (Matched Control)[f]			0.882	0.429
Lower Limit			0.051	0.006
Upper Limit			50.522	32.715
Relative Risk (Pooled Control)[f]			0.288	0.140
Lower Limit			0.032	0.003
Upper Limit			1.274	0.931
Weeks to First Observed Tumor	106	--	93	105
Uterus: Endometrial Stromal Polyp[b]	3/14 (0.21)	6/43 (0.14)	8/33 (0.24)	2/34 (0.06)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			1.131	0.275
Lower Limit			0.335	0.026
Upper Limit			5.920	2.190
Relative Risk (Pooled Control)[f]			1.737	0.422
Lower Limit			0.583	0.044
Upper Limit			5.440	2.175
Weeks to First Observed Tumor	106	--	93	105

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dapsone in the Diet[a]

(continued)

[a]Treated groups received doses of 600 or 1200 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE FED DAPSONE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Dapsone in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	0/11 (0.00)	0/31 (0.00)	5/33 (0.15)	1/32 (0.03)
P Values[c,d]	N.S.	N.S.	P = 0.031**	N.S.
Departure from Linear Trend[e]	P = 0.041	P = 0.009		
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.464	0.020
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			1.206	0.052
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	59	107

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma[b]	0/11 (0.00)	3/29 (0.10)	6/33 (0.18)	2/31 (0.06)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.050			
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.589	0.115
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			1.758	0.624
Lower Limit			0.417	0.055
Upper Limit			10.005	5.058
Weeks to First Observed Tumor	--	--	89	107
Pituitary: Chromophobe Adenoma[b]	0/7 (0.00)	0/18 (0.00)	0/28 (0.00)	1/16 (0.06)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]				Infinite
Lower Limit				0.026
Upper Limit				Infinite
Relative Risk (Pooled Control)[f]				Infinite
Lower Limit				0.062
Upper Limit				Infinite
Weeks to First Observed Tumor	--	--	--	85

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Dapsone in the Diet[a]

(continued)

[a]Treated groups received doses of 500 or 1,000 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Dapsone in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Subcutaneous Tissue: Fibrosarcoma[b]	1/13 (0.08)	1/36 (0.03)	1/31 (0.03)	0/35 (0.00)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.419	0.000
Lower Limit			0.006	0.000
Upper Limit			31.891	6.893
Relative Risk (Pooled Control)[f]			1.161	0.000
Lower Limit			0.015	0.000
Upper Limit			88.229	19.040
Weeks to First Observed Tumor	96	--	94	--
Hematopoietic System: Malignant Lymphoma[b]	1/13 (0.08)	2/36 (0.06)	1/31 (0.03)	1/35 (0.03)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.419	0.371
Lower Limit			0.006	0.005
Upper Limit			31.891	28.358
Relative Risk (Pooled Control)[f]			0.581	0.514
Lower Limit			0.010	0.009
Upper Limit			10.576	9.418
Weeks to First Observed Tumor	107	--	94	108

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Dapsone in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia[b]	2/13 (0.15)	3/36 (0.08)	1/31 (0.03)	1/35 (0.03)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.210	0.186
Lower Limit			0.004	0.003
Upper Limit			3.760	3.348
Relative Risk (Pooled Control)[f]			0.387	0.343
Lower Limit			0.008	0.007
Upper Limit			4.516	4.024
Weeks to First Observed Tumor	103	--	94	108

[a]Treated groups received doses of 500 or 1,000 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) whe $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

☆U.S. GOVERNMENT PRINTING OFFICE: 1977— 260-899:3137

DHEW Publication No. (NIH) 77-820