NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 238

CARCINOGENESIS BIOASSAY OF ZIRAM

(CAS NO. 137-30-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDY)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of chemically induced disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is comprised of four charter DHHS agencies: the National Cancer Institute, National Institutes of Health; the National Institute of Environmental Health Sciences, National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health, Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS BIOSASSAY OF ZIRAM

(CAS NO. 137-30-4)

IN F344/N RATS AND B6C3F$_1$ MICE
(FEED STUDY)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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April 1983

NTP-81-57
NIH Publication No. 83-1794
NTP TR 238

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

NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room A-306, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, NC 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650).

Single copies of this carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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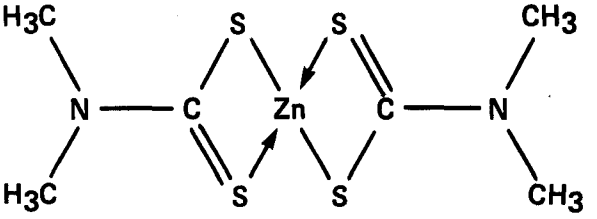

ZIRAM

CAS NO. 137-30-4
$C_6H_{12}N_2S_4Zn$ Mol. Wt. 305.82

ABSTRACT

A carcinogenesis bioassay of ziram (89% pure, with 6.5% thiram), a fungicide and a rubber vulcanization accelerator, was conducted in F344/N rats and in B6C3F$_1$ mice. Groups of 50 rats of each sex received diets containing 300 or 600 ppm of commercial grade ziram for 103 weeks; groups of 49 or 50 mice of each sex received diets containing 600 or 1,200 ppm ziram; and groups of 50 rats and 50 mice of each sex served as untreated controls.

The average daily consumption of ziram by low- and high-dose rats, through the majority of the study, was about 11 and 22 mg/kg for males and 13 and 26 mg/kg for females. The average daily consumption of ziram by low- and high-dose mice, through the majority of the study, was 122 and 196 mg/kg for males and about 131 and 248 mg/kg for females.

Survival and feed consumption and mean body weights of rats of each sex were not adversely affected by ziram; rats of each sex possibly could have tolerated higher doses.

C-Cell carcinomas of the thyroid in male rats occurred with a statistically significant positive trend ($P<0.01$) and the incidence in the high-dose group was significantly higher ($P<0.05$) than that in the controls (control, 0/50, 0%; low dose, 2/49, 4%; high dose, 7/49, 14%) and higher than that previously observed in control male rats at the same laboratory (18/584, 3%; range 0% to 8%). The combined incidence of males with either C-cell adenoma or carcinoma also showed a statistically significant ($P<0.05$) positive trend (control, 4/50, 8%; low dose, 9/49, 18%; high dose, 12/49, 24%). There were no significant histopathologic changes noted in the follicular cells.

Survival of male and female mice was not adversely affected by ziram in feed; mean body weight gain by dosed male mice throughout the study and by high-dose female mice after week 80 was depressed by 15% to 20% relative to the controls. Average daily feed consumption by high-dose males and high-dose females was, respectively, 78% and 85% that of the controls. Mice probably could not have tolerated higher doses.

The incidence of alveolar/bronchiolar adenomas was significantly ($P<0.05$) increased in female mice (control, 2/50, 4%; low-dose, 5/49, 10%; high-dose, 10/50, 20%). The combined incidence of alveolar/bronchiolar adenomas or carcinomas in female mice showed a statistically significant ($P<0.05$) positive trend. The incidence in the high-dose group was significantly ($P<0.05$) higher than that in the controls (control, 4/50, 8%; low-dose, 6/49, 12%; high-dose, 11/50, 22%). Pulmonary adenomatous hyperplasia consistent with chronic Sendai virus infection (confirmed by serologic analyses performed on untreated animals from the same animal shipment and present in the same room) was observed in control and dosed male mice (control, 15/49, 31%; low-dose, 19/50, 38%; high-dose, 16/49, 33%) as well as in control and dosed female mice (control, 18/50, 36%; low-dose, 27/49, 55%; high-dose, 26/50, 52%). Six of the 26 high-dose females with the adenomatous hyperplasia had pulmonary tumors, whereas 4 of the 24 high-dose females without pulmonary adenomatous hyperplasia also had pulmonary tumors. Only 1 of 27 low-dose females with adenomatous hyperplasia had a pulmonary tumor.

There was a significant decrease in the incidence of mammary fibroadenomas in high-dose female rats (control, 16/50, 32%; low-dose, 17/50, 34%; high-dose, 8/50, 16%). Significant dose-related decreased incidences of liver carcinomas in male mice (control, 13/49, 27%; low-dose, 8/50, 16%; high-dose, 1/49, 2%) and of liver adenomas in female mice (control, 7/50, 14%; low-dose, 2/50, 4%; high-dose, 0/50, 0%) were observed.

Under the conditions of these studies, ziram was carcinogenic for male F344/N rats, causing increased incidences of C-cell carcinomas of the thyroid gland. Ziram was not carcinogenic for either female F344/N rats or for male $B6C3F_1$ mice. Increased incidences of alveolar/bronchiolar adenomas and of combined alveolar/bronchiolar adenomas or carcinomas occurred in female $B6C3F_1$ mice. However, the interpretation of this increase in lung tumors is complicated by an intercurrent Sendai virus infection.

CONTRIBUTORS

The bioassay of ziram was conducted at Southern Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The two-year study in rats was begun in April 1978 and completed in April 1980. The two-year study in mice was begun in June 1977 and completed in June 1979.

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The chemicals used in this bioassay of ziram were analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110. Reanalysis of the bulk chemical and dosed feed analyses were conducted at Southern Research Institute.

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SUMMARY OF PEER REVIEW COMMENTS ON THE BIOASSAY OF ZIRAM

On 16 December 1981, this report underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in Conference Room A, Landow Building, 7910 Woodmont Avenue, Bethesda, Maryland.

Dr. Swenberg, a principal reviewer for the report on the bioassay of ziram, said that the reporting of non-tumor toxicology and pathology could be expanded and made into a separate section. He raised an objection to the uniform practice and presentation of the combined incidence of benign and malignant, organ-site tumors for evaluating carcinogenic responses. Dr. Norton Nelson, speaking for the NTP, stated that combining these tumors was appropriate for informational purposes and, further, that for certain tumors this was scientifically valid.

As a second principal reviewer, Dr. Hitchcock agreed with the conclusions for male and female rats and male mice. With regard to female mice, she suggested that the increased incidence of alveolar/bronchiolar adenomas was likely associated with exposure to Sendai virus. She said certain negative trends should be highlighted, including a significant decrease in the incidence of mammary fibroadenomas in high-dose female rats and dose-related decreased incidences of liver carcinomas in male mice and liver adenomas in female mice.

As a third principal reviewer, Dr. Breslow said the evidence for carcinogenesis stemming from the observed increase in C-cell carcinomas in male rats is strengthened by the fact that the thyroid would be expected to be a target organ for ziram. He noted that no comment was made in the abstract or discussion about the increase in malignant lymphocytic lymphoma in high-dose female mice. Some consideration of variations in historical incidence, of the lack of a similar result in male mice or rats, or of the difficulty of pathology diagnosis would be appropriate to support the apparent dismissal of the finding as a statistical fluke. He observed that retinopathy was diagnosed in both male and female rats at levels ranging from 14 to 96 percent among treatment groups, which again raises the issue of finding appropriate ways to account for the effects of cage or position in relation to fluorescent light exposure, if any, and to the carcinogenic process. Finally, Dr. Breslow discussed the large variations seen in several types of non-tumor lesions, particularly between treated and control groups, and requested some discussion be added to the report.

There was a lengthy discussion on whether there were predisposing or possible co-carcinogenic effects of intercurrent Sendai virus infection as related to pulmonary adenomatous hyperplasia observed in female mice. Dr. Holland said that Sendai viral pneumonia has been shown to be co-carcinogenic, and that many of the hyperplastic lesions show morphologic changes indistinguishable from those induced by chemicals; thus, etiology of the pulmonary adenomas remains obscure. Dr. Goldman, NTP, said that these mice as well as other mice tested with two other chemicals were obtained from the same supplier and were housed in the same room. All mice, both in control and dosed groups, of all three test chemical bioassays showed about the same incidence of pulmonary adenomatous hyperplasia, yet only the females in the ziram study showed a statistically significant increase in lung adenomas.

Dr. Swenberg moved that the report on the bioassay of ziram be accepted with the modifications discussed. Dr. Vore seconded the motion and the technical report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

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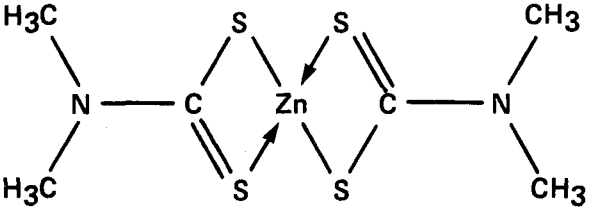

ZIRAM

CAS NO. 137-30-4
$C_6H_{12}N_2S_4Zn$ Mol. Wt. 305.82

Ziram (zinc dimethyldithiocarbamate), a derivative of dithiocarbamate (H2NCSSH), is a ubiquitous chemical produced in large quantities worldwide. It has principal uses as an accelerator in the process of rubber vulcanization (Kirk-Othmer, 1968) and as a contact fungicide in agriculture (Fishbein, 1976) and industry (EPA, 1973). During the past 30 years of use, the dithiocarbamates have gained wide acceptance as replacements for the fixed copper fungicides. In 1979, production of ziram in the United States was approximately 1.7 million kilograms (USITC, 1980); production worldwide was several times higher (IARC, 1976b). Agricultural and food uses of ziram include antifungal treatment of field and storage crops, cereals, seeds, and household flowers. Allowable residues of ziram range from 0.1 ppm on some nuts to 7 ppm for fruits and vegetables (U.S. Code of Fed. Reg., 1976). Minor antifungal uses of ziram include treatment of industrial cooling water, adhesives, paper and paper products, and food packagings.

Ziram, in common with other bisdithiocarbamates, may be goitrogenic in laboratory animals and, possibly, in humans. Earlier studies, however, showed that while both disodium- and zinc-ethylene(bis)dithiocarbamates (nabam and zineb) were goitrogenic in rats (Smith et al., 1953; Hodge et al., 1956), neither ziram nor ferbam (the iron salt of dimethyldithiocarbamate) were goitrogenic (Hodge et al., 1956). Other toxic reactions of ziram, and other dithiocarbamates, include glycogenolysis, accumulation of acetaldehyde in the blood of animals fed ethanol, and testicular atrophy (Fishbein, 1976; IARC, 1976a, 1976b). In a study of workers engaged in the manufacture of thiram, the thyroid appeared as the primary target organ; thyroid enlargement, one adenocarcinoma, as well as "other abnormalities" were reported (Cherpak et al., 1971 and Kaskevich and Bezugly, 1973).

Central nervous system disturbances have been reported following the oral administration of ziram, ferbam, or thiram. Hodge et al. (1956) found cystic brain lesions in female rats fed ferbam, convulsive seizures in beagle dogs fed ziram or ferbam, and a peculiar hind leg grasping reaction plus other motor changes in rats fed ziram or ferbam. Neurotoxicity and central and peripheral nervous system degeneration followed oral administration of thiram (tetramethylthiuram disulfide) to female rats (Lee and Peters, 1976).

The administration of ferbam to pregnant rats during days 6-15 of gestation caused a slight increase in soft and skeletal tissue abnormalities (Minor et al., 1974); ziram and maneb—manganese ethylene(bis) dithiocarbamate—both showed teratogenic and embryotoxic activities in rats, mice, and rabbits (Antonovich et al., 1972).

An IARC review (1976b) of earlier carcinogenicity tests of ziram found the results of these studies to be of questionable value. The review included results published by Innes et al. (1969), Chernov and Khitsenko (1969), Andrianova and Alekseev (1970), and Hodge et al. (1956). Each earlier study was found to be qualitatively or quantitatively inadequate.

The mutagenicity of ziram has been tested many times. Ziram was mutagenic, with and without metabolic activation, when tested against the base substitution-sensitive *Salmonella typhimurium* strains TA 1535 and TA 100 (Hedenstedt et al., 1979; Seiler, 1973); mutagenicity was questionable when tested against the framshift-sensitive mutants TA 1538 and TA 98. Thiram,

the disulfide equivalent of ziram, is also mutagenic to strains TA 1535 and TA 100; with metabolic activation, thiram is also mutagenic to TA 1538 and TA 98. Zdzienicka et al. (1979) reported similar results and added that the mutagenic activity of thiram was abolished in the presence of sulfhydryl groups. There has been one negative result reported for ziram mutagenicity. In tests against standard strains of *Salmonella typhimurium* (TA 1535, TA 1537, TA 1538, TA 98, and TA 100), with and without metabolic activation, DeLorenzo et al. (1978) found that ziram was not mutagenic. Murthy (1979) reported that ziram did not induce gene conversion in *Saccharomyces cerevisiae,* a diploid yeast. Ziram was mutagenic in *S. typhimurium* without exogenous metabolic activation (TA 100) and with 9000 x g liver supernatant (S-9) fractions induced with Aroclor-1254 (TA 98, TA 100, TA 1535); ziram was not mutagenic for TA 1537 (NTP 1982c). Shirasu et al. (1977) had earlier reported that ziram and thiram were weakly positive in the recombination assay using the H17 Rec+O and M45 Rec-(DNA damage) strains of *Bacillus subtilis.*

There has been one report of chromosome and chromatid aberrations in cultured lymphocytes derived from industrial workers handling ziram (Pilinskaya, 1970). The induced chromosomal breaks were non-random, confined mainly to chromosome 2.

Ziram and similar dithiocarbamates are probably metabolized principally by the liver microsomal mixed function oxidase. Neal et al. (1977) have suggested that the known impairment of microsomal drug metabolism by sulfur-containing compounds, and, especially carbon disulfide, is due to binding of an active form of sulfur to the microsomal and cytochrome P450 systems. Zematis and Greene (1979) later showed that thiram and dimethyldithiocarbamate reduced the *in vivo* and *in vitro* activity of several liver microsomal enzymes associated with hepatic drug metabolism and suggested that this reduction could enhance the pharmacologic effects of other drugs taken simultaneously or already present in the affected individual.

Ziram, along with other dithiocarbamates, decomposes under acid conditions to dimethylamine (Lopatecki and Newton, 1952; Houben-Weyl, 1955), probably through the intermediate formation of dimethyldithiocarbamic acid (Eisenbrand et al., 1974). Secondary amines can be nitrosated under acid conditions in the presence of nitrite (IARC, 1972; Mirvish, 1975). Mirvish (1975) and others (Eisenbrand et al., 1974; IARC, 1972) have suggested that nitrosation of dimethylamine (or dimethyldithiocarbamic acid) to dimethylnitrosamine (DMN) can proceed under the acid conditions of the stomach; the nitrite presumably enters via saliva or as a food additive. While both *in vivo* and *in vitro* experiments have shown that DMN can be recovered from the acid-catalyzed reaction of sodium nitrite and ziram (Eisenbrand et al., 1974; IARC, 1972; Mirvish, 1975), these experiments do not take into account the effect of the simultaneous presence in the stomach of ziram, nitrite, and food. It is likely that there would be sufficient alternate nitrogenous compounds present to effectively inhibit the specific formation of DMN in the fed animal. There is ample evidence on the carcinogenicity of DMN; there is not adequate evidence showing that DMN can be formed in the fed animal.

The NTP Bioassay Program tested ziram because of its rate of production, industrial exposure, exposure of the general population via the food and agriculture industries, and because previous tests for carcinogenicity were considered to be inadequate.

II. MATERIALS AND METHODS

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Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

TWO-YEAR STUDIES

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSES

Ziram (CAS No. 137-30-4) was obtained from Uniroyal Chemical (Naugatuck, CT) as the commercial product "Methazate UO" in one batch (Lot No. 319400). The material was analyzed for purity and identity at Midwest Research Institute. Infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with those expected for the structure (Appendix E). The results of elemental analyses for carbon and sulfur were lower than the expected values, while the results for zinc were higher. Two impurities were detected by thin-layer chromatography in two different systems. Two impurities were detected by high-pressure liquid chromatography (HPLC). One of these impurities was identified by comparative retention time measurements as thiram (tetramethyldithiocarbamoyl disulfide), a metabolite of ziram (Vekshtein and Khitsenko, 1971). Quantitation with a thiram standard showed that this lot of ziram contained 6.47% of thiram. The other impurity, about 2% of the HPLC area, was not identified. Within the limits of HPLC detection, this lot of ziram contained no bis(dimethylthiocarbamoyl) sulfide.

This lot of ziram also contained an acetonitrile-insoluble impurity (see Appendix E, Section D). According to the manufacturer of ziram, Uniroyal Chemical, the manufacturer's specifications allow "as much as 2% (benzene or toluene) insolubles," which are probably unreacted zinc salts used in the manufacturing process. This would also account for the discrepancies in the elemental analysis noted above.

The ziram used in the present study, accordingly, contained about 89% ziram, 6.5% thiram, 2% other zinc salts, and 2% of an unidentified additional impurity. Southern Research Institute periodically analyzed this chemical by HPLC and infrared spectrometry throughout the study and noted no change in composition. Ziram used in this study was stored in the dark at 5° C.

DOSAGE AND DIETARY PREPARATION

The dosage mixture in the single-dose study was obtained by combining weighed portions of ziram with corn oil immediately before administration (Table 1). In the 14-day study and the 13-week study, a measured amount of ziram was placed in a plastic bag with approximately one cup of Wayne Lab Blox® and shaken by hand until uniformly mixed (Table 1). This premix was added to the remaining feed and mixed in an 8-quart Patterson-Kelly® Twin Shell blender for 15 minutes. In the two-year study, the appropriate amount of weighed chemical was mixed with about the same amount of weighed feed (Table 1). The remaining weighed feed was combined with the premix in a 16-quart Patterson-Kelly® Twin Shell blender equipped with an intensifier bar and mixed for 15 minutes. This mixing time resulted in the most homogeneous mixture. Fresh formulated diets were prepared every 14 days in the 13-week study and in the two-year study.

Analysis of the stability of ziram in formulated diets was performed at Midwest Research Institute by assaying samples of feed mixtures containing 99,500 ppm test chemical that had been stored for 2 weeks at temperatures of -20°, 5°, 25°, or 45° C. Ziram was found to be stable for 2 weeks at temperatures up to 45° C (Appendix F). Analyses were initially (in the 13-week study and for the first 18 months of the two-year study) based on the spectrophotometric determination of the copper complex of bis(dimethyldithiocarbamate) following solvent extraction of the dosed feed sample. A more satisfactory method of analysis was developed based on zinc analysis by atomic absorption. Blank, spiked samples (for a standard curve) and dosed feed samples all were made from the same lot of feed.

SHORT-TERM STUDIES

Male and female F344/N rats and B6C3F$_1$ mice obtained from Frederick Cancer Research Center (Frederick, MD) were used for all prechronic studies. Details of the experimental design, animal maintenance, and preparation of chemical-vehicle or chemical-feed mixtures for these studies are presented in Table 1.

Single-Dose Study

Animals were held for 10 days before the test began and were 6 weeks old when placed on study. Groups of five rats and five mice of each sex were administered ziram in corn oil by gavage at doses of 125, 250, 500, 1,000, or 2,000 mg/kg body weight and then observed for mortality for 14 days. Necropsies were not performed.

Fourteen-Day Study

Rats and mice were held for 10 days before the test began and were 6 weeks old when placed on study. Groups of five male and five female rats were fed diets containing 6,000, 12,500, 25,000, 50,000, or 100,000 ppm ziram for 14 days, and groups of five male and five female mice were fed diets containing 1,200, 2,500, 5,000, 10,000, or 20,000 ppm ziram for the same period. No controls were used. The rats and mice were observed twice daily for mortality and were weighed weekly. Animals were fed undosed control diet from day 15 until they were killed (days 16 or 17). Necropsies were performed on animals when they died or when they were killed at termination of the study (days 16 or 17).

Thirteen-Week Study

The thirteen-week study was conducted to evaluate the 90-day cumulative toxicity of ziram and to determine the concentrations to be used in the two-year study.

Four-week-old rats and mice were observed for 7 days and then assigned to cages and test groups according to tables of random numbers. Groups of 10 rats and 10 mice of each sex were fed diets containing 0, 300, 600, 1,200, 2,500, or 5,000 ppm ziram for 13 weeks.

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were judged moribund were killed and necropsied. Each animal was given a clinical examination weekly, including palpation for tissue masses or other abnormalities. Body weight and feed consumption data were collected weekly.

On days 92-101, survivors were killed with carbon dioxide, and necropsies were performed on animals that survived to the end of the study and on all animals not completely autolyzed or cannibalized. 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. The following tissues were examined for control groups and for groups administered 2,500 or 5,000 ppm ziram: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, thigh muscle, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, and pituitary. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

TWO-YEAR STUDIES

Three-week-old male and female F344/N rats from Harlan Industries (Indianapolis, IN) were observed for 13 days and assigned to cages according to a table of random numbers; the cages were then assigned to control and dosed groups according to another table of random numbers. Four-week-old male and female B6C3F$_1$ mice from Frederick Cancer Research Center (Frederick, MD) were observed for 7 days and then assigned to cages and groups according to the procedures used for rats (Table 1).

Mice fed ziram were housed in the same room as mice fed eugenol (CAS No. 97-53-0) for the first year of the study and with mice fed D-mannitol (CAS No. 69-65-8) for the entire study. Rats fed ziram were housed in a separate room where no other chemicals were on test.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of morbidity or mortality. Body weights and feed consumption by cage, along with clinical signs, were recorded monthly. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. The average feed consumption per animal was calculated by dividing the total feed consumption measured for all cages by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed with carbon dioxide and necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord. Special staining techniques were used as necessary.

Necropsies were performed on all animals not excessively autolyzed or cannibalized. The number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts verified, and histotechnique evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10 percent of the animals were evaluated by an experienced rodent pathologist. Slides of all target tissues and those on which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology working Group (PWG) for evaluation. Representative slides selected by the PWG Chairperson were reviewed blindly by the PWG's experienced rodent pathologists, who reached a consensus and compared their findings with the original diagnoses. When conflicts were found, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure has been described, in part, by Ward et al., 1978). The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group. In this study the tumor target tissues were the thyroid (male and female rats), lung (male and female mice) and liver (male mice).

Data Recording and Statistical Methods

Data on this experiment were recorded in 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).

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.

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 to the number of animals in which that site was examined. 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 (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959).

Tests of significance included pairwise comparisons of high- and low-dosed groups with controls and tests for overall dose-response trends.

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel methods to obtain an overall P-value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

The second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill period, and the terminal kill period. The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher's exact test for pairwise comparisons and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P-values are one-sided.

For studies in which there is little effect of compound administration on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	Single-Dose	14-Day Study	13-Week Study	2-Year Study
Experimental Design				
Size of Test Groups	5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	49 or 50 males and 50 females of each species
Doses	125, 250, 500, 1,000, or 2,000 mg/kg body weight ziram in corn oil	Rats: 6,000, 12,500, 25,000, 50,000 or 100,000 ppm ziram in feed Mice: 1,200, 2,500 5,000, 10,000, or 20,000 ppm ziram in feed	0, 300, 600, 1,200, 2,500 or 5,000 ppm ziram in feed	Rats: 0, 300, or 600 ppm ziram in feed Mice: 0, 600, or 1,200 ppm ziram in feed
Duration of Dosing	Single dose	14 days; control diets fed on day 15; rats killed day 17, mice killed days 16-17	13 weeks; rats killed days 92-101; mice killed days 92-100.	103 weeks; rats killed days 729-745; mice killed days 729-742.
Type and Frequency of Observation	Observed twice daily for mortality for 14 days	Observed twice daily for mortality and weighed weekly	Observed twice daily for mortality and signs of morbidity; body weight and feed consumption data collected weekly.	Observed twice daily for signs of morbidity or mortality; clinical signs, body weights, and feed consumption recorded monthly.
Necropsy and Histopathologic Examination	None performed	All animals necropsied	All animals necropsied; animals in the two highest dose groups received histopathological examination	All animals necropsied and examined histopathologically.
Animals and Animal Maintenance				
Species	F344/N Rats; B6C3F$_1$ Mice	F344/N Rats; B6C3F$_1$ Mice	F344/N Rats; B6C3F$_1$ mice	F344/N Rats; B6C3F$_1$ Mice
Animal Source	Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)	Rats: Harlan Research Labs (Indianapolis, IN); Mice: Frederick Cancer Research Center (Frederick, MD)
Time Held Before Start of Test	10 days	10 days	7 days	Rats: 13 days Mice: 7 days

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose	14-Day Study	13-Week Study	2-Year Study
Animals and Animal Maintenance (Continued)				
Age When Placed on Study	6 weeks	6 weeks	5 weeks	Rats: 5 weeks Mice: 6 weeks
Age When Killed	8 weeks	8 weeks	18-20 weeks	109-112 weeks
Method of Animal Distribution	Assigned to cages according to a table of random numbers, then to dosed groups according to a second table of random numbers	Same as single-dose study	Same as single-dose study	Same as single-dose study
Feed	Wayne® Lab Blox, Allied Mills (Chicago, IL)	Same as single-dose study	Same as single-dose study	Same as single-dose study; feeders changed weekly
Bedding	Beta Chips® Northeastern Products Corp. (Warrensburg, NY)	Same as single-dose study	Same as single-dose study. Bedding changed twice weekly	Mice: same as single-dose study, except changed to sawdust for days 234-344, 371-555, 620-630; Rats: sawdust for days 1-177, 242-272; bedding changed twice weekly.
Water	Tap water in bottles available *ad libitum*	Same as single-dose study	Same as single-dose study. Water bottles changed weekly	Automatic Edstrom Industries, Inc. (Waterford, WI)
Cages	Stainless steel Hahn Roofing & Sheet Metal Co. (Birmingham, AL)	Same as single-dose study	Same as single-dose study. Cages changed twice weekly	Polycarbonate cages suspended on stainless steel racks; changed twice weekly; Lab Products, Inc. (Garfield, NJ)
Cage Filters	Fiberglass	Same as single-dose study	Same as single-dose study	Reemay spun-bonded polyester; changed every two weeks. Snow Filtration (Cincinnati, OH)

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose	14-Day Study	13-Week Study	2-Year Study
Animals per Cage	5	5	5	5
Animal Room Environment	21° ±3°C, 30%-60% humidity, air changed 15 times per hour; 9 hrs of fluorescent light per day	Same as single-dose study	Same as single-dose study	21° ±3°C, 30%-60% humidity; room air changed at least 15 times per hour; illumination by fluorescent lighting 12 hrs per day.
Other Chemicals on Test in the same room	Stannous chloride, propyl gallate, D-mannitol, zearalenone	Mice: D-mannitol, stannous chloride, propyl gallate; Rats: propyl gallate, D-mannitol, zearalenone	Mice: D-mannitol, stannous chloride, ethyl acrylate, eugenol, allyl isothiocyanate, propyl gallate, zearalenone; Rats: D-mannitol, stannous chloride, propyl gallate, zearalenone	Mice: 1st year: D-mannitol and eugenol; 2nd year: D-mannitol Rats: none
Chemical-Vehicle or Chemical-Feed Mixture Preparation	Weighed portions of ziram mixed with corn oil immediately preceding administration	A measured amount of ziram was placed in a plastic bag with approximately 1 cup of feed and shaken until uniform. This mixture was added to the remaining feed and mixed in an 8-qt. Patterson-Kelly®Twin Shell blender for 15 minutes.	Same as 14-day study	Weighed chemical was premixed with approximately the same amount of weighed feed. Remaining weighed feed was then combined with the premix in a 16-qt. Patterson-Kelly®Twin Shell blender equipped with intensifier bar; ziram/feed mixture was mixed for 15 minutes.
Maximum Storage Time	Used when mixed	14 days	14 days	14 days
Storage Conditions			Sealed plastic containers at 21°C ±3°C	Doubled plastic bags inside sealed, labeled, rigid plastic containers; stored in the dark at 4°C for 7 days, followed by no more than 7 days at 21° ±3°C.

III. RESULTS

RATS

SHORT-TERM STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SHORT-TERM STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SHORT-TERM STUDIES

Single-Dose Study

All rats administered 2,000 mg/kg ziram were dead by day 4. No other compound-related deaths occurred (Table 2). Diarrhea was observed in rats of each sex receiving 1,000 or 2,000 mg/kg, but not in animals receiving lower doses.

Fourteen-Day Study

All rats receiving 12,500, 25,000, 50,000, or 100,000 ppm ziram died; two of the five male rats receiving 6,000 ppm died (Table 3). All rats receiving 12,500 - 100,000 ppm ziram had diarrhea. No compound-related gross pathologic effects were observed.

Thirteen-Week Study

One female rat receiving the highest dose (5,000 ppm) died (Table 4). No other deaths occurred. Mean body weight gain was depressed by more than 16% in males receiving 1,200, 2,500, or 5,000 ppm and in females receiving 600-5,000 ppm. No compound-related histopathologic effects were observed.

Because of the weight-gain decrement observed in the 13-week study, doses selected for rats in the two-year study were 300 and 600 ppm ziram in feed.

TABLE 2. SURVIVAL OF RATS ADMINISTERED A SINGLE DOSE OF ZIRAM BY GAVAGE

Dose (mg/kg)	Survival *(a)*	
	Males	Females
125	5/5	5/5
250	5/5	2/5 *(b)*
500	5/5	5/5
1,000	5/5	2/5 *(b)*
2,000	0/5 *(c)*	0/5 *(d)*

(a) Number surviving/number per group.
(b) Deaths due to gavage error.
(c) One animal died on day 2; the rest died on day 3.
(d) One animal died on day 1, one animal died on day 3, and three animals died on day 4.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING ZIRAM FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Day of Death	Mean Body Weights (grams)		
			Initial	Final	Change
Males					
6,000	3/5	12,13	84	84	0
12,500	0/5	5,5,5,6,6	85	-	-
25,000	0/5	4,5,5,5,5	82	-	-
50,000	0/5	5,5,5,5,6	83	-	-
100,000	0/5	5,5,5,5,6	89	-	-
Females					
6,000	5/5		78	79	+1
12,500	0/5	6,6,6,6,8	74	-	-
25,000	0/5	5,6,6,6,7	81	-	-
50,000	0/5	5,5,5,6,6	81	-	-
100,000	0/5	5,5,5,6,6	76	-	-

(a) Number surviving/number per group.

TABLE 4 SURVIVAL, MEAN BODY WEIGHTS, AND COMPOUND CONSUMPTION OF RATS FED DIETS CONTAINING ZIRAM FOR 13 WEEKS

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Controls (c) (Percent)	Average Daily Feed Consumption (grams)	Average Daily Dose Consumed (mg/kg)	
		Initial	Final	Change			Initial	Final
Males								
0	10/10	96.6 ± 3.11	304.1 ± 10.26	+207.5 ± 8.95		16		
300	10/10	93.5 ± 1.98	330.1 ± 4.96	+236.6 ± 4.45	+14.0	16	51.3	20.3
600	10/10	92.5 ± 2.86	314.1 ± 5.25	+221.6 ± 4.41	+ 6.8	14	90.8	26.7
1,200	10/10	91.7 ± 2.26	265.7 ± 4.31	+174.0 ± 3.55	16.1	15	179	67.9
2,500	10/10	92.0 ± 2.16	263.0 ± 5.32	+171.0 ± 4.65	17.6	13	353	124
5,000	10/10	92.5 ± 1.74	218.5 ± 3.93	+126.0 ± 4.04	39.3	14	757	320
Females								
0	10/10	80.8 ± 3.3	194.1 ± 4.1	+113.3 ± 2.6		11		
300	10/10	77.3 ± 2.1	184.0 ± 3.5	+106.7 ± 3.4	5.8	10	38.8	16.3
600	10/10	79.9 ± 1.7	172.3 ± 2.3	+ 92.4 ± 2.0	18.4	9	67.6	31.3
1,200	10/10	80.5 ± 2.3	174.8 ± 4.6	+ 94.3 ± 3.1	16.8	10	149	68.6
2,500	10/10	75.2 ± 2.6	153.6 ± 1.3	+ 78.4 ± 1.8	30.8	9	299	146
5,000	9/10(d)	76.0 ± 2.4	143.6 ± 2.1	+ 67.6 ± 2.7	40.3	9	592	313

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.
(b) Mean weight change of the survivors of the group ± standard error of mean.
(c) Weight change of the dosed group relative to that of the controls = $\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$
(d) Death occurred on day 15

TWO-YEAR STUDIES

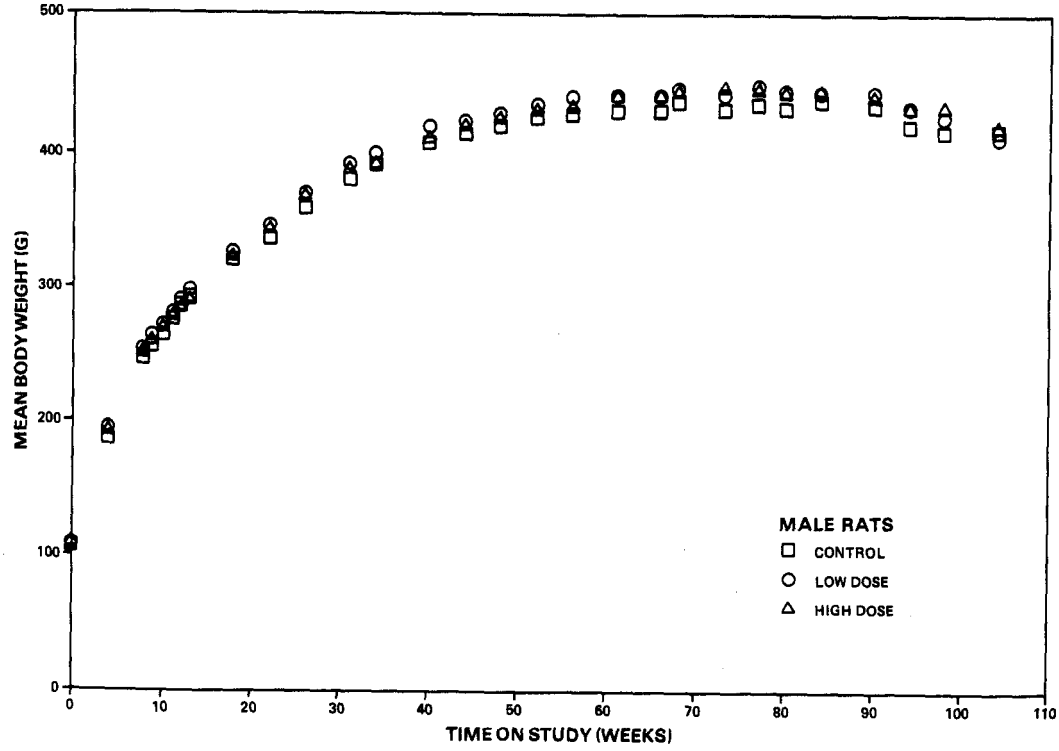
Body Weights and Clinical Signs

Throughout the last year of the study, mean body weights of high-dose male rats were slightly higher than those of the controls. Mean body weights of high-dose female rats were slightly lower than those of the controls (Table 5 and Figure 1). The average daily feed consumption per animal by low- and high-dose rats was 102% and 101% that of the controls for males and 99% and 95% for females (Table 6). The average daily consumption of ziram per animal by low- and high-dose rats, after the first 26 weeks of the study, was about 11 and 22 mg/kg for male rats and about 13 and 26 mg/kg for female rats (Table 7). These daily intake amounts should be considered as useful approximations that are dependent on the accuracy of the measurement of feed consumption. There were no remarkable clinical signs.

TABLE 5 CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF RATS FED DIETS CONTAINING ZIRAM IN THE 2-YEAR STUDY

	Week No	Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls	
		Control	Low Dose	High Dose	Low Dose	High Dose
Males	0	106 (b)	107 (b)	108 (b)		
	4	81	88	84	+9	+4
	26	253	263	262	+4	+4
	48	315	323	319	+3	+1
	68	331	340	338	+3	+2
	84	333	338	338	+2	+2
	104	312	306	312	2	0
	Final Weight	418	413	420	-1	+1
Females	0	93 (b)	93 (b)	93 (b)		
	4	36	39	36	+8	0
	26	106	105	103	1	-3
	48	138	136	130	1	-6
	68	181	174	166	4	-8
	84	196	200	188	+2	-4
	104	212	219	204	+3	-4
	Final Weight	305	312	297	+2	-3

(a) Weight change of the dosed group relative to that of the controls = $\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$
(b) Initial weight



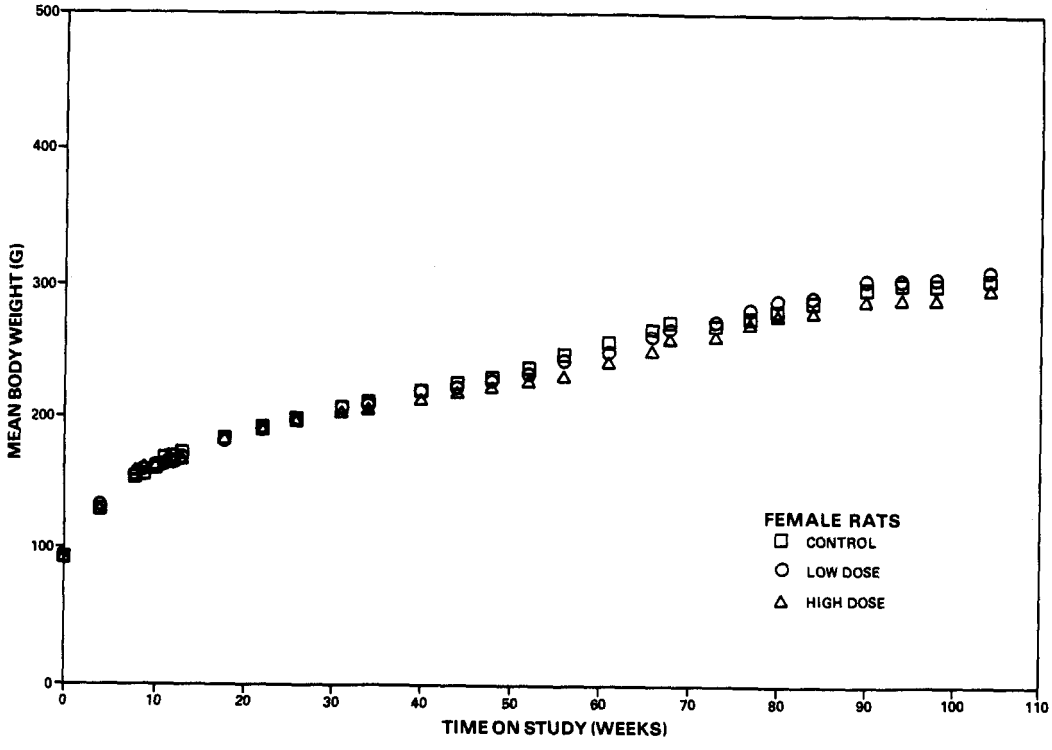


Figure 1. Growth Curves for Rats Fed Diets Containing Ziram

TABLE 6. FEED CONSUMPTION BY RATS RECEIVING ZIRAM IN THE 2-YEAR STUDY

Week	Control	Low Dose		High Dose	
	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
Males					
4	15.4	15.4	1.0	14.5	0.9
26	15.0	16.0	1.1	16.0	1.1
48	17.6	17.6	1.0	17.6	1.0
68	16.0	15.9	1.0	16.0	1.0
84	13.7	13.7	1.0	13.8	1.0
104	13.6	14.5	1.1	13.6	1.0
Mean	15.2	15.5	1.0	15.3	1.0
SD *(c)*	1.5	1.3	0.1	1.6	0.1
CV *(d)*	9.9	8.4	10.0	10.5	10.0
Females					
4	9.6	10.0	1.0	9.6	1.0
26	11.0	11.0	1.0	10.0	0.9
48	11.4	11.4	1.0	10.4	0.9
68	11.0	11.0	1.0	11.0	1.0
84	10.3	10.3	1.0	10.3	1.0
104	11.8	10.9	0.9	10.9	0.9
Mean	10.9	10.8	1.0	10.4	1.0
SD *(c)*	0.8	0.5	0.0	0.5	0.1
CV *(d)*	7.3	4.6	0.0	4.8	10.0

(a) Grams of feed consumed per animal per day.
(b) Grams of feed consumed per day by the dosed group divided by that for the controls.
(c) Standard deviation.
(d) Coefficient of variation = (standard deviation/mean) x 100

TABLE 7. COMPOUND CONSUMPTION BY RATS RECEIVING ZIRAM IN THE 2-YEAR STUDY

	Week No.	Low Dose			High Dose		
		Body Weight *(a)*	Grams Feed/Day *(b)*	Dose, mg/kg/Day *(c)*	Body Weight *(a)*	Grams Feed/Day *(b)*	Dose, mg/kg/Day *(d)*
Males	4	195	15.4	23.7	192	14.5	45.3
	26	370	16.0	13.0	370	16.0	25.9
	48	430	17.6	12.3	427	17.6	24.7
	68	447	15.9	10.7	446	16.0	21.5
	84	445	13.7	9.2	446	13.8	18.6
	104	413	14.5	10.5	420	13.6	19.4
Females	4	132	10.0	22.7	129	9.6	44.7
	26	198	11.0	16.7	196	10.0	30.6
	48	229	11.4	14.9	223	10.4	28.0
	68	267	11.0	12.4	259	11.0	25.4
	84	293	10.3	10.5	281	10.3	22.0
	104	312	10.9	10.4	297	10.9	22.0

(a) Group body weight average from Table 5
(b) From Table 6
(c) Low-dose = 300 mg/kg of feed. Dose calculation =

$$\left[\frac{\text{Grams Feed/Day}}{\text{Body Wt (Kg)}}\right] \times 300/1000$$

(d) High Dose = 600 mg/kg of feed. Dose calculation =

$$\left[\frac{\text{Grams Feed/Day}}{\text{Body Wt (Kg)}}\right] \times 600/1000$$

Survival

Estimates of the probabilities of survival of male and female rats fed diets containing ziram at the concentrations used in the 2-year study, and those of the controls, are shown by the Kaplan and Meier curves in Figure 2. The survival of female rats in the high-dose group was significantly higher (P=0.023) than that in the control group. No other significant differences were observed between the survival of any groups of rats of either sex.

Among male rats, 33/50 (66%) of the controls, 34/50 (68%) of the low-dose group, and 40/50 (80%) of the high-dose group lived to the end of the study at 104-106 weeks. Among female rats, 37/50 (74%) of the controls, 44/50 (88%) of the low-dose group, and 46/50 (92%) of the high-dose group lived to the end of the study at 104-106 weeks. The numbers of low-dose animals include two males and one female that died natural deaths during the termination period of the study; these were included in the statistical analysis of the terminal incidence shown in Tables 8 and 9.

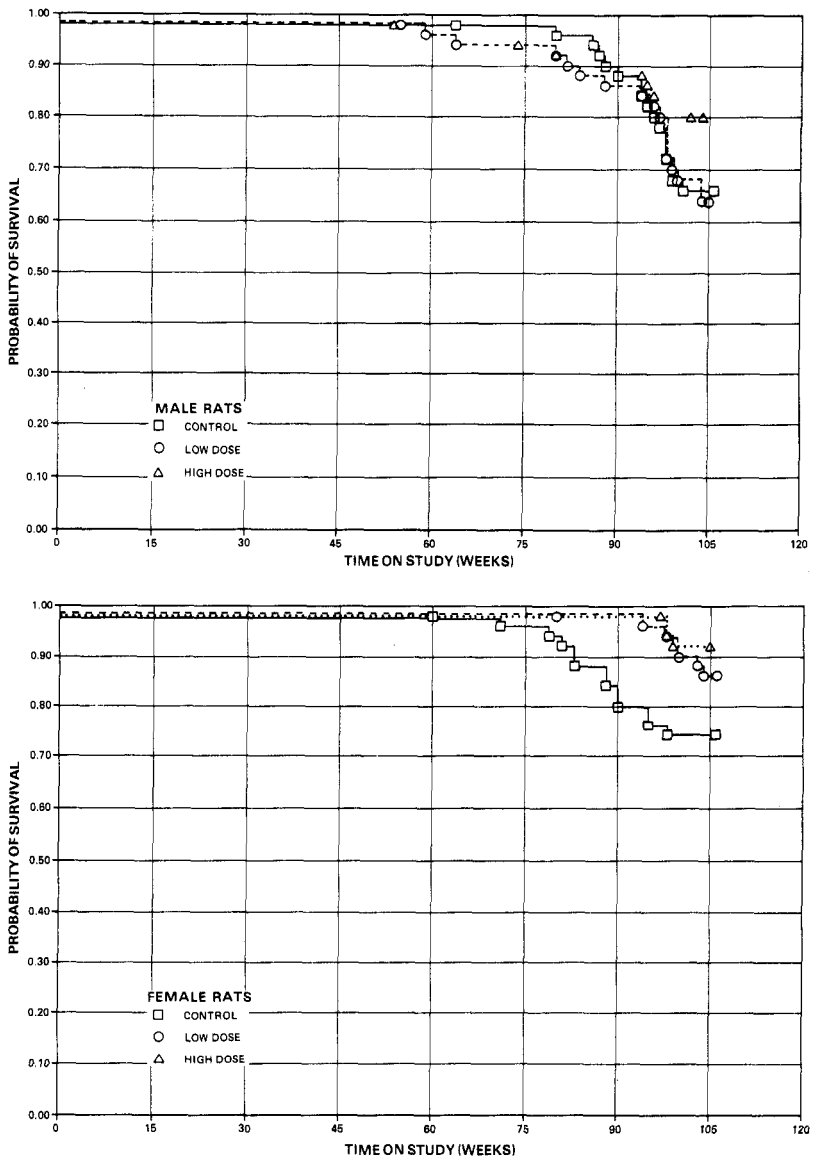


Figure 2. Survival Curves for Rats Fed Diets Containing Ziram

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for each individual animal in the male and female rat studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Tables 8 and 9 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Thyroid: C-cell carcinomas occurred at a significantly increased incidence ($P<0.05$) in high-dose male rats, and with a significant ($P<0.01$) dose-related trend (control 0/50; low-dose, 2/49, 4%; high-dose, 7/49, 14%). The dose-related trend was significant ($P<0.05$) for male rats with C-cell adenomas or carcinomas (control 4/50, 8%; low-dose, 9/49, 18%; high-dose 12/49; 24%). Neither C-cell adenomas nor C-cell carcinomas were significantly increased in dosed female rats. C-cell hyperplasia of the thyroid gland was observed in male rats (control, 7/50, 14%; low-dose, 12/49, 24%; high-dose, 11/49, 22%) and in female rats (control, 16/50, 32%; low-dose, 11/50, 22%; high-dose, 19/50, 38%). Thyroglossal duct cysts occurred in male rats (control, 0/50; low-dose 3/49, 6%; high-dose, 1/49, 2%) and in female rats (control, 0/50; low-dose, 7/50, 14%; high-dose, 5/50, 10%). Follicular-cell adenomas or carcinomas occurred at all incidences in all groups of male and female rats (Tables A1 and A2).

Mammary Gland: Fibroadenomas were observed in decreased incidence in the mammary gland of high-dose female rats ($P<0.05$), even though more high-dose than control females lived to the end of the study. There was evidence of a dose-related decrease in the incidence of females with adenocarcinomas ($P=0.040$, life table trend test).

Eye: Retinopathy was observed at increased incidences in high-dose males and in dosed females (control males, 32/50, 64%; low-dose males, 7/50, 14%; high-dose males, 45/50, 90%; control females, 9/50, 18%; low-dose females, 48/50, 96%; high-dose females, 30/50, 60%).

TABLE 8. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)*

	Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(b)*	2/50(4%)	6/50(12%)	0/50(0%)
Adjusted *(c)*	6.1%	14.2%	0.0%
Terminal *(d)*	2/33(6%)	1/34(3%)	0/40(0%)
Statistical Tests *(e)*			
Life Table	P=0.222N	P=0.145	P=0.197N
Incidental Tumor Test	P=0.440N	P=0.099	P=0.197N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.253N	P=0.134	P=0.247N
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(b)*	10/50(20%)	11/50(22%)	10/50(20%)
Adjusted *(c)*	25.3%	26.8%	22.5%
Terminal *(d)*	5/33(15%)	5/34(15%)	6/40(15%)
Statistical Tests *(e)*			
Life Table	P=0.408N	P=0.516	P=0.451N
Incidental Tumor Test	P=0.389	P=0.401	P=0.521
Cochran-Armitage Trend, Fisher Exact Tests	P=0.549	P=0.500	P=0.598
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	10/50(20%)	11/50(22%)	11/50(22%)
Adjusted *(c)*	25.3%	26.8%	24.2%
Terminal *(d)*	5/33(15%)	5/34(15%)	6/40(15%)
Statistical Tests *(e)*			
Life Table	P=0.497N	P=0.516	P=0.541N
Incidental Tumor Test	P=0.275	P=0.401	P=0.386
Cochran-Armitage Trend, Fisher Exact Tests	P=0.452	P=0.500	P=0.500
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	13/50(26%)	9/50(18%)	8/49(16%)
Adjusted *(c)*	32.5%	25.2%	19.3%
Terminal *(d)*	7/33(21%)	8/34(24%)	6/39(15%)
Statistical Tests *(e)*			
Life Table	P=0.078N	P=0.231N	P=0.102N
Incidental Tumor Test	P=0.185N	P=0.274N	P=0.273N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.141N	P=0.235N	P=0.176N
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	15/50(30%)	11/50(22%)	10/49(20%)
Adjusted *(c)*	37.7%	30.9%	23.3%
Terminal *(d)*	9/33(27%)	10/34(29%)	7/39(18%)
Statistical Tests *(e)*			
Life Table	P=0.082N	P=0.238N	P=0.107N
Incidental Tumor Test	P=0.166N	P=0.281N	P=0.231N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.160N	P=0.247N	P=0.193N

TABLE 8. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	7/50(14%)	6/50(12%)	7/50(14%)
Adjusted *(c)*	17.5%	15.9%	17.5%
Terminal *(d)*	3/33(9%)	4/34(12%)	7/40(18%)
Statistical Tests *(e)*			
Life Table	P=0.443N	P=0.493N	P=0.494N
Incidental Tumor Test	P=0.457	P=0.562N	P=0.504
Cochran-Armitage Trend, Fisher Exact Tests	P=0.558	P=0.500N	P=0.613
Thyroid: Follicular-Cell Carcinoma			
Tumor Rates			
Overall *(b)*	1/50(2%)	3/49(6%)	1/49(2%)
Adjusted *(c)*	2.6%	8.1%	2.6%
Terminal *(d)*	0/33(0%)	2/34(6%)	1/39(3%)
Statistical Tests *(e)*			
Life Table	P=0.563N	P=0.317	P=0.734N
Incidental Tumor Test	P=0.563	P=0.275	P=0.716
Cochran-Armitage Trend, Fisher Exact Tests	P=0.602	P=0.301	P=0.747
Thyroid: Follicular-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	1/50(2%)	5/49(10%)	1/49(2%)
Adjusted *(c)*	2.6%	13.9%	2.6%
Terminal *(d)*	0/33(0%)	4/34(12%)	1/39(3%)
Statistical Tests *(e)*			
Life Table	P=0.533N	P=0.113	P=0.734N
Incidental Tumor Test	P=0.575	P=0.094	P=0.716
Cochran-Armitage Trend, Fisher Exact Tests	P=0.584	P=0.098	P=0.747
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	4/50(8%)	7/49(14%)	5/49(10%)
Adjusted *(c)*	12.1%	18.2%	12.8%
Terminal *(d)*	4/33(12%)	4/34(12%)	5/39(13%)
Statistical Tests *(e)*			
Life Table	P=0.538	P=0.281	P=0.605
Incidental Tumor Test	P=0.456	P=0.243	P=0.605
Cochran-Armitage Trend, Fisher Exact Tests	P=0.422	P=0.251	P=0.487
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(b)*	0/50(0%)	2/49(4%)	7/49(14%)
Adjusted *(c)*	0.0%	5.9%	17.9%
Terminal *(d)*	0/33(0%)	2/34(6%)	7/39(18%)
Statistical Tests *(e)*			
Life Table	P=0.006	P=0.245	P=0.016
Incidental Tumor Test	P=0.006	P=0.245	P=0.016
Cochran-Armitage Trend, Fisher Exact Tests	P=0.003	P=0.242	P=0.006

TABLE 8. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	4/50(8%)	9/49(18%)	12/49(24%)
Adjusted *(c)*	12.1%	23.7%	30.8%
Terminal *(d)*	4/33(12%)	6/34(18%)	12/39(31%)
Statistical Tests *(e)*			
Life Table	P=0.048	P=0.132	P=0.055
Incidental Tumor Test	P=0.032	P=0.109	P=0.055
Cochran-Armitage Trend, Fisher Exact Tests	P=0.020	P=0.109	P=0.024
Pancreatic Islets: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	2/50(4%)	4/50(8%)	3/50(6%)
Adjusted *(c)*	6.1%	10.7%	7.0%
Terminal *(d)*	2/33(6%)	2/34(6%)	1/40(3%)
Statistical Tests *(e)*			
Life Table	P=0.499	P=0.350	P=0.577
Incidental Tumor Test	P=0.343	P=0.316	P=0.445
Cochran-Armitage Trend, Fisher Exact Tests	P=0.417	P=0.339	P=0.500
Preputial Gland: Adenoma			
Tumor Rates			
Overall *(b)*	3/50(6%)	5/50(10%)	2/50(4%)
Adjusted *(c)*	7.9%	14.7%	5.0%
Terminal *(d)*	1/33(3%)	5/34(15%)	2/40(5%)
Statistical Tests *(e)*			
Life Table	P=0.337N	P=0.373	P=0.437N
Incidental Tumor Test	P=0.399N	P=0.342	P=0.555N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.421N	P=0.357	P=0.500N
Preputial Gland: Carcinoma			
Tumor Rates			
Overall *(b)*	4/50(8%)	3/50(6%)	4/50(8%)
Adjusted *(c)*	10.8%	6.9%	9.1%
Terminal *(d)*	1/33(3%)	0/34(0%)	2/40(5%)
Statistical Tests *(e)*			
Life Table	P=0.519N	P=0.494N	P=0.573N
Incidental Tumor Test	P=0.407	P=0.498N	P=0.413
Cochran-Armitage Trend, Fisher Exact Tests	P=0.576	P=0.500N	P=0.643
Preputial Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	7/50(14%)	8/50(16%)	6/50(12%)
Adjusted *(c)*	17.9%	20.6%	13.9%
Terminal *(d)*	2/33(6%)	5/34(15%)	4/40(10%)
Statistical Tests *(e)*			
Life Table	P=0.517	P=0.407N	P=0.407N
Incidental Tumor Test	P=0.551N	P=0.489	P=0.518
Cochran-Armitage Trend, Fisher Exact Tests	P=0.443N	P=0.500	P=0.500N

TABLE 8. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Testis: Interstitial-Cell Tumor			
Tumor Rates			
Overall *(b)*	41/50(82%)	42/50(84%)	45/50(90%)
Adjusted *(c)*	93.0%	93.3%	93.7%
Terminal *(d)*	30/33(91%)	31/34(91%)	37/40(93%)
Statistical Tests *(e)*			
Life Table	P=0.317N	P=0.560	P=0.351N
Incidental Tumor Test	P=0.119	P=0.338	P=0.191
Cochran-Armitage Trend, Fisher Exact Tests	P=0.162	P=0.500	P=0.194

(a) Dosed groups received doses of 300 or 600 ppm of ziram in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 9. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)*

	Control	Low Dose	High Dose
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(b)*	3/50(6%)	1/50(2%)	0/50(0%)
Adjusted *(c)*	7.3%	2.1%	0.0%
Terminal *(d)*	1/37(3%)	0/44(0%)	0/46(0%)
Statistical Tests *(e)*			
Life Table	P=0.042N	P=0.247N	P=0.092N
Incidental Tumor Test	P=0.229N	P=0.554N	P=0.457N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.061N	P=0.309N	P=0.121N
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(b)*	4/50(8%)	4/50(8%)	4/50(8%)
Adjusted *(c)*	10.0%	8.5%	8.4%
Terminal *(d)*	2/37(5%)	2/44(5%)	3/46(7%)
Statistical Tests *(e)*			
Life Table	P=0.451N	P=0.537N	P=0.520N
Incidental Tumor Test	P=0.571	P=0.608N	P=0.629
Cochran-Armitage Trend, Fisher Exact Tests	P=0.573	P=0.643	P=0.643
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	7/50(14%)	5/50(10%)	4/50(8%)
Adjusted *(c)*	16.7%	10.4%	8.4%
Terminal *(d)*	3/37(8%)	2/44(5%)	3/46(7%)
Statistical Tests *(e)*			
Life Table	P=0.127N	P=0.269N	P=0.166N
Incidental Tumor Test	P=0.378N	P=0.486N	P=0.509N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.210N	P=0.380N	P=0.262N
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	19/50(38%)	18/49(37%)	19/49(39%)
Adjusted *(c)*	47.1%	39.0%	42.2%
Terminal *(d)*	16/37(43%)	15/43(35%)	19/45(42%)
Statistical Tests *(e)*			
Life Table	P=0.265N	P=0.285N	P=0.294N
Incidental Tumor Test	P=0.393N	P=0.353N	P=0.452N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.510N	P=0.531N	P=0.551N
Pituitary: Carcinoma			
Tumor Rates			
Overall *(b)*	3/50(6%)	0/49(0%)	2/49(4%)
Adjusted *(c)*	7.8%	0.0%	4.4%
Terminal *(d)*	2/37(5%)	0/43(0%)	2/45(4%)
Statistical Tests *(e)*			
Life Table	P=0.321N	P=0.096N	P=0.410N
Incidental Tumor Test	P=0.317N	P=0.079N	P=0.404N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.398N	P=0.125N	P=0.510N

TABLE 9. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	22/50(44%)	18/49(37%)	21/49(43%)
Adjusted *(c)*	53.3%	39.0%	46.7%
Terminal *(d)*	18/37(49%)	15/43(35%)	21/45(47%)
Statistical Tests *(e)*			
Life Table	P=0.189N	P=0.118N	P=0.203N
Incidental Tumor Test	P=0.291	P=0.137N	P=0.328N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.493N	P=0.298N	P=0.535N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	1/50(2%)	1/50(2%)	3/50(6%)
Adjusted *(c)*	2.7%	2.3%	6.3%
Terminal *(d)*	1/37(3%)	1/44(2%)	2/46(4%)
Statistical Tests *(e)*			
Life Table	P=0.263	P=0.723N	P=0.392
Incidental Tumor Test	P=0.260	P=0.723N	P=0.393
Cochran-Armitage Trend, Fisher Exact Tests	P=0.202	P=0.753	P=0.309
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	6/50(12%)	8/50(16%)	6/50(12%)
Adjusted *(c)*	14.5%	18.2%	13.0%
Terminal *(d)*	3/37(8%)	8/44(18%)	6/46(13%)
Statistical Tests *(e)*			
Life Table	P=0.400N	P=0.518	P=0.475N
Incidental Tumor Test	P=0.380	P=0.230	P=0.359
Cochran-Armitage Trend, Fisher Exact Tests	P=0.558	P=0.387	P=0.620
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(b)*	3/50(6%)	1/50(2%)	3/50(6%)
Adjusted *(c)*	8.1%	2.3%	6.3%
Terminal *(d)*	3/37(8%)	1/44(2%)	2/46(4%)
Statistical Tests *(e)*			
Life Table	P=0.499N	P=0.246N	P=0.555N
Incidental Tumor Test	P=0.498N	P=0.246N	P=0.552N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.593	P=0.309N	P=0.661
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	9/50(18%)	9/50(18%)	9/50(18%)
Adjusted *(c)*	22.0%	20.5%	19.1%
Terminal *(d)*	6/37(16%)	9/44(20%)	8/46(17%)
Statistical Tests *(e)*			
Life Table	P=0.361N	P=0.449N	P=0.412N
Incidental Tumor Test	P=0.450	P=0.496	P=0.462
Cochran-Armitage Trend, Fisher Exact Tests	P=0.551	P=0.602	P=0.602

TABLE 9. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Mammary Gland: Adenocarcinoma			
Tumor Rates			
Overall *(b)*	3/50(6%)	1/50(2%)	0/50(0%)
Adjusted *(c)*	8.1%	2.1%	0.0%
Terminal *(d)*	3/37(8%)	0/44(0%)	0/46(0%)
Statistical Tests *(e)*			
Life Table	P=0.040N	P=0.242N	P=0.086N
Incidental Tumor Test	P=0.038N	P=0.221N	P=0.086N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.061N	P=0.309N	P=0.121N
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	16/50(32%)	17/50(34%)	8/50(16%)
Adjusted *(c)*	39.7%	37.6%	17.0%
Terminal *(d)*	13/37(35%)	16/44(36%)	7/46(15%)
Statistical Tests *(e)*			
Life Table	P=0.011N	P=0.437N	P=0.015N
Incidental Tumor Test	P=0.024N	P=0.548N	P=0.019N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.046N	P=0.500	P=0.050N
Clitoral Gland: Carcinoma			
Tumor Rates			
Overall *(b)*	3/50(6%)	5/50(10%)	4/50(8%)
Adjusted *(c)*	8.1%	11.4%	8.7%
Terminal *(d)*	3/37(8%)	5/44(11%)	4/46(9%)
Statistical Tests *(e)*			
Life Table	P=0.552	P=0.455	P=0.618
Incidental Tumor Test	P=0.552	P=0.455	P=0.618
Cochran-Armitage Trend, Fisher Exact Tests	P=0.427	P=0.357	P=0.500
Clitoral Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	5/50(10%)	7/50(14%)	5/50(10%)
Adjusted *(c)*	13.5%	15.9%	10.9%
Terminal *(d)*	5/37(14%)	7/44(16%)	5/46(11%)
Statistical Tests *(e)*			
Life Table	P=0.410N	P=0.505	P=0.489N
Incidental Tumor Test	P=0.410N	P=0.505	P=0.489N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.562	P=0.380	P=0.630
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	5/50(10%)	7/49(14%)	7/50(14%)
Adjusted *(c)*	12.4%	15.9%	14.8%
Terminal *(d)*	3/37(8%)	7/44(16%)	6/46(13%)
Statistical Tests *(e)*			
Life Table	P=0.477	P=0.498	P=0.529
Incidental Tumor Test	P=0.353	P=0.388	P=0.406
Cochran-Armitage Trend, Fisher Exact Tests	P=0.327	P=0.365	P=0.380

TABLE 9. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(b)*	6/50(12%)	7/49(14%)	7/50(14%)
Adjusted *(c)*	14.1%	15.9%	14.8%
Terminal *(d)*	3/37(8%)	7/44(16%)	6/46(13%)
Statistical Tests (e)			
Life Table	P=0.523N	P=0.611	P=0.587N
Incidental Tumor Test	P=0.353	P=0.388	P=0.406
Cochran-Armitage Trend, Fisher Exact Tests	P=0.442	P=0.484	P=0.500

(a) Dosed groups received doses of 300 or 600 ppm of ziram in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

SHORT-TERM STUDIES

Single-Dose Study

Four of five males and 1/5 females administered 2,000 mg/kg, 1/5 males receiving 1,000 mg/kg, and 1/5 males receiving 250 mg/kg died (Table 10). All mice receiving 250, 500, 1,000, or 2,000 mg/kg had dose-related diarrhea.

Fourteen-Day Study

All mice receiving 10,000 or 20,000 ppm ziram died (Table 11). Dose-related diarrhea was observed. No compound-related gross pathologic effects were noted.

TABLE 10. SURVIVAL OF MICE ADMINISTERED A SINGLE DOSE OF ZIRAM BY GAVAGE

Dose (mg/kg)	Survival *(a)*	
	Males	Females
125	5/5	5/5
250	4/5 *(b)*	5/5
500	5/5	5/5
1,000	4/5 *(c)*	5/5
2,000	1/5 *(d)*	4/5 *(e)*

(a) Number surviving/number per group.
(b) Deaths occurred on day 4.
(c) Deaths occurred on day 2.
(d) Two deaths occurred on day 2, and one death on each of days 5 and 6.
(e) Death occurred on day 9.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING ZIRAM FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)		
		Initial	Final	Change
Males				
1,200	5/5	21	26	+5
2,500	5/5	20	24	+4
5,000	5/5	19	19	0
10,000	0/5 *(b)*	19	—	—
20,000	0/5 *(b)*	20	—	—
Females				
1,200	5/5	16	19	+3
2,500	5/5	15	18	+3
5,000	5/5	16	16	0
10,000	0/5 *(c)*	16	—	—
20,000	0/5 *(d)*	16	—	—

(a) Number surviving/number per group.
(b) All deaths occurred on day 6.
(c) All deaths occurred on day 7.
(d) One animal died on day 5 and the rest on day 6.

Thirteen-Week Study

Eight of ten male mice and 8/10 female mice fed diets containing 5,000 ppm, and 1/10 male mice receiving 600 ppm ziram died (Table 12). Weight gain was depressed 26% or more in males and females receiving 2,500 or 5,000 ppm. The depressions in mean body weight gains were dose-related. No compound-related histopathologic effects were observed.

Doses of 600 and 1,200 ppm ziram in feed were selected for mice in the two-year study due to the weight gain decrements observed in the 13-week study.

TABLE 12. SURVIVAL, MEAN BODY WEIGHTS, AND COMPOUND CONSUMPTION OF MICE FED DIETS CONTAINING ZIRAM FOR 13 WEEKS

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Controls (c) (Percent)	Average Daily Feed Consumption (grams)	Average Daily Dose Consumed (mg/kg)	
		Initial	Final	Change			Initial	Final
Males								
0	10/10	20.9 ±0.55	32.2 ± 0.59	+11.3 ±0.50		9		
300	10/10	21.3 ±0.47	30.0 ± 0.63	+ 8.7 ±0.45	-23.0	8	113	80
600	9/10 (d)	21.0 ±0.60	29.4 ± 0.69	+ 8.4 ±0.44	-25.7	9	257	183
1,200	10/10	21.2 ±0.63	29.5 ± 0.93	+ 8.3 ±0.63	-26.5	9	509	366
2,500	10/10	21.3 ±0.45	27.1 ± 0.78	+ 5.8 ±0.63	-48.7	7	821	646
5,000	2/10 (e)	20.0 ±2.00	22.0 ± 1.00	+ 2.0 ±1.00	-82.3	7	1750	1590
Females								
0	10/10	16.7 ±0.33	24.0 ± 0.47	+ 7.3 ±0.21		9		
300	9/10 (f)	17.4 ±0.24	25.3 ± 0.50	+ 7.9 ±0.42	+ 8.2	6	103	71
600	10/10	17.2 ±0.36	25.2 ± 0.44	+ 8.0 ±0.42	+ 9.6	6	209	143
1,200	10/10	17.0 ±0.30	23.6 ± 0.34	+ 6.6 ±0.40	- 9.6	5	353	254
2,500	8/10 (f)	17.1 ±0.30	22.5 ± 0.42	+ 5.4 ±0.38	-26.0	5	731	556
5,000	2/10 (g)	17.5 ±0.50	18.5 ± 1.50	+ 1.0 ±2.00	-86.3	8	2286	2162

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.
(b) Mean weight change of the survivors of the group ± standard error of mean.
(c) Weight change of the dosed group relative to that of the controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(d) Death occurred on day 8.
(e) Five mice died during week 3; three mice died during week 4.
(f) Animals were missing.
(g) Three animals died during week 3, three animals died during week 4, one animal died during week 5, and one animal during week 8.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed male mice were lower than those of the controls throughout the study. For the first 80 weeks of the study, mean body weights of high-dose and control females were comparable; during the rest of the study, mean body weights of the high-dose females were lower than those of the controls. The mean body weights of low-dose females were higher than those of the controls throughout most of the study (Figure 3 and Table 13). The average daily feed consumption per mouse by low- and high-dose mice was 94% and 78% that of the controls for males and 96% and 85% for females (Table 14). No other compound-related clinical signs

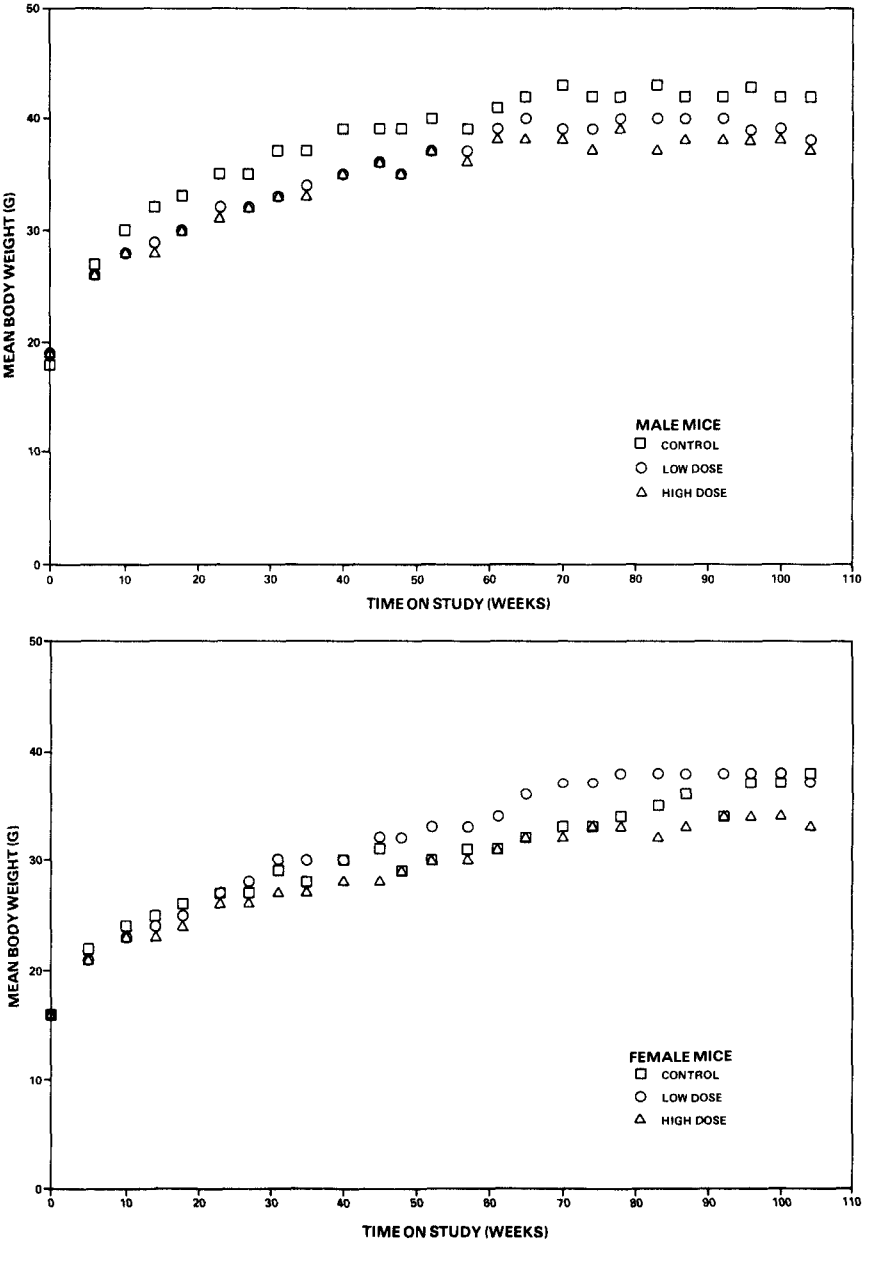


Figure 3. Growth Curves for Mice Fed Diets Containing Ziram

were observed. The daily ziram consumption per animal by low-dose male mice, after the first half-year of the study, ranged from 169 to 75 mg/kg with an average of 122 mg/kg; the high-dose male mice consumed from 263 to 126 mg/kg with an average of 196 mg/kg during the same period. The corresponding daily compound intake by low-dose female mice ranged from 193 to 79 mg/kg with an average of 131 mg/kg, and for the high-dose female mice from 323 to 145 mg/kg with an average of 248 mg/kg (Table 15). These daily intake amounts should be considered as useful approximations that are dependent on the accuracy of the measurement of feed consumption.

TABLE 13. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF MICE FED DIETS CONTAINING ZIRAM IN THE 2-YEAR STUDY

		Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls (Percent)	
	Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males	0	18 *(b)*	19 *(b)*	19 *(b)*		
	6	9	7	7	-22	-22
	27	17	13	13	-24	-24
	48	21	16	16	-24	-24
	65	24	21	19	-13	-21
	87	24	21	19	-13	-21
	104	24	19	18	-21	-25
	Final Weight	42	38	37	-10	-12
Females	0	16 *(b)*	16 *(b)*	16 *(b)*		
	6	6	5	5	-17	-17
	27	11	12	10	+ 9	- 9
	48	13	16	13	+23	0
	65	16	20	16	+25	0
	87	20	22	17	+10	-15
	104	22	21	17	- 5	-23
	Final Weight	38	37	33	- 3	-13

(a) Weight change of the dosed group relative to that of the controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial weight

TABLE 14. FEED CONSUMPTION BY MICE RECEIVING ZIRAM IN THE 2-YEAR STUDY

Week	Control	Low Dose		High Dose	
	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
Males					
6	10.0	10.0	1.0	10.0	1.0
27	9.0	9.0	1.0	7.0	0.8
48	9.0	8.0	0.9	7.0	0.8
65	9.0	9.0	1.0	7.0	0.8
87	7.0	5.0	0.7	4.0	0.6
104	6.0	6.0	1.0	4.0	0.7
Mean	8.3	7.8	0.9	6.5	0.8
SD *(c)*	1.5	1.9	0.1	2.3	0.1
CV *(d)*	18.1	24.4	11.1	35.4	12.5
Females					
6	10.0	10.0	1.0	10.0	1.0
27	9.0	9.0	1.0	7.0	0.8
48	8.0	7.0	0.9	7.0	0.9
65	8.0	9.0	1.1	8.0	1.0
87	7.0	5.0	0.7	5.0	0.7
104	6.0	6.3	1.1	4.0	0.7
Mean	8.0	7.7	1.0	6.8	0.9
SD *(c)*	1.4	1.9	0.2	2.1	0.1
CV *(d)*	17.5	24.7	20.0	30.9	11.1

(a) Grams of feed consumed per animal per day.
(b) Grams of feed consumed per day by the dosed group divided by that for the controls.
(c) Standard deviation.
(d) Coefficient of variation = (standard deviation/mean) x 100

TABLE 15. COMPOUND CONSUMPTION BY MICE RECEIVING ZIRAM IN THE 2-YEAR STUDY

	Week No.	Low Dose			High Dose		
		Body Weight *(a)*	Grams Feed/Day *(b)*	Dose, mg/kg/Day *(c)*	Body Weight *(a)*	Grams Feed/Day *(b)*	Dose, mg/kg/Day *(d)*
Males	6	26	10.0	231	26	10.0	462
	27	32	9.0	169	32	7.0	262
	48	35	8.0	137	35	7.0	240
	65	40	9.0	135	38	7.0	221
	87	40	5.0	75	38	4.0	126
	104	38	6.0	95	37	4.0	130
Females	6	21	10.0	286	21	10.0	571
	27	28	9.0	193	26	7.0	323
	48	32	7.0	131	29	7.0	289
	65	36	9.0	150	32	8.0	300
	87	38	5.0	79	33	5.0	182
	104	37	6.3	102	33	4.0	145

(a) Group body weight average from Table 13
(b) From Table 14
(c) Low-dose = 300 mg/kg of feed. Dose calculation =

$$\left[\frac{\text{Grams Feed/Day}}{\text{Body Wt (Kg)}}\right] \times 600/1000$$

(d) High Dose = 600 mg/kg of feed. Dose calculation =

$$\left[\frac{\text{Grams Feed/Day}}{\text{Body Wt (Kg)}}\right] \times 1200/1000$$

Survival

Estimates of the probabilities of survival of male and female mice fed diets containing ziram at the concentrations used in this bioassay and the estimates for the control groups are shown by the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed among any groups of male or female mice.

In male mice, 40/50 (80%) of the controls, 35/50 (70%) of the low-dose group, and 37/49 (76%) of the high-dose group lived to the end of the study at 104-106 weeks. In female mice, 32/50 (64%) of the controls, 40/50 (80%) of the low-dose, and 40/50 (80%) of the high-dose group lived to the end of the study at weeks 104-106. These figures include two control males, two high-dose males, one control female, one low-dose female, and three high-dose females that died during the termination period of the study; these animals were included in the analysis of the terminal incidence shown in Tables 16 and 17. One female was discovered in the high-dose male group and was eliminated from the study.

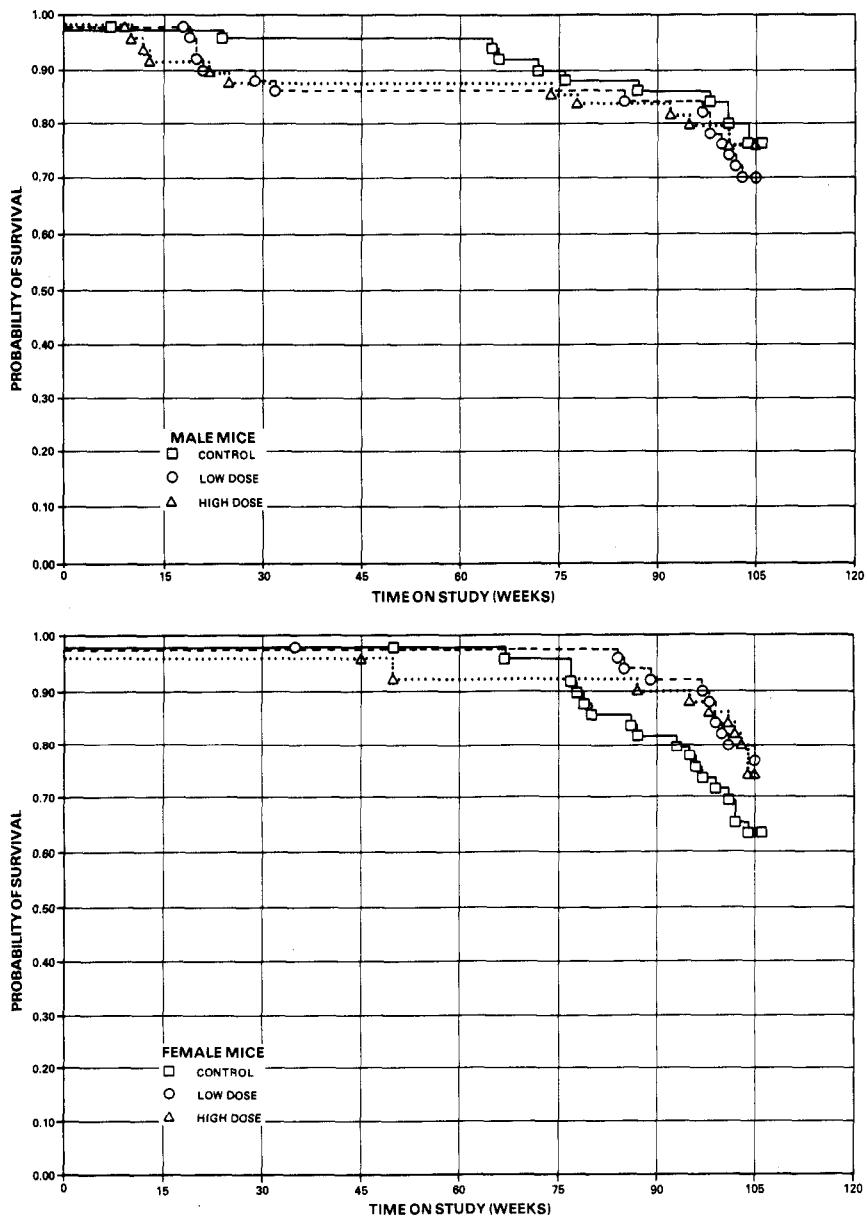


Figure 4. Survival Curves for Mice Fed Diets Containing Ziram

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms occurring in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status for each individual animal in the male and female mouse studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Tables 16 and 17 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Lung: The incidence of alveolar/bronchiolar adenomas in female mice was 2/50 (4%) in the controls, 5/49 (10%) in the low-dose, and 10/50 (20%) in the high-dose group. The incidence in the high-dose group was significantly ($P<0.05$) increased relative to controls and the dose response trend was significant ($P<0.05$) as well. When alveolar/bronchiolar adenomas or carcinomas were combined, the life table trend test was not significant (P=0.071), while the Cochran-Armitage and the incidental tumor trend tests remained significant ($P<0.05$). The combined incidence of alveolar/bronchiolar adenomas or carcinomas in female mice was 4/50 (8%) in the controls, 6/49 (12%) in the low-dose, and 11/50 (22%) in the high-dose group.

The incidence of male mice with adenomas or carcinomas (combined) was 8/49 (16%) in the controls, 8/50 (16%) in the low-dose group, and 12/49 (24%) in the high-dose group. Pulmonary adenomatous hyperplasia consistent with chronic Sendai virus infection (confirmed by serologic analyses performed on untreated animals from the same animal shipment and present in the same room) was observed in control and dosed male mice (control, 15/49, 31%; low-dose 19/50, 38%; high-dose, 16/49, 33%) as well as in control and dosed female mice (control, 18/50, 36%; low-dose, 27/49, 55%; high-dose, 26/50, 52%). Six of the 26 high-dose females with adenomatous hyperplasia had pulmonary tumors, whereas 4 of the 24 high-dose females without pulmonary adenomatous hyperplasia also had pulmonary tumors. Only 1 of 27 low-dose females with adenomatous hyperplasia had a pulmonary tumor.

Hematopoietic System: Malignant lymphomas were observed at increased incidences in high-dose female mice (controls, 6/50, 12%; low-dose, 6/50, 12%; high-dose, 12/50, 24%), but none of the statistical tests were significant at a P=0.05 level. The incidence of female mice with malignant lymphocytic lymphomas showed a statistically significant ($P<0.05$) increasing trend. Lymphoid hyperplasia was observed at increased incidences in dosed females (controls, 0/50; low-dose, 2/50, 4%; high-dose, 7/50, 14%). No significant results were observed in the incidences of male mice with lymphomas of any type.

Thyroid: Cystic follicles occurred at increased incidences in high-dose females (controls, 0/47; low-dose, 1/43, 2%; high-dose, 21/48, 44%).

Liver: Carcinomas were observed in male mice in a significant decreasing trend ($P\leq0.002$). In female mice the incidence of liver adenomas showed a significant dose-related decrease ($P\leq0.003$).

TABLE 16. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)*

	Control	Low Dose	High Dose
Lung Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	6/49(12%)	5/50(10%)	8/49(16%)
Adjusted *(c)*	15.0%	14.3%	20.4%
Terminal *(d)*	6/40(15%)	5/35(14%)	6/37(16%)
Statistical Tests *(e)*			
Life Table	P=0.276	P=0.594N	P=0.330
Incidental Tumor Test	P=0.276	P=0.594N	P=0.335
Cochran-Armitage Trend, Fisher Exact Tests	P=0.325	P=0.486N	P=0.387
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(b)*	3/49(6%)	4/50(8%)	4/49(8%)
Adjusted *(c)*	7.5%	11.0%	9.9%
Terminal *(d)*	3/40(8%)	3/35(9%)	2/37(5%)
Statistical Tests *(e)*			
Life Table	P=0.386	P=0.432	P=0.463
Incidental Tumor Test	P=0.348	P=0.500	P=0.419
Cochran-Armitage Trend, Fisher Exact Tests	P=0.424	P=0.511	P=0.500
Lung Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	8/49(16%)	8/50(16%)	12/49(24%)
Adjusted *(c)*	20.0%	22.2%	29.1%
Terminal *(d)*	8/40(20%)	7/35(20%)	8/37(22%)
Statistical Tests *(e)*			
Life Table	P=0.146	P=0.496	P=0.181
Incidental Tumor Test	P=0.128	P=0.544	P=0.164
Cochran-Armitage Trend, Fisher Exact Tests	P=0.184	P=0.590N	P=0.226
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(b)*	1/49(2%)	0/50(0%)	4/49(8%)
Adjusted *(c)*	2.5%	0.0%	10.5%
Terminal *(d)*	1/40(3%)	0/35(0%)	3/37(8%)
Statistical Tests *(e)*			
Life Table	P=0.075	P=0.526N	P=0.160
Incidental Tumor Test	P=0.070	P=0.526N	P=0.164
Cochran-Armitage Trend, Fisher Exact Tests	P=0.082	P=0.495N	P=0.181
Hematopoietic System: All Malignant Lymphoma			
Tumor Rates			
Overall *(b)*	3/49(6%)	1/50(2%)	5/49(10%)
Adjusted *(c)*	7.5%	2.4%	13.1%
Terminal *(d)*	3/40(8%)	0/35(0%)	4/37(11%)
Statistical Tests *(e)*			
Life Table	P=0.236	P=0.347N	P=0.315
Incidental Tumor Test	P=0.234	P=0.267N	P=0.320
Cochran-Armitage Trend, Fisher Exact Tests	P=0.263	P=0.301N	P=0.357

TABLE 16. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	3/49(6%)	4/50(8%)	3/49(6%)
Adjusted *(c)*	7.5%	10.1%	7.3%
Terminal *(d)*	3/40(8%)	1/35(3%)	1/37(3%)
Statistical Tests *(e)*			
Life Table	P=0.539	P=0.444	P=0.628
Incidental Tumor Test	P=0.505	P=0.584	P=0.584
Cochran-Armitage Trend, Fisher Exact Tests	P=0.579	P=0.511	P=0.661
Liver: Adenoma			
Tumor Rates			
Overall *(b)*	6/49(12%)	1/50(2%)	8/49(16%)
Adjusted *(c)*	15.0%	2.4%	21.6%
Terminal *(d)*	6/40(15%)	0/35(0%)	8/37(22%)
Statistical Tests *(e)*			
Life Table	P=0.264	P=0.081N	P=0.325
Incidental Tumor Test	P=0.265	P=0.057N	P=0.325
Cochran-Armitage Trend, Fisher Exact Tests	P=0.308	P=0.053N	P=0.387
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	13/49(27%)	8/50(16%)	1/49(2%)
Adjusted *(c)*	28.5%	21.2%	2.6%
Terminal *(d)*	8/40(20%)	6/35(17%)	0/37(0%)
Statistical Tests *(e)*			
Life Table	P=0.002N	P=0.256N	P=0.002N
Incidental Tumor Test	P=0.002N	P=0.326N	P=0.002N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.001N	P=0.150N	P=0.001N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	19/49(39%)	9/50(18%)	9/49(18%)
Adjusted *(c)*	41.9%	23.2%	23.6%
Terminal *(d)*	14/40(35%)	6/35(17%)	8/37(22%)
Statistical Tests *(e)*			
Life Table	P=0.031N	P=0.061N	P=0.046N
Incidental Tumor Test	P=0.033N	P=0.054N	P=0.052N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.013N	P=0.019N	P=0.022N
Thyroid: Follicular-Cell Adenoma			
Tumor Rates			
Overall *(b)*	2/49(4%)	0/50(0%)	5/48(10%)
Adjusted *(c)*	5.0%	0.0%	13.5%
Terminal *(d)*	2/40(5%)	0/35(0%)	5/37(14%)
Statistical Tests *(e)*			
Life Table	P=0.104	P=0.268N	P=0.185
Incidental Tumor Test	P=0.104	P=0.268N	P=0.185
Cochran-Armitage Trend, Fisher Exact Tests	P=0.113	P=0.242N	P=0.209

TABLE 16. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

(a) Dosed groups received doses of 600 or 1,200 ppm of ziram in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 17. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	2/50(4%)	5/49(10%)	10/50(20%)
Adjusted *(c)*	5.9%	12.0%	24.4%
Terminal *(d)*	1/32(3%)	4/40(10%)	9/40(23%)
Statistical Tests *(e)*			
Life Table	P=0.022	P=0.311	P=0.041
Incidental Tumor Test	P=0.012	P=0.248	P=0.024
Cochran-Armitage Trend, Fisher Exact Tests	P=0.009	P=0.210	P=0.014
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	4/50(8%)	6/49(12%)	11/50(22%)
Adjusted *(c)*	10.1%	14.2%	26.8%
Terminal *(d)*	1/32(3%)	4/40(10%)	10/40(25%)
Statistical Tests *(e)*			
Life Table	P=0.071	P=0.486	P=0.108
Incidental Tumor Test	P=0.013	P=0.240	P=0.023
Cochran-Armitage Trend, Fisher Exact Tests	P=0.031	P=0.357	P=0.045
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(b)*	1/50(2%)	1/50(2%)	7/50(14%)
Adjusted *(c)*	3.1%	2.3%	16.9%
Terminal *(d)*	1/32(3%)	0/40(0%)	6/40(15%)
Statistical Tests *(e)*			
Life Table	P=0.019	P=0.713N	P=0.064
Incidental Tumor Test	P=0.011	P=0.755	P=0.049
Cochran-Armitage Trend, Fisher Exact Tests	P=0.011	P=0.753	P=0.030
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(b)*	0/50(0%)	4/50(8%)	2/50(4%)
Adjusted *(c)*	0.0%	10.0%	4.4%
Terminal *(d)*	0/32(0%)	4/40(10%)	0/40(0%)
Statistical Tests *(e)*			
Life Table	P=0.284	P=0.095	P=0.275
Incidental Tumor Test	P=0.180	P=0.095	P=0.073
Cochran-Armitage Trend, Fisher Exact Tests	P=0.222	P=0.059	P=0.247
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(b)*	3/50(6%)	1/50(2%)	2/50(4%)
Adjusted *(c)*	8.4%	2.4%	5.0%
Terminal *(d)*	2/32(6%)	0/40(0%)	2/40(5%)
Statistical Tests *(e)*			
Life Table	P=0.328N	P=0.247N	P=0.416N
Incidental Tumor Test	P=0.447N	P=0.318N	P=0.529N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.400N	P=0.309N	P=0.500N

TABLE 17. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: All Malignant Lymphoma			
Tumor Rates			
Overall *(b)*	6/50(12%)	6/50(12%)	12/50(24%)
Adjusted *(c)*	17.0%	14.2%	27.6%
Terminal *(d)*	4/32(13%)	4/40(10%)	9/40(23%)
Statistical Tests *(e)*			
Life Table	P=0.146	P=0.476N	P=0.212
Incidental Tumor Test	P=0.051	P=0.583N	P=0.073
Cochran-Armitage Trend, Fisher Exact Tests	P=0.067	P=0.620	P=0.096
Hematopoietic System: Lymphocytic Leukemia			
Tumor Rates			
Overall *(b)*	5/50(10%)	1/50(2%)	2/50(4%)
Adjusted *(c)*	11.3%	2.1%	5.0%
Terminal *(d)*	0/32(0%)	0/40(0%)	2/40(5%)
Statistical Tests *(e)*			
Life Table	P=0.110N	P=0.085N	P=0.181N
Incidental Tumor Test	P=0.591N	P=0.409N	P=0.657N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.133N	P=0.103N	P=0.218N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	11/50(22%)	7/50(14%)	14/50(28%)
Adjusted *(c)*	26.4%	16.0%	32.3%
Terminal *(d)*	4/32(13%)	4/40(10%)	11/40(28%)
Statistical Tests *(e)*			
Life Table	P=0.443	P=0.136N	P=0.520
Incidental Tumor Test	P=0.064	P=0.416N	P=0.093
Cochran-Armitage Trend, Fisher Exact Tests	P=0.271	P=0.218N	P=0.322
Liver: Adenoma			
Tumor Rates			
Overall *(b)*	7/50(14%)	2/50(4%)	0/50(0%)
Adjusted *(c)*	21.1%	5.0%	0.0%
Terminal *(d)*	6/32(19%)	2/40(5%)	0/40(0%)
Statistical Tests *(e)*			
Life Table	P=0.001N	P=0.041N	P=0.004N
Incidental Tumor Test	P=0.002N	P=0.048N	P=0.006N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.003N	P=0.080N	P=0.007N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	9/50(18%)	4/50(8%)	1/50(2%)
Adjusted *(c)*	26.1%	10.0%	2.5%
Terminal *(d)*	7/32(22%)	4/40(10%)	1/40(3%)
Statistical Tests *(e)*			
Life Table	P=0.002N	P=0.055N	P=0.004N
Incidental Tumor Test	P=0.003N	P=0.070N	P=0.006N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.005N	P=0.117N	P=0.008N

TABLE 17. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

(a) Dosed groups received doses of 600 or 1,200 ppm of ziram in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

IV. DISCUSSION AND CONCLUSIONS

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The doses selected for rats in the 2-year study, 300 or 600 ppm ziram in feed, were chosen because of the depressions in mean body weight gains found in the 13-week study. However, in the 2-year study the mean body weights of dosed male and female rats did not vary greatly from the mean body weights of the control animals. In addition, survival and feed consumption of male and female rats were not affected by administration of ziram. These findings indicate that male and female rats could have tolerated higher doses of ziram.

In mice, survival was not adversely affected by administration of ziram, but mean body weight gain was depressed by more than 10% (relative to that of controls) in dosed males throughout the chronic study and in high-dose females after week 80. Final body weights were less than those of controls for low- (10%) and high- (12%) dose male mice and for low- (3%) and high- (13%) dose female mice. Average daily feed consumption by high-dose males and females was 78% and 85% that of the controls. Since feed consumption was inversely related to dose, further decreases in feed consumption might have resulted from the administration of higher doses. Mice could not have tolerated higher doses of ziram.

The thyroid has been recognized as a target organ for the thiocarbamate compounds, such as ziram, and their metabolites. Unidentified metabolites of ^{35}S-ziram have been located in the thyroid of female rats 24 hours after a single dose of ziram was administered by gavage (Izmirova and Marinov, 1972). The iron analog of ziram (ferbam, the ferric salt of dimethyldithiocarbamic acid) increased the concentration of protein iodine in the serum of Wistar rats when administered by gavage (Mlynarozyk et al., 1981). Both ferbam and thiram (another metabolite of ziram) have been associated with squamous metaplasia of the thyroid in rats administered 20 or 52 mg/kg per day for 80 days (Lee et al., 1978). Several thiourea compounds have been shown to have antithyroid effects (Gilman et al., 1980); thus thyroid effects from tetramethylthiourea (another ziram metabolite) are likely.

In the present 2-year study the thyroid C-cell was a target site in male rats fed diets containing ziram. C-cell carcinomas of the thyroid occurred in male rats with a statistically significant ($P<0.01$) positive trend, and the incidence in the high-dose group was significantly ($P<0.05$) higher than that in the controls (control, 0/50, 0%; low-dose, 2/49, 4%; high-dose, 7/49, 14%). This tumor has been found in control male F344/N rats at the same laboratory at an incidence of 18/584 (3.1%, range, 0/50 to 3/40) and in control males in all bioassay laboratories at an incidence of 87/3160 (2.8%). (Appendix H, Table H1).

There was a statistically significant ($P<0.05$) positive dose-related trend in the combined incidence of C-cell adenomas or carcinomas of the thyroid in male rats fed ziram (control 4/50, 8%; low-dose 9/49, 18%; high-dose, 12/49, 24%). However, pair-wise comparison between high-dose and control male rats shows a marginal ($P=0.055$) increase in the incidence of total C-cell tumors. Historically, the combined incidence of control male F344/N rats with thyroid C-cell adenomas or carcinomas is 65/584 (11.1%) at the same laboratory and 251/3160 (7.9%, range 0/47, 0% to 10/49, 20%) for all bioassay laboratories (Appendix H). The observed incidence of thyroid C-cell tumors in high-dose male rats fed ziram exceeded even the maximum historical control rate. Although the morphological criteria for distinguishing between thyroid C-cell adenomas and carcinomas are difficult and perhaps controversial, the NTP Pathology Working group has developed and uses set criteria for these diagnoses.

In the present study the incidence of thyroid C-cell adenomas or carcinomas was not significantly increased in dosed female rats. C-cell adenomas or carcinomas were not found in mice of either sex. Neither rats nor mice had any ziram-related increases in follicular-cell tumors.

Fibroadenomas of the mammary gland occurred at a decreased ($P<0.05$) incidence in high-dose female rats; there was also evidence of a negative trend for adenocarcinomas of the mammary gland (Table 9). In both cases, the incidences of dosed animals with tumors in the present study fell within the historical incidence ranges for control animals with these tumors both in the laboratory which carried out this bioassay as well as in the Bioassay Program as a whole. The incidence of mammary gland adenocarcinomas in the control female rats (3/50, 6%) was higher in this bioassay than in previous ones carried out at the Southern Research Institute (See Appendix H, Table H2). The significance of these observations is not clear.

Retinopathy, observed at increased incidences in high-dose male rats and in dosed female rats, has been found previously in rats in the top positions of the cage racks at the same laboratory.

This effect is considered to be related to the animals' proximity to fluorescent light and not to administration of ziram.

Administration of ziram, its metabolites, or compounds structurally related to ziram has produced various pulmonary effects in mice. Pathologic "pre-cancerous" changes were reported in rats administered ziram orally (dose and duration not specified; World Health Organization, 1975). Lung congestion, with patches of bronchopneumonia and emphysema, was observed in rats administered 0.05 ml carbon disulfide (a ziram metabolite) in 0.2 ml olive oil by intramuscular injection daily for 40 to 60 days (Issa et al., 1977); Vekshtein and Khitsenko (1971) demonstrated the formation of carbon disulfide by rats given ziram orally. Lung tumors have been found at increased incidences in B6C3F$_1$ mice in carcinogenesis bioassays of tellurium diethyl dithiocarbamate (NCI, 1979a), sodium diethyl dithiocarbamate (NCI, 1979b), and tetraethyl thiuram disulfide (NCI, 1979c)—compounds structurally related to ziram (Table 18). These compounds have carbon disulfide as a common metabolite (Fishbein, 1976; Stromme, 1965; Vekshtein and Khitsenko, 1971).

Pulmonary effects of ziram in mice were also seen in the present study. Alveolar/bronchiolar adenomas occurred in female mice with a statistically significant ($P<0.05$) positive trend. The incidence in the high-dose group was significantly higher than in the controls ($P<0.05$). Alveolar/bronchiolar adenomas or carcinomas (combined) were observed with a statistically significant positive trend in female mice ($P<0.05$), and the incidence in the high-dose group was significantly higher than that in the controls ($P<0.05$). The incidence of high-dose female mice in this study with alveolar/bronchiolar adenomas was 10/50 (20%); for alveolar/bronchiolar adenomas or carcinomas (combined), the incidence was 11/50 (22%). Life table analysis for these lung tumors showed only a weak trend ($P=0.071$), primarily because three of the four control animals with lung tumors died before the end of the study. Since these tumors are not considered life threatening, use of life table analyses would be misleading. Alveolar/bronchiolar adenomas have been observed in 18/501 (3.6%) of the control female B6C3F$_1$ mice at this bioassay laboratory and in 134/2788 (4.8%) of the female mouse controls across the Bioassay Program with a range of 0/50 to 7/50 (14%). The combined incidence of alveolar/bronchiolar adenomas or carcinomas in control female B6C3F$_1$ mice at this bioassay laboratory is 25/501 (5.0%) and in all Bioassay Program laboratories it is 184/2788 (6.6%) with a range of 0/50 to 8/50 (16%). (See Appendix H, Table H3.) The lung tumor rate in the high-dose female mice was greater than the maximum historical control incidence.

Pulmonary adenomatous hyperplasia, consistent with the chronic pulmonary lesions following Sendai virus infection, confirmed by serological test, was observed in more than 30% of the male and female mice in both control and dosed groups. The lesions consisted of alveolar macrophages, increased Type II pneumocytes and areas of squamous metaplasia. The histopathological interpretation of lung microscopic sections clearly differentiates between this hyperplasia and pulmonary alveolar/bronchiolar adenomas or carcinomas. The mice on the ziram study were obtained from the same supplier and housed in the same room as mice on two other Bioassay Program tests, D-mannitol and eugenol (Table 1). All mice, both in control and dosed groups of all three test chemical bioassays, showed about the same incidence of pulmonary adenomatous hyperplasia. Only the female mice administered ziram showed a statistically significant increase in pulmonary tumor incidence (Table 19). Thus, it is unlikely that the increase in lung tumors in female mice receiving ziram was produced by the combined action of the test chemical and the infection. No correlation was found between the presence of pulmonary adenomatous hyperplasia and pulmonary tumors in the dosed female mice. In the high-dose female mice, 6 of the 26 animals with adenomatous hyperplasia had pulmonary tumors, whereas 4 of the 24 without the adenomatous hyperplasia had pulmonary tumors. In the low-dose females, only 1 of 27 animals with adenomatous hyperplasia had a pulmonary tumor. Rats on the ziram study showed serological evidence of Sendai infection, but histopathological examination showed neither pulmonary adenomatous hyperplasia nor tumors.

Hepatocellular carcinomas in high-dose male mice and hepatocellular adenomas in high-dose female mice were observed at statistically significant decreased incidences. Hepatocellular carcinomas occurred in 13/49 (27%) control males, 8/50 (16%) low-dose males, and 1/49 (2%) high-dose males in this study. Hepatocellular carcinomas occurred in 94/490 (19.2%) control males at this laboratory and in 602/2690 (22.4%) control males in all Bioassay Program laboratories.

Hepatocellular adenomas occurred in 7/50 (14%) of control females, 2/50 (4%) of low-dose females, and 0/50 (0%) of high-dose females in the present study. Hepatocellular adenomas occurred in 14/498 (2.8%) control females at this laboratory and in 89/2795 (3.2%) control females in all Bioassay Program laboratories. Incidences from all Bioassay Program laboratories are presented in Appendix H, Tables H4 and H5.

Conclusions: Under the conditions of these studies, ziram was carcinogenic for male F344/N rats, causing increased incidences of C-cell carcinomas of the thyroid gland. Ziram was not carcinogenic for either female F344/N rats or for male B6C3F$_1$ mice. Increased incidences of alveolar/bronchiolar adenomas and of combined alveolar/bronchiolar adenomas or carcinomas occurred in female B6C3F$_1$ mice. However, the interpretation of this increase in lung tumors is complicated by an intercurrent Sendai virus infection.

TABLE 18. COMPARISON OF LUNG TUMOR INCIDENCES IN B6C3F$_1$ MICE IN BIOASSAY PROGRAM STUDIES OF SOME DITHIOCARBAMATES AND RELATED COMPOUNDS

Study	Sex	Dose (ppm)	Duration (weeks)	Adenomas			Carcinomas			Adenomas or Carcinomas			Reference
				Control	Low Dose	High Dose	Control	Low Dose	High Dose	Control	Low Dose	High Dose	
Zinc dimethyl dithiocarbamate	F	600 or 1,200	103	2/50	5/49	10/50 *(a)*	2/50	1/49	2/50	4/50	6/49	11/50 *(b)*	This study
Tellurium diethyl dithiocarbamate	M	1,255 or 3,132	106	0/17	2/46	0/46	0/17	14/46 *(c)*	11/46 *(c)*	0/17	16/46 *(d)*	11/46 *(d)*	(NCI, 1979a)
	F	2,132 or 4,915 (time weighted avg)		1/19	4/49	6/48	2/19	5/49	6/48	3/19	9/49	12/48	
Sodium diethyl dithiocarbamate	F	500 or 4,000	108-109	0/20	4/49	4/50	0/20	3/49	4/50	0/20	7/49	8/50	(NCI, 1979b)
Tetraethylthiuram disulfide	F	100 or 500	108	0/20	0/49	5/49	1/20	4/49	4/49	1/20	4/49	9/49 *(e)*	(NCI, 1979c)

(a) $P \leq 0.022$ for all trend tests; for comparison between high-dose and control group, P=0.024 for incidental tumor test and P=0.014 for Fisher exact test

(b) $P \leq 0.031$ for trend (Incidental tumor and Cochran-Armitage tests); for comparison between high-dose and control group, P=0.023 in the incidental tumor test and P=0.045 for Fisher exact test

(c) For Fisher exact test comparison between low-dose and control incidences and between high-dose and control incidence, P=0.006 and P=0.022, respectively

(d) For Fisher exact test comparison between low-dose and control incidences and between high-dose and control incidences, P=0.003 and P=0.022, respectively

(e) P=0.036 for trend by the Cochran-Armitage test

TABLE 19. RELATIONSHIP BETWEEN TEST CHEMICAL EXPOSURE, LUNG TUMOR INCIDENCE, AND ADENOMATOUS HYPERPLASIA IN B6C3F$_1$ MICE *(a)*

	Ziram *(b)*			D-Mannitol *(c)*			Eugenol *(d)*		
	Control	Low	High	Control	Low	High	Control	Low	High
Males									
1 Alveolar/bronchiolar adenomas	6/49 (12%)	5/50 (10%)	8/49 (16%)	6/50 (12%)	7/50 (14%)	7/49 (14%)	9/49 (18%)	7/49 (14%)	8/50 (16%)
2 Alveolar/bronchiolar carcinomas	3/49 (6%)	4/50 (8%)	4/49 (8%)	3/50 (6%)	6/50 (12%)	4/49 (8%)	5/49 (10%)	2/49 (4%)	3/50 (6%)
3 Alveolar/bronchiolar adenomas or carcinomas	8/49 (16%)	8/50 (16%)	12/49 (24%)	9/50 (18%)	12/50 (24%)	11/49 (22%)	13/49 (27%)	8/49 (16%)	9/50 (18%)
4 Adenomatous hyperplasia	15/49 (31%)	19/50 (38%)	16/49 (33%)	11/50 (22%)	10/50 (20%)	26/49 (53%)	17/49 (35%)	21/49 (43%)	18/50 (36%)
Females									
1 Alveolar/bronchiolar adenomas	2/50 (4%)	5/49 (10%)	10/50 (20%)	1/48 (2%)	1/48 (2%)	1/49 (2%)	4/50 (8%)	5/49 (10%)	4/48 (8%)
2 Alveolar/bronchiolar adenomas or carcinomas	4/50 (8%)	6/49 (12%)	11/50 (22%)	3/48 (6%)	2/48 (4%)	1/49 (2%)	4/50 (8%)	6/49 (12%)	5/48 (10%)
3 Adenomatous hyperplasia	18/50 (36%)	27/49 (55%)	26/50 (52%)	10/48 (21%)	19/48 (40%)	16/49 (33%)	22/50 (44%)	22/49 (45%)	26/48 (54%)

(a) All mice were from the same supplier
(b) This study
(c) NTP Technical Report on D-Mannitol (NTP, 1982a)
(d) NTP Technical Report on Eugenol (NTP, 1982b)

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED DIETS CONTAINING ZIRAM

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIETS CONTAINING ZIRAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	2 (4%)	1 (2%)
SQUAMOUS CELL CARCINOMA			1 (2%)
BASAL-CELL CARCINOMA		1 (2%)	
SEBACEOUS ADENOMA		1 (2%)	
KERATOACANTHOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
TRICHOEPITHELIOMA		1 (2%)	
KERATOACANTHOMA	1 (2%)		
SARCOMA, NOS			2 (4%)
FIBROMA	2 (4%)	6 (12%)	
NEURILEMOMA	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
CARCINOMA,NOS	1 (2%)		
SQUAMOUS CELL CARCINOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
UNDIFFERENTIATED LEUKEMIA	7 (14%)	10 (20%)	9 (18%)
#SPLEEN	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(50)	(50)
UNDIFFERENTIATED LEUKEMIA	3 (6%)	1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
*FOOT	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	
#SPLEEN	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(50)	(50)	(50)
MUCINOUS ADENOCARCINOMA			1 (2%)
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	2 (4%)	1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)	
#STOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY/PELVIS	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA			1 (2%)
#URINARY BLADDER	(50)	(50)	(48)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(50)	(49)
CARCINOMA,NOS	2 (4%)	2 (4%)	2 (4%)
ADENOMA, NOS	13 (26%)	9 (18%)	8 (16%)
CRANIOPHARYNGIOMA		1 (2%)	
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	2 (4%)	2 (4%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PHEOCHROMOCYTOMA	7 (14%)	6 (12%)	7 (14%)
#THYROID	(50)	(49)	(49)
FOLLICULAR-CELL ADENOMA		2 (4%)	
FOLLICULAR-CELL CARCINOMA	1 (2%)	3 (6%)	1 (2%)
C-CELL ADENOMA	4 (8%)	7 (14%)	5 (10%)
C-CELL CARCINOMA		2 (4%)	7 (14%)
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL ADENOMA	2 (4%)	2 (4%)	2 (4%)
ISLET-CELL CARCINOMA	1 (2%)	2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
FIBROADENOMA	1 (2%)	1 (2%)	2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	4 (8%)	3 (6%)	4 (8%)
ADENOMA, NOS	3 (6%)	5 (10%)	2 (4%)
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	41 (82%)	42 (84%)	45 (90%)
NERVOUS SYSTEM			
#CRANIAL DURA MATER	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE			1 (2%)
#BRAIN	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE	1 (2%)		
GLIOMA, NOS		1 (2%)	
ASTROCYTOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*EAR CANAL	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA		1 (2%)	
*ZYMBAL'S GLAND	(50)	(50)	(50)
CYSTADENOMA, NOS		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF NECK	(50)	(50)	(50)
FOLLICULAR-CELL CARCINOMA, INVAS	1 (2%)		
C-CELL CARCINOMA, INVASIVE			1 (2%)
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	4	1
MORIBUND SACRIFICE	14	14	9
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	28	32	40
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	48	50	50
TOTAL PRIMARY TUMORS	104	125	109
TOTAL ANIMALS WITH BENIGN TUMORS	47	46	49
TOTAL BENIGN TUMORS	80	91	73
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	24	29
TOTAL MALIGNANT TUMORS	21	32	34
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		2
TOTAL SECONDARY TUMORS	2		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	2	2
TOTAL UNCERTAIN TUMORS	3	2	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 FED DIETS CONTAINING ZIRAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL CARCINOMA	1 (2%)		
FIBROMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
UNDIFFERENTIATED LEUKEMIA	4 (8%)	4 (8%)	4 (8%)
#MESENTERIC L. NODE	(49)	(50)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#THYMUS	(48)	(50)	(50)
THYMOMA	1 (2%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(49)
CARCINOMA,NOS	3 (6%)		2 (4%)
ADENOMA, NOS	19 (38%)	18 (37%)	19 (39%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	2 (4%)	1 (2%)	1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	3 (6%)
#THYROID	(50)	(50)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)	2 (4%)
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)	
C-CELL ADENOMA	6 (12%)	8 (16%)	6 (12%)
C-CELL CARCINOMA	3 (6%)	1 (2%)	3 (6%)
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL ADENOMA	1 (2%)	1 (2%)	
ISLET-CELL CARCINOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	3 (6%)	1 (2%)	
PAPILLARY ADENOMA		1 (2%)	
FIBROADENOMA	16 (32%)	17 (34%)	8 (16%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	3 (6%)	5 (10%)	4 (8%)
ADENOMA, NOS	2 (4%)	2 (4%)	1 (2%)
#UTERUS	(50)	(49)	(50)
ENDOMETRIAL STROMAL POLYP	5 (10%)	7 (14%)	7 (14%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)
PAPILLARY ADENOCARCINOMA			1 (2%)
NERVOUS SYSTEM			
#CEREBELLUM	(49)	(50)	(50)
MENINGIOMA	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)
NEUROFIBROSARCOMA	1 (2%)		
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	50	50	50
NATURAL DEATH@	5	1	1
MORIBUND SACRIFICE	8	6	3
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	43	46
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	43	42	39
TOTAL PRIMARY TUMORS	79	74	63
TOTAL ANIMALS WITH BENIGN TUMORS	37	38	32
TOTAL BENIGN TUMORS	54	61	48
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	12	14
TOTAL MALIGNANT TUMORS	25	13	15
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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ZIRAM

CONTROL

ANIMAL NUMBER	50011	50012	50013	50014	50015	50016	50017	50018	50019	50020	50021	50022	50023	50024	50025	50026	50027	50028	50029	50030	50031	50032	50033	50034	50035
WEEKS ON STUDY	104	104	104	104	098	104	081	106	096	106	090	095	101	106	106	106	099	096	106	106	097	106	096	106	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA													X										X		
KERATOACANTHOMA																X									
FIBROMA																									
NEURILEMOMA												X													
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ALVEOLAR/BRONCHIOLAR ADENOMA								X																	
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									X
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
UNDIFFERENTIATED LEUKEMIA				X									X											X	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																	X								
ADENOMA, NOS												X		X	X	X		X				X	X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA							X			X								X							
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA					X																				
C-CELL ADENOMA								X																	
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA		X												X											
ISLET-CELL CARCINOMA														X											
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																		N							
ADENOMA, NOS				X	X																	X			
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE																									
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA, INVASI					X																				
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																									
UNDIFFERENTIATED LEUKEMIA										X	X									X	X				

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	52606	52707	52808	52909	53001	53112	53287	53316	53401	53506	53616	53798	53898	53906	54001	54116	54202	54303	54404	54505	54606	54707	54816	54909	55016	TOTAL
WEEKS ON STUDY	1 0 6	1 0 6	1 0 6	0 6 4	0 9 4	0 8 8	0 8 7	1 0 6	1 0 6	1 0 6	1 0 6	0 9 8	0 9 8	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	0 9 4	1 0 6	1 0 9	1 0 6	0 8 6	1 0 6	1 0 6	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA	X																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
KERATOACANTHOMA																										1
FIBROMA																	X									2
NEURILEMOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																										1
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA																X										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE														X		X										2
UNDIFFERENTIATED LEUKEMIA																										3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																X										2
ADENOMA, NOS		X			X			X				X		X							X					13
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA								X				X														2
PHEOCHROMOCYTOMA						X					X	X											X			7
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA																										1
C-CELL ADENOMA	X												X	X												4
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																										2
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROADENOMA						X																				1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X		X			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		41
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
CARCINOMA,NOS	X												X								X					4
ADENOMA, NOS																										3
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, INVASIVE																X										1
MUSCULOSKELETAL SYSTEM																										
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA, INVASI																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
MESOTHELIOMA, NOS																							X			1
UNDIFFERENTIATED LEUKEMIA					X							X							X							7

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ZIRAM

LOW DOSE

ANIMAL NUMBER	50012	50023	50034	50045	50056	50067	50078	50089	50100	50111	50122	50133	50144	50155	50166	50177	50188	50199	50201	50212	50223	50234	50245
WEEKS ON STUDY	11105	10105	05109	09108	10105	09107	09108	10105	10109	10105	10105	10104	10105	09104	09106	10105	10104	09108	10105	10105	10105	10104	05105
INTEGUMENTARY SYSTEM																							
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA							X																
BASAL-CELL CARCINOMA																							
SEBACEOUS ADENOMA					X																		
KERATOACANTHOMA		X																					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRICHOEPITHELIOMA																							
FIBROMA				X		X						X											
NEURILEMOMA																							
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA						X																	
ALVEOLAR/BRONCHIOLAR CARCINOMA																			X				
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA				X																			
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																							
HEPATOCELLULAR CARCINOMA								X															
UNDIFFERENTIATED LEUKEMIA																X							
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																				X			
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS									X							X							
ADENOMA, NOS							X				X											X	
CRANIOPHARYNGIOMA																							
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA		X															X						
PHEOCHROMOCYTOMA																							
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA													X										
FOLLICULAR-CELL CARCINOMA					X									X								X	
C-CELL ADENOMA		X				X		X													X		X
C-CELL CARCINOMA																	X						
PARATHYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																				X			
ISLET-CELL CARCINOMA						X																	
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA													X										
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS			X					X										X					
ADENOMA, NOS		X										X							X				
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GLIOMA, NOS																							
ASTROCYTOMA																							X
SPECIAL SENSE ORGANS																							
EAR	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SEBACEOUS ADENOCARCINOMA																							
ZYMBAL'S GLAND	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CYSTADENOMA, NOS		X																					
BODY CAVITIES																							
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS					X																		
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UNDIFFERENTIATED LEUKEMIA		X		X				X							X		X	X					
FOOT NOS																							
HEMANGIOMA							X																

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	52606	52705	52809	52905	53051	53115	53205	53305	53400	53505	53605	53705	53805	53905	54081	54119	54205	54304	54408	54505	54606	54705	54805	54906	55010	TOTAL
WEEKS ON STUDY	10 5	10 5	09 8	10 5	10 5	10 5	10 5	10 5	10 0	10 5	10 5	10 5	11 0 5	10 5	10 8	09 9	08 8 4	08 8 0	08 8 2	10 5	10 5	10 5	11 1 5	10 6 4	10 6 5	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA										X																2
BASAL-CELL CARCINOMA													X													1
SEBACEOUS ADENOMA																										1
KERATOACANTHOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRICHOEPITHELIOMA																							X			1
FIBROMA															X	X			X							6
NEURILEMOMA			X																							1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE					X																					1
HEPATOCELLULAR CARCINOMA																										1
UNDIFFERENTIATED LEUKEMIA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																										2
ADENOMA, NOS				X						X			X	X				X					X			9
CRANIOPHARYNGIOMA	X																									1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA								X												X						2
PHEOCHROMOCYTOMA			X			X						X			X											6
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA					X																					2
FOLLICULAR-CELL CARCINOMA																										3
C-CELL ADENOMA			X	X																						7
C-CELL CARCINOMA										X																2
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																							X			2
ISLET-CELL CARCINOMA																X										2
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROADENOMA																										1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X		X	X	X			X	X	X		X	X	X	X	X		X	42
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
CARCINOMA,NOS																										3
ADENOMA, NOS										X	X															5
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GLIOMA, NOS																			X							1
ASTROCYTOMA																										1
SPECIAL SENSE ORGANS																										
EAR	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SEBACEOUS ADENOCARCINOMA																								X		1
ZYMBAL'S GLAND	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
CYSTADENOMA, NOS																										1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SARCOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
UNDIFFERENTIATED LEUKEMIA				X		X			X								X									10
FOOT NOS																										
HEMANGIOMA																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ZIRAM

HIGH DOSE

ANIMAL NUMBER	50011	50012	50013	50014	50015	50016	50017	50018	50019	50020	50111	50112	50113	50114	50115	50116	50117	50118	50119	50120	50121	50122	50123	50124	50125
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	0 9 5	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	0 7 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	0 7 4	0 9 6
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA	X																								
SQUAMOUS CELL CARCINOMA																			X						
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									X
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																							X		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE													X												
UNDIFFERENTIATED LEUKEMIA																									X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KIDNEY/PELVIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL CARCINOMA																									
URINARY BLADDER	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA								X																	
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																		X							
ADENOMA, NOS					X															X	X		X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA														X	X		X		X		X				
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA													X												
C-CELL ADENOMA								X											X				X		
C-CELL CARCINOMA							X							X			X	X							
PARATHYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA										X															
ISLET-CELL CARCINOMA					X																				
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
FIBROADENOMA								X			X														
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS	X				X				X																
ADENOMA, NOS																			X						
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE																									
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA, INVASIVE																		X							
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																									
MALIGNANT LYMPHOMA, MIXED TYPE																									
UNDIFFERENTIATED LEUKEMIA				X							X						X						X		
INTESTINAL TRACT																									
MUCINOUS ADENOCARCINOMA																						X			

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	52 26	52 27	52 28	52 29	53 30	53 31	53 32	53 33	53 34	53 35	53 36	53 37	53 38	53 39	54 40	54 41	54 42	54 43	54 44	54 45	54 46	54 47	54 48	54 49	55 50	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	1 01	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL PAPILLOMA																										1
SQUAMOUS CELL CARCINOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS													X													2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA												X														2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										1
UNDIFFERENTIATED LEUKEMIA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
KIDNEY/PELVIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRANSITIONAL-CELL CARCINOMA					X																					1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	48
TRANSITIONAL-CELL PAPILLOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA,NOS													X													2
ADENOMA, NOS														X		X	X				X					8
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA			X		X																					7
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
FOLLICULAR-CELL CARCINOMA																										1
C-CELL ADENOMA				X																					X	5
C-CELL CARCINOMA			X					X												X						7
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	-	+	+	+	45
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA													X													2
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS						X																				1
FIBROADENOMA																										2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
CARCINOMA,NOS									X																	4
ADENOMA, NOS												X														2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, INVASIVE													X													1
MUSCULOSKELETAL SYSTEM																										
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
C-CELL CARCINOMA, INVASIVE																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MESOTHELIOMA, NOS																								N		1
MALIGNANT LYMPHOMA, MIXED TYPE							X																			1
UNDIFFERENTIATED LEUKEMIA													X	X						X	X				X	9
INTESTINAL TRACT																										
MUCINOUS ADENOCARCINOMA																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ZIRAM

CONTROL

ANIMAL NUMBER	50101	50102	50103	50104	50105	50106	50107	50108	50109	50110	50111	50112	50113	50114	50115	50116	50117	50118	50119	50120	50121	50122	50123	50124	50125
WEEKS ON STUDY	060	104	104	095	104	104	104	095	106	106	084	106	106	088	079	106	106	105	106	071	106	106	106	106	106
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA							X																		
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA					X																				
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, MIXED TYPE		X																							
THYMUS	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMOMA																X									
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS				X										X											
ADENOMA, NOS			X		X				X	X	X				X	X		X			X		X		X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA					X					X				X											
C-CELL CARCINOMA																			X						
PARATHYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																						X			
ISLET-CELL CARCINOMA																				X					
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																X									
FIBROADENOMA		X		X			X	X															X		
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS										X									X						
ADENOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																				X					
ENDOMETRIAL STROMAL SARCOMA	X																								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
MENINGIOMA														X											
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEUROFIBROSARCOMA			X																						
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																			X						
UNDIFFERENTIATED LEUKEMIA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	52607	52707	52807	52907	53011	53111	53212	53312	53412	53506	53606	53706	53806	53906	54011	54106	54206	54306	54406	54506	54606	54706	54806	54906	55006	TOTAL TISSUES TUMORS
WEEKS ON STUDY	098	006	006	106	006	006	006	006	088	006	006	006	006	006	006	006	081	090	006	006	084	006	090	006	006	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
BASAL-CELL CARCINOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
TRACHEA	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIGNANT LYMPHOMA, MIXED TYPE																										1
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMOMA																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS										X																3
ADENOMA, NOS	X	X	X					X			X			X		X			X							19
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA															X							X				2
PHEOCHROMOCYTOMA										X																1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA																X										1
C-CELL ADENOMA																		X					X	X		6
C-CELL CARCINOMA								X																	X	3
PARATHYROID	-	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+	+	+	-	+	41
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																										1
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	•	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS											X			X												3
FIBROADENOMA			X		X		X	X		X		X			X	X				X	X	X				14
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
CARCINOMA,NOS												X														3
ADENOMA, NOS															X	X										2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP	X				X	X	X																			5
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MENINGIOMA																										1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
NEUROFIBROSARCOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																		X					X			2
UNDIFFERENTIATED LEUKEMIA	X								X						X											4

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ZIRAM

LOW DOSE

ANIMAL NUMBER	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525
WEEKS ON STUDY	105	105	105	105	099	100	105	105	105	105	105	105	098	105	105	105	105	105	105	105	105	105	105	105	106
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE FIBROMA	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY SQUAMOUS CELL PAPILLOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH SQUAMOUS CELL PAPILLOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	-	+	+	+	+ X	+ X	+ X	+	+	+	+	+	+ X	+ X	+ X	+ X	+	+	+	+	+	+	+	+	+
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+
THYROID FOLLICULAR-CELL ADENOMA FOLLICULAR-CELL CARCINOMA C-CELL ADENOMA C-CELL CARCINOMA	+	+ X	+	+	+ X	+	+	+	+ X	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS ISLET-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS PAPILLARY ADENOMA FIBROADENOMA	+	+ X	+	+	+	+ X	+ X	+ X	+	+ X	+	+	+	+	+	+	+	+	+	+	+ X	+	+ X	+	+ X
PREPUTIAL/CLITORAL GLAND CARCINOMA,NOS ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N X	N	N X	N	N	N	N	N	N	N	N	N	N	N X	N X	N
UTERUS ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+	+	+ X	+ X	+	+	+	+	+	+	+	+ X	+	+	+	+	+ X	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS MALIG.LYMPHOMA, HISTIOCYTIC TYPE UNDIFFERENTIATED LEUKEMIA	N	N	N	N	N	N X	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	52 26	52 27	52 28	52 29	53 30	53 31	53 32	53 33	53 34	53 35	53 36	53 37	53 38	53 39	54 01	54 11	54 42	54 43	54 44	54 45	54 46	54 47	54 48	54 49	55 00	TOTAL
WEEKS ON STUDY	10 06	10 03	10 06	10 06	10 08	10 06	10 06	10 06	09 04	10 04	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 00	10 06	10 06	10 06	10 06	10 06	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA		X													X											2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL PAPILLOMA																						X				1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS						X	X			X					X	X			X	X		X	X	X	X	18
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA			X																							1
FOLLICULAR-CELL CARCINOMA												X														1
C-CELL ADENOMA				X									X								X				X	8
C-CELL CARCINOMA																										1
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS																										1
PAPILLARY ADENOMA																				X						1
FIBROADENOMA			X		X	X				X						X		X	X		X			X		17
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA, NOS													X												X	5
ADENOMA, NOS																	X									2
UTERUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP	X																	X	X							7
OVARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
UNDIFFERENTIATED LEUKEMIA									X	X							X									4

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ZIRAM

HIGH DOSE

ANIMAL NUMBER	5011	5012	5013	5014	5015	5016	5017	5018	5019	5020	5111	5112	5113	5114	5115	5116	5117	5118	5119	5120	5121	5122	5123	5124	5125
WEEKS ON STUDY	104	104	104	104	099	104	104	104	098	104	104	097	104	104	104	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS	X			X						X			X		X	X	X	X				X	X		X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																				X					
PHEOCHROMOCYTOMA												X													
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
C-CELL ADENOMA			X								X		X												
C-CELL CARCINOMA									X							X									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA		X			X					X			X		X	X									
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS													X												
ADENOMA, NOS																X									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOCARCINOMA																				X					
ENDOMETRIAL STROMAL POLYP						X	X									X									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS	X																								
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UNDIFFERENTIATED LEUKEMIA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES / TUMORS
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	50
TRACHEA	50
HEMATOPOIETIC SYSTEM	
BONE MARROW	50
SPLEEN	50
LYMPH NODES	50
THYMUS	50
CIRCULATORY SYSTEM	
HEART	50
DIGESTIVE SYSTEM	
SALIVARY GLAND	49
LIVER	50
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50*
PANCREAS	50
ESOPHAGUS	50
STOMACH	50
SMALL INTESTINE	49
LARGE INTESTINE	50
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	50
ENDOCRINE SYSTEM	
PITUITARY	49
CARCINOMA,NOS	2
ADENOMA, NOS	19
ADRENAL	50
CORTICAL ADENOMA	1
PHEOCHROMOCYTOMA	3
THYROID	50
FOLLICULAR-CELL ADENOMA	2
C-CELL ADENOMA	6
C-CELL CARCINOMA	3
PARATHYROID	48
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50*
FIBROADENOMA	8
PREPUTIAL/CLITORAL GLAND	50*
CARCINOMA,NOS	4
ADENOMA, NOS	2
UTERUS	50
PAPILLARY ADENOCARCINOMA	1
ENDOMETRIAL STROMAL POLYP	7
OVARY	50
NERVOUS SYSTEM	
BRAIN	50
BODY CAVITIES	
MESENTERY	50*
SARCOMA, NOS	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50*
UNDIFFERENTIATED LEUKEMIA	4

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE FED DIETS CONTAINING ZIRAM

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIETS CONTAINING ZIRAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(49)	(50)	(49)
BASAL-CELL CARCINOMA		1 (2%)	
MALIGNANT MELANOMA	1 (2%)		
SARCOMA, NOS	2 (4%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (12%)	5 (10%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	4 (8%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		4 (8%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(49)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(49)	(50)	(48)
HEMANGIOSARCOMA	2 (4%)	2 (4%)	1 (2%)
*FEMUR	(49)	(50)	(49)
HEMANGIOSARCOMA		1 (2%)	
*SKELETAL MUSCLE	(49)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LUNG	(49)	(50)	(49)
HEMANGIOMA		1 (2%)	
#HEART	(49)	(50)	(48)
HEMANGIOSARCOMA, METASTATIC			1 (2%)
#MYOCARDIUM	(49)	(50)	(48)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
#LIVER	(49)	(50)	(49)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
*MESENTERY	(49)	(50)	(49)
HEMANGIOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(49)
HEPATOCELLULAR ADENOMA	6 (12%)	1 (2%)	8 (16%)
HEPATOCELLULAR CARCINOMA	13 (27%)	8 (16%)	1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
#SMALL INTESTINE	(46)	(49)	(47)
ADENOCARCINOMA, NOS	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(49)	(49)	(49)
CORTICAL ADENOMA	1 (2%)		
#THYROID	(49)	(50)	(48)
FOLLICULAR-CELL ADENOMA	2 (4%)		5 (10%)
#PANCREATIC ISLETS	(48)	(50)	(48)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*EPIDIDYMIS	(49)	(50)	(49)
SARCOMA, NOS	1 (2%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(49)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	6	6
MORIBUND SACRIFICE	6	9	8
SCHEDULED SACRIFICE	2		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	35	35
ANIMAL MISSING			

@ 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*	31	24	25
TOTAL PRIMARY TUMORS	42	28	36
TOTAL ANIMALS WITH BENIGN TUMORS	13	9	18
TOTAL BENIGN TUMORS	15	9	22
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	17	13
TOTAL MALIGNANT TUMORS	27	19	14
TOTAL ANIMALS WITH SECONDARY TUMORS#	4	3	1
TOTAL SECONDARY TUMORS	4	3	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED DIETS CONTAINING ZIRAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	5 (10%)	10 (20%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	2 (4%)
SARCOMA, NOS, METASTATIC	2 (4%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	7 (14%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		3 (6%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	3 (6%)		2 (4%)
LYMPHOCYTIC LEUKEMIA	5 (10%)	1 (2%)	2 (4%)
#SPLEEN	(49)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#MESENTERIC L. NODE	(49)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#LIVER	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
*MESENTERY	(50)	(50)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
*SPINAL CORD	(50)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*MEDIASTINUM	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	
*SKIN	(50)	(50)	(50)
HEMANGIOMA	1 (2%)		
#SPLEEN	(49)	(49)	(50)
HEMANGIOMA		2 (4%)	
HEMANGIOSARCOMA		2 (4%)	
*MESENTERY	(50)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
#UTERUS	(50)	(50)	(50)
HEMANGIOMA			1 (2%)
#OVARY	(44)	(50)	(50)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
BILE DUCT CARCINOMA	1 (2%)		
HEPATOCELLULAR ADENOMA	7 (14%)	2 (4%)	
HEPATOCELLULAR CARCINOMA	2 (4%)	2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CA, METASTA	1 (2%)		
#SMALL INTESTINE	(46)	(46)	(48)
MUCINOUS ADENOCARCINOMA	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(40)	(40)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS		1 (3%)	
#ADRENAL	(47)	(50)	(50)
PHEOCHROMOCYTOMA			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(47)	(43)	(48)
FOLLICULAR-CELL ADENOMA	1 (2%)		
FOLLICULAR-CELL CARCINOMA			1 (2%)
#PANCREATIC ISLETS	(48)	(48)	(47)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	2 (4%)
#UTERUS	(50)	(50)	(50)
ENDOMETRIAL STROMAL POLYP	2 (4%)		1 (2%)
#OVARY/OVIDUCT	(50)	(50)	(50)
PAPILLARY ADENOMA	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
LIPOMA		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)	1 (2%)	

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	50	50	50
NATURAL DEATH@	8	4	6
MORIBUND SACRIFICE	10	7	7
SCHEDULED SACRIFICE	1		
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	30	39	37
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	19	23
TOTAL PRIMARY TUMORS	34	27	34
TOTAL ANIMALS WITH BENIGN TUMORS	13	11	14
TOTAL BENIGN TUMORS	14	13	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	11	17
TOTAL MALIGNANT TUMORS	20	14	20
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	1	
TOTAL SECONDARY TUMORS	3	2	
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

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ZIRAM

CONTROL

ANIMAL NUMBER	00101	00102	00103	00104	00105	00106	00107	00108	00109	00110	00111	00112	00113	00114	00115	00116	00117	00118	00119	00120	00121	00122	00123	00124	00125
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	098	106	087	106	106	106	106	106	064	106	111	106	106	071	106
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	A	+
MALIGNANT MELANOMA																									
SARCOMA, NOS							X																		
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
HEPATOCELLULAR CARCINOMA, METASTA																					X	X			
ALVEOLAR/BRONCHIOLAR ADENOMA	X			X													X								
ALVEOLAR/BRONCHIOLAR CARCINOMA			X	X																					
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
HEMANGIOSARCOMA																	X								
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
HEPATOCELLULAR ADENOMA															X	X									
HEPATOCELLULAR CARCINOMA	X			X			X		X		X										X	X	X		X
HEPATOCELLULAR CARCINOMA, METASTA																									
HEMANGIOSARCOMA, METASTATIC																	X								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	A	+	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	
ADENOCARCINOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
CORTICAL ADENOMA		X																							
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
FOLLICULAR-CELL ADENOMA															X										
PARATHYROID	+	+	+	+	+	+	-	+	-	-	-	+	-	+	+	+	+	+	+	+	+	+	+	A	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	+
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N
SARCOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N
HEMANGIOSARCOMA																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	031	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	016	014	014	072	014	006	006	006	016	016	016	016	011	076	016	006	006	006	056	016	014	006	016	006	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
MALIGNANT MELANOMA														X												1
SARCOMA, NOS					X																					2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA																										2
ALVEOLAR/BRONCHIOLAR ADENOMA																	X	X			X					6
ALVEOLAR/BRONCHIOLAR CARCINOMA																						X				3
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																						X				2
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA	X																X		X					X		6
HEPATOCELLULAR CARCINOMA								X					X		X					X						13
HEPATOCELLULAR CARCINOMA, METASTA																				X						1
HEMANGIOSARCOMA, METASTATIC																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	46
ADENOCARCINOMA, NOS																		X								1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	-	+	+	+	+	+	43
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																									X	2
PARATHYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	42
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
SARCOMA, NOS															X											1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
HEMANGIOSARCOMA				X																						1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE						X						X														2
MALIGNANT LYMPHOMA, MIXED TYPE																	X									1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
!: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ZIRAM

LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	105	105	105	098	105	020	012	119	020	105	105	051	051	105	098	105	105	097	105	105	105	105	105	104	101
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA																		X							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA			X																						
ALVEOLAR/BRONCHIOLAR ADENOMA	X				X																			X	
ALVEOLAR/BRONCHIOLAR CARCINOMA					X		X				X				X										
HEMANGIOMA										X															
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	•	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA	X																								
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA, METASTATIC																									
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA				X																					
HEPATOCELLULAR CARCINOMA			X										X	X				X							X
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ADRENAL	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	+	-	+	-	-	-	-	+	+	-	-	-	+	+	+	+	-	+	+	+	-	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA													X												
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	N	+	N	+	N	N	N	+	N	N	N	N	+	N	N	N	N	+	+	N	N	+
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																		X							
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOSARCOMA																									
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEPATOCELLULAR CARCINOMA, METASTA																		X							
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X											

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	085	101	105	105	105	105	021	103	105	105	029	052	032	051	105		
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
BASAL-CELL CARCINOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																									1
ALVEOLAR/BRONCHIOLAR ADENOMA		X						X																	5
ALVEOLAR/BRONCHIOLAR CARCINOMA																									4
HEMANGIOMA																									1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																	X								2
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA, METASTATIC																	X								1
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																									1
HEPATOCELLULAR CARCINOMA												X		X									X		8
HEMANGIOSARCOMA										X															1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	•	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
PITUITARY	+	•	+	–	+	+	+	•	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PARATHYROID	+	+	–	+	+	+	–	+	–	–	+	–	–	+	–	–	–	+	+	+	+	–	+		29
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	•	+	+	•	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																									1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	N	+	+	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
SARCOMA, NOS																									1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
HEMANGIOSARCOMA											X														1
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
HEPATOCELLULAR CARCINOMA, METASTA																									1
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
HEMANGIOMA																			X						1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									1

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ZIRAM

HIGH DOSE

ANIMAL NUMBER	001	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025	026
WEEKS ON STUDY	104	104	012	092	104	104	104	104	104	104	104	095	104	104	104	104	104	104	022	078	110	104	104	094	104
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA											X	X		X											
ALVEOLAR/BRONCHIOLAR CARCINOMA				X														X		X					
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
SPLEEN	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA												X													
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA, METASTATIC												X													
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X				X																			
HEPATOCELLULAR CARCINOMA																				X					
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	-	-	+	-	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	-
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
FOLLICULAR-CELL ADENOMA																	X		X						
PARATHYROID	+	+	+	-	-	+	+	-	-	+	-	+	-	-	-	+	-	-	+	+	-	-	+	-	+
PANCREATIC ISLETS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA												X													
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS		X																							
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
HEMANGIOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE								X																	
MALIGNANT LYMPHOMA, MIXED TYPE												X													

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	02 7	02 8	02 9	03 0	03 1	03 2	03 3	03 4	03 5	03 6	03 7	03 8	03 9	04 0	04 1	04 2	04 3	04 4	04 5	04 6	04 7	04 8	04 9	05 0	TOTAL
WEEKS ON STUDY	10 4	10 4	10 4	10 4	10 4	11 3	10 4	02 5	01 1	01 4	01 4	01 4	01 4	01 4	01 4	01 4	01 4	01 4	01 4	01 4	07 4	01 4	01 5	01 5	TISSUES TUMORS
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA									X	X				X					X			X			8
ALVEOLAR/BRONCHIOLAR CARCINOMA															X										4
TRACHEA	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	49
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																									1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA, METASTATIC																									1
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA								X				X			X		X			X		X			8
HEPATOCELLULAR CARCINOMA																									1
HEMANGIOSARCOMA								X																	1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	49M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	38
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA										X							X	X							5
PARATHYROID	+	–	+	+	+	–	+	+	–	+	+	+	–	–	–	+	+	+	+	–	+	–	+	+	28
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL ADENOMA																									1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	49M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49M
SARCOMA, NOS																									1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49M
HEMANGIOSARCOMA																					X				1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49M
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																X									1
MALIGNANT LYMPHOMA, MIXED TYPE									X						X										4

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
•: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ZIRAM

CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035
WEEKS ON STUDY	106	106	106	102	106	081	106	106	093	104	106	106	095	106	106	106	106	106	106	098	099	101	087	097	086
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA									X																
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA		X																				X			
ALVEOLAR/BRONCHIOLAR CARCINOMA																							X		
SARCOMA, NOS, METASTATIC						X																			
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																	X								
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT CARCINOMA									X																
HEPATOCELLULAR ADENOMA				X			X										X	X							
HEPATOCELLULAR CARCINOMA									X																
ALVEOLAR/BRONCHIOLAR CA, METASTAT																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	+
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+
MUCINOUS ADENOCARCINOMA	X																								
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	~	+	+	-	+	+	+
CARCINOMA,NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA										X															
PARATHYROID	-	-	+	-	-	-	+	+	-	+	-	+	-	-	-	+	-	+	+	-	-	-	+	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOMA					X																				
ENDOMETRIAL STROMAL POLYP																					X		X		
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS						X																			
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																									
MALIGNANT LYMPHOMA, NOS				X																					
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE															X										
LYMPHOCYTIC LEUKEMIA																									X

+: TISSUE EXAMINED MICROSCOPICALLY
~: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	102	106	096	103	106	091	106	106	077	106	106	106	067	106	106	106	106	106	104	106	106	106	106	078	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	50	50
HEMANGIOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ALVEOLAR/BRONCHIOLAR ADENOMA																										2
ALVEOLAR/BRONCHIOLAR CARCINOMA														X												2
SARCOMA, NOS, METASTATIC																				X						2
TRACHEA	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	-	-	-	-	+	40	
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
MALIGNANT LYMPHOMA, NOS																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49	
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	47	
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	-	+	+	-	+	46	
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
BILE DUCT CARCINOMA																										1
HEPATOCELLULAR ADENOMA															X		X		X							7
HEPATOCELLULAR CARCINOMA																						X				2
ALVEOLAR/BRONCHIOLAR CA, METASTAT														X												1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	N	+	50	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49	
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
MUCINOUS ADENOCARCINOMA																										1
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
URINARY BLADDER	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	46	
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	44	
CARCINOMA,NOS																								X		1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	47	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	47	
FOLLICULAR-CELL ADENOMA																										1
PARATHYROID	+	-	-	-	-	+	+	+	-	+	+	+	-	-	+	-	+	-	-	-	+	-	-	-	20	
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	50	
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
PAPILLARY ADENOMA																										1
ENDOMETRIAL STROMAL POLYP																										2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	-	+	-	+	44	
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
MUSCULOSKELETAL SYSTEM																										
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
SARCOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50	
SARCOMA, NOS																				X						1
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																					X					1
MALIGNANT LYMPHOMA, MIXED TYPE								X														X	X			3
LYMPHOCYTIC LEUKEMIA				X						X	X															5

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ZIRAM

LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	105	101	95	105	105	095	105	105	105	100	105	099	085	098	105	105	105	105	105	105	105	097	095	085	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
ALVEOLAR/BRONCHIOLAR ADENOMA												X			X										
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																				X					
HEMANGIOSARCOMA	X													X											
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE															X										
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA							X																		
HEPATOCELLULAR CARCINOMA	X																								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	N	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	N	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	-	+	-	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																				X					
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-
PARATHYROID	+	-	+	+	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-	+	-	+	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+
ADENOCARCINOMA, NOS															X										
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPINAL CORD	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N
HEMANGIOSARCOMA, METASTATIC														X											
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOMA																				X					
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA																						X			
HEMANGIOSARCOMA, METASTATIC														X											
MALIGNANT LYMPHOMA, MIXED TYPE																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS										X															
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE												X													
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
LYMPHOCYTIC LEUKEMIA													X												

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	49
ALVEOLAR/BRONCHIOLAR ADENOMA	5
ALVEOLAR/BRONCHIOLAR CARCINOMA	1
TRACHEA	49
HEMATOPOIETIC SYSTEM	
BONE MARROW	49
SPLEEN	49
HEMANGIOMA	2
HEMANGIOSARCOMA	2
LYMPH NODES	50
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1
THYMUS	47
CIRCULATORY SYSTEM	
HEART	49
DIGESTIVE SYSTEM	
SALIVARY GLAND	49
LIVER	50
HEPATOCELLULAR ADENOMA	2
HEPATOCELLULAR CARCINOMA	2
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50*
PANCREAS	48
ESOPHAGUS	50
STOMACH	49
SMALL INTESTINE	46
LARGE INTESTINE	49
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	50
ENDOCRINE SYSTEM	
PITUITARY	40
ADENOMA, NOS	1
ADRENAL	50
THYROID	43
PARATHYROID	26
PANCREATIC ISLETS	48
ISLET-CELL ADENOMA	1
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50*
ADENOCARCINOMA, NOS	1
UTERUS	50
OVARY	50
NERVOUS SYSTEM	
BRAIN	50
SPINAL CORD	50*
HEMANGIOSARCOMA, METASTATIC	1
BODY CAVITIES	
MEDIASTINUM	50*
HEMANGIOMA	1
MESENTERY	50*
LIPOMA	1
HEMANGIOSARCOMA, METASTATIC	1
MALIGNANT LYMPHOMA, MIXED TYPE	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50*
SARCOMA, NOS	1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3
LYMPHOCYTIC LEUKEMIA	1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ZIRAM

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	050	104	104	104	104	104	104	105	105	105	105	105	105	087	091	105	105	105	105	105	105	102	096	104	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA				X								X						X							
ALVEOLAR/BRONCHIOLAR CARCINOMA							X																		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA															X										
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	N	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	+	+	+	+	-
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																							X		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA			X																						
PARATHYROID	-	+	+	+	+	+	+	-	+	+	-	-	+	-	-	+	-	+	-	-	-	-	-	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																									
HEMANGIOMA														X											
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS			X																						
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X																	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X											
MALIGNANT LYMPHOMA, MIXED TYPE																									
LYMPHOCYTIC LEUKEMIA					X																				

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	02261	02278	02290	03110	03112	03134	03135	03136	03171	03189	03190	04111	04123	04145	04156	04167	04189	04590	04615	04756	04818	04945	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	105	104	105	105	103	105	105	105	105	105	105	105	105	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA			X		X					X			X	X	X			X					10
ALVEOLAR/BRONCHIOLAR CARCINOMA										X													2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	46
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA																X							1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																							1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	N	+	50*
PANCREAS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
ENDOCRINE SYSTEM																							
PITUITARY	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	-	•	+	+	+	-	40
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA																							1
THYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL CARCINOMA																							1
PARATHYROID	-	-	-	+	+	+	-	-	+	-	-	-	-	-	-	-	+	+	+	+	-	+	23
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS											X				X								2
UTERUS	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP				X																			1
HEMANGIOMA																							1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA																					X		1
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIGNANT LYMPHOMA, NOS																							1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X												X		X	X	X				X		7
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																							1
MALIGNANT LYMPHOMA, MIXED TYPE				X						X													2
LYMPHOCYTIC LEUKEMIA											X												2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED DIETS CONTAINING ZIRAM

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIETS CONTAINING ZIRAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
CYST, NOS		1 (2%)	
EPIDERMAL INCLUSION CYST	2 (4%)		1 (2%)
ULCER, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS			1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		
HYPERKERATOSIS			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
HEMORRHAGIC CYST		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
CONGESTION, NOS	1 (2%)	1 (2%)	
INFLAMMATION, INTERSTITIAL		1 (2%)	1 (2%)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		1 (2%)	
HEMATOPOIESIS		1 (2%)	
#BONE MARROW	(50)	(50)	(50)
FIBRIN BODY			1 (2%)
ATROPHY, NOS	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL	1 (2%)	2 (4%)	
LIPOIDOSIS			1 (2%)
HEMATOPOIESIS	2 (4%)	1 (2%)	
#MANDIBULAR L. NODE	(50)	(50)	(50)
HYPERPLASIA, PLASMA CELL			1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#CERVICAL LYMPH NODE	(50)	(50)	(50)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	3 (6%)	1 (2%)	
#PEYER'S PATCH	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID	6 (12%)	5 (10%)	2 (4%)
CIRCULATORY SYSTEM			
*FOOT	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#MANDIBULAR L. NODE	(50)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)
#LUNG	(50)	(49)	(50)
THROMBUS, FIBRIN		1 (2%)	
#HEART	(50)	(49)	(50)
INFLAMMATION, CHRONIC			1 (2%)
#HEART/ATRIUM	(50)	(49)	(50)
THROMBUS, MURAL		1 (2%)	
#AURICULAR APPENDAGE	(50)	(49)	(50)
THROMBUS, MURAL		2 (4%)	
#MYOCARDIUM	(50)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	
INFLAMMATION, CHRONIC	33 (66%)	35 (71%)	28 (56%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*ARTERY	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#SALIVARY GLAND	(49)	(50)	(49)
THROMBUS, FIBRIN	1 (2%)		
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#PANCREAS	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
*MESENTERY	(50)	(50)	(50)
PERIARTERITIS	1 (2%)	1 (2%)	
#ADRENAL	(50)	(50)	(50)
THROMBUS, CANALIZED		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(50)	(49)
INFLAMMATION, NOS	1 (2%)		
#LIVER	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		2 (4%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
CYTOPLASMIC CHANGE, NOS		1 (2%)	2 (4%)
CYTOPLASMIC VACUOLIZATION		6 (12%)	3 (6%)
BASOPHILIC CYTO CHANGE			1 (2%)
FOCAL CELLULAR CHANGE	4 (8%)	2 (4%)	3 (6%)
ANGIECTASIS		1 (2%)	2 (4%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)	
#LIVER/HEPATOCYTES	(50)	(50)	(50)
DEGENERATION, CYSTIC		1 (2%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	4 (8%)	7 (14%)	6 (12%)
#PANCREAS	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC FOCAL			1 (2%)
ATROPHY, NOS		3 (6%)	3 (6%)
ATROPHY, FOCAL			2 (4%)
#PANCREATIC ACINUS	(50)	(50)	(50)
ATROPHY, NOS		1 (2%)	
ATROPHY, FOCAL			1 (2%)
#GASTRIC SUBMUCOSA	(50)	(50)	(50)
EDEMA, NOS		1 (2%)	
#COLON	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NEMATODIASIS	1 (2%)	1 (2%)	
#COLONIC SUBMUCOSA	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
INFLAMMATION, CHRONIC	45 (90%)	44 (88%)	42 (84%)
DEGENERATION, HYALINE		1 (2%)	
NEPHROSIS, NOS		1 (2%)	
PIGMENTATION, NOS	1 (2%)		1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS	1 (2%)	1 (2%)	
#U. BLADDER/MUCOSA	(50)	(50)	(48)
HEMORRHAGE		1 (2%)	
#U.BLADDER/SUBMUCOSA	(50)	(50)	(48)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(50)	(49)
CYST, NOS	1 (2%)	1 (2%)	
HEMORRHAGIC CYST	2 (4%)		
HYPERPLASIA, FOCAL			1 (2%)
ANGIECTASIS		1 (2%)	
#ADRENAL	(50)	(50)	(50)
CYST, NOS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, ISCHEMIC	1 (2%)		
CYTOPLASMIC VACUOLIZATION	1 (2%)		
ANGIECTASIS			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(50)
CYST, NOS	1 (2%)		
CYTOPLASMIC VACUOLIZATION		7 (14%)	4 (8%)
#ADRENAL MEDULLA	(50)	(50)	(50)
CYST, NOS		1 (2%)	
HYPERPLASIA, FOCAL	2 (4%)	3 (6%)	3 (6%)
#THYROID	(50)	(49)	(49)
THYROGLOSSAL DUCT CYST		3 (6%)	1 (2%)
ULTIMOBRANCHIAL CYST	1 (2%)		
CYSTIC FOLLICLES		1 (2%)	3 (6%)
FOLLICULAR CYST, NOS	1 (2%)	3 (6%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
PIGMENTATION, NOS			1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)
HYPERPLASIA, C-CELL	7 (14%)	12 (24%)	11 (22%)
#PARATHYROID	(49)	(47)	(45)
HYPERPLASIA, FOCAL	1 (2%)		
#PANCREATIC ISLETS	(50)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	7 (14%)	6 (12%)	5 (10%)
HYPERPLASIA, CYSTIC		2 (4%)	
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
*PENIS	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*PREPUCE	(50)	(50)	(50)
INFLAMMATION, NECROTIZING		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)		1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
#PROSTATE	(49)	(50)	(49)
INFLAMMATION, SUPPURATIVE	11 (22%)	12 (24%)	3 (6%)
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV			4 (8%)
ABSCESS, CHRONIC			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#TESTIS	(50)	(50)	(50)
ATROPHY, NOS		4 (8%)	1 (2%)
HYPERPLASIA, INTERSTITIAL CELL	2 (4%)	7 (14%)	5 (10%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, NOS			1 (2%)
HEMORRHAGE			1 (2%)
GLIOSIS		1 (2%)	
*SPINAL CORD	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE	3 (6%)		5 (10%)
RETINOPATHY	32 (64%)	7 (14%)	45 (90%)
PHTHISIS BULBI			1 (2%)
*EYE/RETINA	(50)	(50)	(50)
DEGENERATION, NOS			1 (2%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
CATARACT	2 (4%)		3 (6%)
*EYE APPENDAGE	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
*EAR	(50)	(50)	(50)
ULCER, FOCAL			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*EAR CANAL	(50)	(50)	(50)
KERATIN-PEARL FORMATION		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL WALL	(50)	(50)	(50)
ADHESION, NOS		1 (2%)	
*PERITONEUM	(50)	(50)	(50)
ADHESION, NOS	1 (2%)		
*MESENTERY	(50)	(50)	(50)
STEATITIS		6 (12%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
NECROSIS, FAT	6 (12%)	4 (8%)	3 (6%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, NECROTIZING	1 (2%)		
OMENTUM			
NECROSIS, FAT	1		1
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED DIETS CONTAINING ZIRAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
ULCER, NOS	1 (2%)		
ULCER, FOCAL		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
FIBROSIS, FOCAL			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
ABSCESS, CHRONIC	1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)	1 (2%)	1 (2%)
#LUNG/ALVEOLI	(50)	(50)	(50)
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(50)
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL	1 (2%)	1 (2%)	1 (2%)
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
FIBROSIS	1 (2%)		
HEMOSIDEROSIS	2 (4%)		1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIESIS	1 (2%)		3 (6%)
#RENAL LYMPH NODE	(49)	(50)	(50)
ANGIECTASIS		1 (2%)	
#INGUINAL LYMPH NODE	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		2 (4%)	3 (6%)
#PEYER'S PATCH	(48)	(50)	(49)
HYPERPLASIA, LYMPHOID	4 (8%)	2 (4%)	2 (4%)
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(49)	(50)	(50)
LYMPHANGIECTASIS	1 (2%)		
#HEART	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#HEART/ATRIUM	(50)	(50)	(50)
THROMBUS, MURAL		1 (2%)	
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	21 (42%)	21 (42%)	20 (40%)
INFLAMMATION, CHRONIC FOCAL	2 (4%)		
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
#SALIVARY GLAND	(49)	(50)	(49)
CYSTIC DUCTS			1 (2%)
#LIVER	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			6 (12%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MITOTIC ALTERATION	1 (2%)		
CYTOPLASMIC CHANGE, NOS	1 (2%)		
CYTOPLASMIC VACUOLIZATION	1 (2%)	3 (6%)	
FOCAL CELLULAR CHANGE	5 (10%)	2 (4%)	
ATROPHY, NOS			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#PANCREAS	(50)	(50)	(50)
INFLAMMATION, CHRONIC	2 (4%)		
NECROSIS, FAT	1 (2%)		
ATROPHY, NOS	2 (4%)	1 (2%)	1 (2%)
#PANCREATIC ACINUS	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)		
ATROPHY, FOCAL		1 (2%)	
#GASTRIC SUBMUCOSA	(49)	(50)	(50)
EDEMA, NOS	1 (2%)	1 (2%)	
#PEYER'S PATCH	(48)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)		
#COLON	(50)	(50)	(50)
NEMATODIASIS	1 (2%)		1 (2%)
*RECTUM	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, CHRONIC	7 (14%)	5 (10%)	3 (6%)
#URINARY BLADDER	(48)	(50)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(49)
CYST, NOS		1 (2%)	1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGIC CYST		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	1 (2%)
ANGIECTASIS		1 (2%)	1 (2%)
#ADRENAL	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
ANGIECTASIS		2 (4%)	2 (4%)
#ADRENAL CORTEX	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	3 (6%)	5 (10%)	5 (10%)
ANGIECTASIS	1 (2%)		
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, FOCAL	1 (2%)		
#THYROID	(50)	(50)	(50)
THYROGLOSSAL DUCT CYST		7 (14%)	5 (10%)
CYSTIC FOLLICLES			1 (2%)
FOLLICULAR CYST, NOS		1 (2%)	
HYPERPLASIA, C-CELL	16 (32%)	11 (22%)	19 (38%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	20 (40%)	16 (32%)	13 (26%)
HYPERPLASIA, CYSTIC	1 (2%)	2 (4%)	3 (6%)
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	3 (6%)	3 (6%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
*CLITORAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	3 (6%)	3 (6%)	
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#UTERUS	(50)	(49)	(50)
ABSCESS, CHRONIC		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)
CYST, NOS	2 (4%)	1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE	1 (2%)		
HYPERPLASIA, NOS		2 (4%)	
HYPERPLASIA, FOCAL	1 (2%)		
HYPERPLASIA, CYSTIC	2 (4%)	4 (8%)	3 (6%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	1 (2%)	
#OVARY	(50)	(49)	(50)
CYSTIC FOLLICLES			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
HEMORRHAGE	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE		3 (6%)	1 (2%)
RETINOPATHY	9 (18%)	48 (96%)	30 (60%)
*EYELID	(50)	(50)	(50)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
TORSION	1 (2%)		
STEATITIS	1 (2%)	9 (18%)	
INFLAMMATION, CHRONIC	1 (2%)		
NECROSIS, FAT	8 (16%)	3 (6%)	4 (8%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED DIETS CONTAINING ZIRAM

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIETS CONTAINING ZIRAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	2 (4%)		
FIBROSIS		1 (2%)	
FIBROSIS, FOCAL		1 (2%)	
KELOID	1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(49)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
ABSCESS, CHRONIC		3 (6%)	
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(49)	(50)	(49)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)		
#LUNG	(49)	(50)	(49)
INFLAMMATION, SUPPURATIVE			2 (4%)
BRONCHOPNEUMONIA SUPPURATIVE		3 (6%)	
INFLAMMATION, NECROTIZING		2 (4%)	
INFLAMMATION, GRANULOMATOUS		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)	1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		2 (4%)
PERIVASCULAR CUFFING		1 (2%)	
CHOLESTEROL DEPOSIT			1 (2%)
PIGMENTATION, NOS		1 (2%)	
ALVEOLAR MACROPHAGES	3 (6%)	2 (4%)	
HYPERPLASIA, ADENOMATOUS	15 (31%)	19 (38%)	16 (33%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, ALVEOLAR EPITHELIUM	4 (8%)	2 (4%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(49)
LEUKOCYTOSIS, NEUTROPHILIC	1 (2%)		
HYPERPLASIA, LYMPHOID			3 (6%)
#BONE MARROW	(49)	(49)	(48)
MYELOFIBROSIS			1 (2%)
HYPERPLASIA, NEUTROPHILIC	1 (2%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)		
#SPLEEN	(49)	(50)	(48)
HEMATOPOIESIS	1 (2%)		
#MESENTERIC L. NODE	(49)	(50)	(49)
ANGIECTASIS	2 (4%)		
HEMATOPOIESIS	2 (4%)		
#INGUINAL LYMPH NODE	(49)	(50)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#LUNG/BRONCHUS	(49)	(50)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LUNG	(49)	(50)	(49)
LEUKOCYTOSIS, NOS		1 (2%)	1 (2%)
#LIVER	(49)	(50)	(49)
HEMATOPOIESIS			1 (2%)
#PEYER'S PATCH	(46)	(49)	(47)
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)	
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(48)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#MYOCARDIUM	(49)	(50)	(48)
MINERALIZATION	1 (2%)		
INFLAMMATION, INTERSTITIAL		1 (2%)	3 (6%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*PULMONARY VEIN	(49)	(50)	(49)
THROMBOSIS, NOS			2 (4%)
#KIDNEY/GLOMERULUS	(49)	(50)	(49)
EMBOLUS, SEPTIC		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(48)
PERIVASCULAR CUFFING			1 (2%)
#LIVER	(49)	(50)	(49)
CYST, NOS			2 (4%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
NECROSIS, FOCAL			1 (2%)
NECROSIS, COAGULATIVE	4 (8%)	1 (2%)	2 (4%)
INFARCT, NOS	1 (2%)		1 (2%)
CYTOPLASMIC CHANGE, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		1 (2%)
FOCAL CELLULAR CHANGE		1 (2%)	
ANGIECTASIS			1 (2%)
#LIVER/KUPFFER CELL	(49)	(50)	(49)
HYPERPLASIA, FOCAL			1 (2%)
*GALLBLADDER	(49)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
#BILE DUCT	(49)	(50)	(49)
DILATATION, NOS			1 (2%)
CYST, NOS	1 (2%)		
MULTIPLE CYSTS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#PANCREAS	(48)	(50)	(48)
CYSTIC DUCTS		1 (2%)	
#STOMACH	(49)	(50)	(48)
INFLAMMATION, SUPPURATIVE			1 (2%)
#GASTRIC MUCOSA	(49)	(50)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#GASTRIC SUBMUCOSA	(49)	(50)	(48)
INFLAMMATION, SUPPURATIVE	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#GASTRIC MUSCULARIS	(49)	(50)	(48)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#SMALL INTESTINE	(46)	(49)	(47)
INFLAMMATION, NECROTIZING		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(49)
MINERALIZATION			1 (2%)
PYELONEPHRITIS, FOCAL		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)		2 (4%)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
GLOMERULONEPHRITIS, CHRONIC			1 (2%)
PERIVASCULAR CUFFING		1 (2%)	1 (2%)
#KIDNEY/PELVIS	(49)	(50)	(49)
DILATATION, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
#URINARY BLADDER	(49)	(50)	(49)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
PERIVASCULAR CUFFING			1 (2%)
#U. BLADDER/MUCOSA	(49)	(50)	(49)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#U.BLADDER/SUBMUCOSA	(49)	(50)	(49)
FIBROSIS	1 (2%)		
ENDOCRINE SYSTEM			
#THYROID	(49)	(50)	(48)
CYSTIC FOLLICLES		2 (4%)	2 (4%)
FOLLICULAR CYST, NOS			1 (2%)
DEGENERATION, CYSTIC	1 (2%)	3 (6%)	
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)
#THYROID FOLLICLE	(49)	(50)	(48)
HYPERPLASIA, CYSTIC			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*PENIS	(49)	(50)	(49)
HEMORRHAGE			1 (2%)
*PREPUCE	(49)	(50)	(49)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
*PREPUTIAL GLAND	(49)	(50)	(49)
DILATATION, NOS		1 (2%)	1 (2%)
CYST, NOS		1 (2%)	
CYSTIC DUCTS	1 (2%)	2 (4%)	2 (4%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			2 (4%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		2 (4%)	
ABSCESS, CHRONIC			1 (2%)
*SEMINAL VESICLE	(49)	(50)	(49)
DILATATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	3 (6%)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)
*EPIDIDYMIS	(49)	(50)	(49)
INFLAMMATION, GRANULOMATOUS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(49)
CORPORA AMYLACEA	1 (2%)	17 (34%)	
#BRAIN/THALAMUS	(49)	(50)	(49)
CORPORA AMYLACEA	27 (55%)		
#CEREBELLUM	(49)	(50)	(49)
PERIVASCULAR CUFFING		1 (2%)	
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(49)	(50)	(49)
CYST, NOS			1 (2%)

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			
*KNEE JOINT	(49)	(50)	(49)
METAPLASIA, CARTILAGINOUS		1 (2%)	
BODY CAVITIES			
*MESENTERY	(49)	(50)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)		
NECROSIS, FAT	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(49)
INFLAMMATION, SUPPURATIVE		2 (4%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	3	7
AUTOLYSIS/NO NECROPSY	1		

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED DIETS CONTAINING ZIRAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ULCER, NOS		1 (2%)	
INFLAMMATION, CHRONIC	3 (6%)		
GRANULATION, TISSUE			1 (2%)
FIBROSIS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(49)	(50)
HYPERPLASIA, NOS			1 (2%)
#LUNG	(50)	(49)	(50)
INFLAMMATION, FOCAL	4 (8%)		
INFLAMMATION, MULTIFOCAL	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)		1 (2%)
PNEUMONIA, ASPIRATION			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
BRONCHOPNEUMONIA SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			2 (4%)
PNEUMONIA, CHRONIC MURINE		2 (4%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)	2 (4%)	1 (2%)
REACTION, FOREIGN BODY			2 (4%)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
PERIVASCULAR CUFFING		2 (4%)	
PIGMENTATION, NOS	1 (2%)		
HYPERPLASIA, ADENOMATOUS	18 (36%)	27 (55%)	26 (52%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	4 (8%)	10 (20%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)	7 (14%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIESIS			1 (2%)
*BLOOD	(50)	(50)	(50)
LEUKEMOID REACTION	1 (2%)		
#BONE MARROW	(50)	(49)	(50)
ATROPHY, NOS		1 (2%)	
MYELOFIBROSIS		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
HYPERPLASIA, NEUTROPHILIC	1 (2%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)		
#SPLEEN	(49)	(49)	(50)
ANGIECTASIS			1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
HEMATOPOIESIS	3 (6%)	1 (2%)	
#MANDIBULAR L. NODE	(49)	(50)	(50)
EDEMA, NOS		1 (2%)	
#LUMBAR LYMPH NODE	(49)	(50)	(50)
HYPERPLASIA, PLASMA CELL	1 (2%)		
#MESENTERIC L. NODE	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)	
#LUNG/BRONCHUS	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)	
#LUNG	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)		
#PEYER'S PATCH	(46)	(46)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
#URINARY BLADDER	(46)	(50)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(49)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*PULMONARY ARTERY	(50)	(50)	(50)
HYPERTROPHY, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
NECROSIS, COAGULATIVE	1 (2%)		
CYTOPLASMIC VACUOLIZATION		1 (2%)	1 (2%)
FOCAL CELLULAR CHANGE		1 (2%)	
ANGIECTASIS			2 (4%)
*GALLBLADDER	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#PANCREAS	(48)	(48)	(47)
CYSTIC DUCTS		1 (2%)	
EDEMA, NOS	1 (2%)		
INFLAMMATION, NECROTIZING	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
#PANCREATIC ACINUS	(48)	(48)	(47)
ATROPHY, NOS		1 (2%)	
#GASTRIC SUBMUCOSA	(49)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)		
INFLAMMATION, NECROTIZING	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(47)	(50)	(50)
CYST, NOS	1 (2%)		
#THYROID	(47)	(43)	(48)
CYSTIC FOLLICLES		1 (2%)	21 (44%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FOLLICULAR CYST, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
DEGENERATION, CYSTIC	3 (6%)	3 (7%)	
ATROPHY, SENILE	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		1 (2%)
#THYROID FOLLICLE	(47)	(43)	(48)
ATROPHY, FOCAL			1 (2%)
HYPERPLASIA, CYSTIC			5 (10%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)		
#UTERUS	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	3 (6%)	1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	4 (8%)	2 (4%)	
HYPERPLASIA, CYSTIC	19 (38%)		
#ENDOMETRIAL GLAND	(50)	(50)	(50)
HYPERPLASIA, CYSTIC	23 (46%)	41 (82%)	46 (92%)
#OVARY	(44)	(50)	(50)
CYSTIC FOLLICLES	1 (2%)		3 (6%)
FOLLICULAR CYST, NOS	2 (5%)		
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
ABSCESS, NOS	1 (2%)		
ABSCESS, CHRONIC		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
MALACIA		1 (2%)	
#BRAIN/THALAMUS	(50)	(50)	(50)
CORPORA AMYLACEA	5 (10%)		
PSAMMOMA BODIES	4 (8%)		
SPECIAL SENSE ORGANS			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*FEMUR	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY			1 (2%)
*ABDOMINAL MUSCLE	(50)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
*MESENTERY	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
NECROSIS, FAT	3 (6%)	1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	1

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

APPENDIX E

ANALYSIS OF ZIRAM (LOT NO. 319400)
MIDWEST RESEARCH INSTITUTE

APPENDIX E

A. ELEMENTAL ANALYSIS

Element	C	H	N	S	Zn
Theory	23.56	3.96	9.16	41.94	21.38
Determined	22.79 22.97	3.93 4.00	8.95 9.16	39.56 39.59	23.1 ± 0.3 (δ)%

B. MELTING POINT

Determined	Literature Values
249° to 255°C (capillary visual) gray residue remained 255° to 258°C (Dupont 900 DTA)	249° to 252°C (Maasen, 1958)

C. THIN-LAYER CHROMATOGRAPHY

1. System 1

   Plates: Silica gel 60 F-254
   Amount spotted: 50 and 150 μg

   Solvent system: Chloroform, 100%

   R_f: 0.80 (major), 0.67 (minor), 0.20 (minor, streak to origin)

   R_{st}: 0.99, 0.67, 0.25

   Ref. Standard: Ziram (Chem Service, Lot No. PS21)
   Visualization: Ultraviolet, 254 nm and 366 nm, and zincon (Fisher Chemical Co.)

2. System 2

   Plates: Aluminum oxide, type E, activated 1 hour at 140°C

   Amount spotted: 100 and 300 μg

   Solvent system: Methanol: concentrated aqueous ammonium hydroxide (75:25)

   R_f: 0.61 (major), 0.52 (minor), origin (minor)

   R_{st}: 0.94, 0.80, origin

APPENDIX E

D. HIGH-PRESSURE LIQUID CHROMATOGRAPHY

Instrument: Waters ALC 202

Column: C_{18} μBondapak, 300 x 4 mm I.D.

Detector: Ultraviolet, 254 nm

Solvent: 45% acetonitrile in water

Flow: 1.5 ml/min

Results: Major peak and two minor peaks, one of which had the same retention time as a thiram standard.

This sample has a fairly large percent composition of inert material which was not soluble in acetonitrile. A suspension formed, and solutions had to be centrifuged.

Peak	Retention Time (min)	Retention Time (Relative to Ziram)	Area (Relative to Ziram)
1	6.7	0.39	11.0
2	13.4	0.79	2.8
3	17.0	1.00	100.0

Peak No. 1 had the same retention time as thiram; when compared with a thiram standard, ziram contained 6.47% by weight thiram. There was no peak with the same retention time as the bis(dimethylthiocarbamyl) sulfide standard.

E. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12

Cell: 1% potassium bromide pellet

Results: See Figure 5

Peaks at ~3,500 and 1,630 cm^{-1} in literature spectrum (Sadtler Standard Spectra) but not in sample spectrum

2. Ultraviolet/Visible

Instrument: Cary 118

Determined:

λ max(nm)	ε x 10^3
430	0.154 ± 0.08 (δ)
275	0.177 ± 0.6 (δ)
257	30.1 ± 2 (δ)

Solvent: Acetonitrile

Literature Values:

λ max(nm)	ε x 10^3
~281	~18.9
262	29.0
(no visible absorption reported) (Romagnoli et al., 1969)	

Solvent: Chloroform

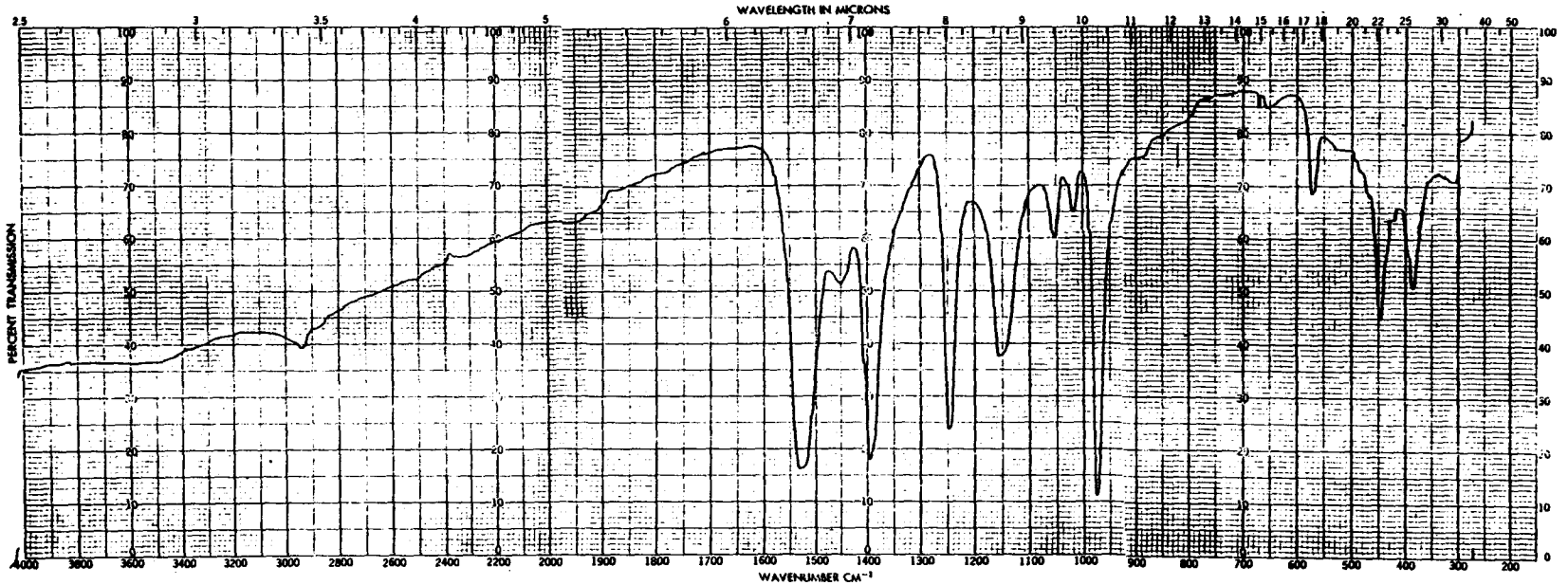

Figure 5. Infrared Absorption Spectrum of Ziram (Lot No. 319400)

3. Nuclear Magnetic Resonance

Instrument: Varian HA-100

Solvent: Dimethylsulfoxide-d_6 with internal tetramethylsilane

Spectrum recorded on the supernatant solution

Assignments: (See Figure 6)

(a) s, δ 3.40 ppm
(b) s, δ 3.35 ppm (impurity)

Integration Ratios:

(a) 12.0
(b) Could not be integrated separately from ziram peak

No literature spectrum found

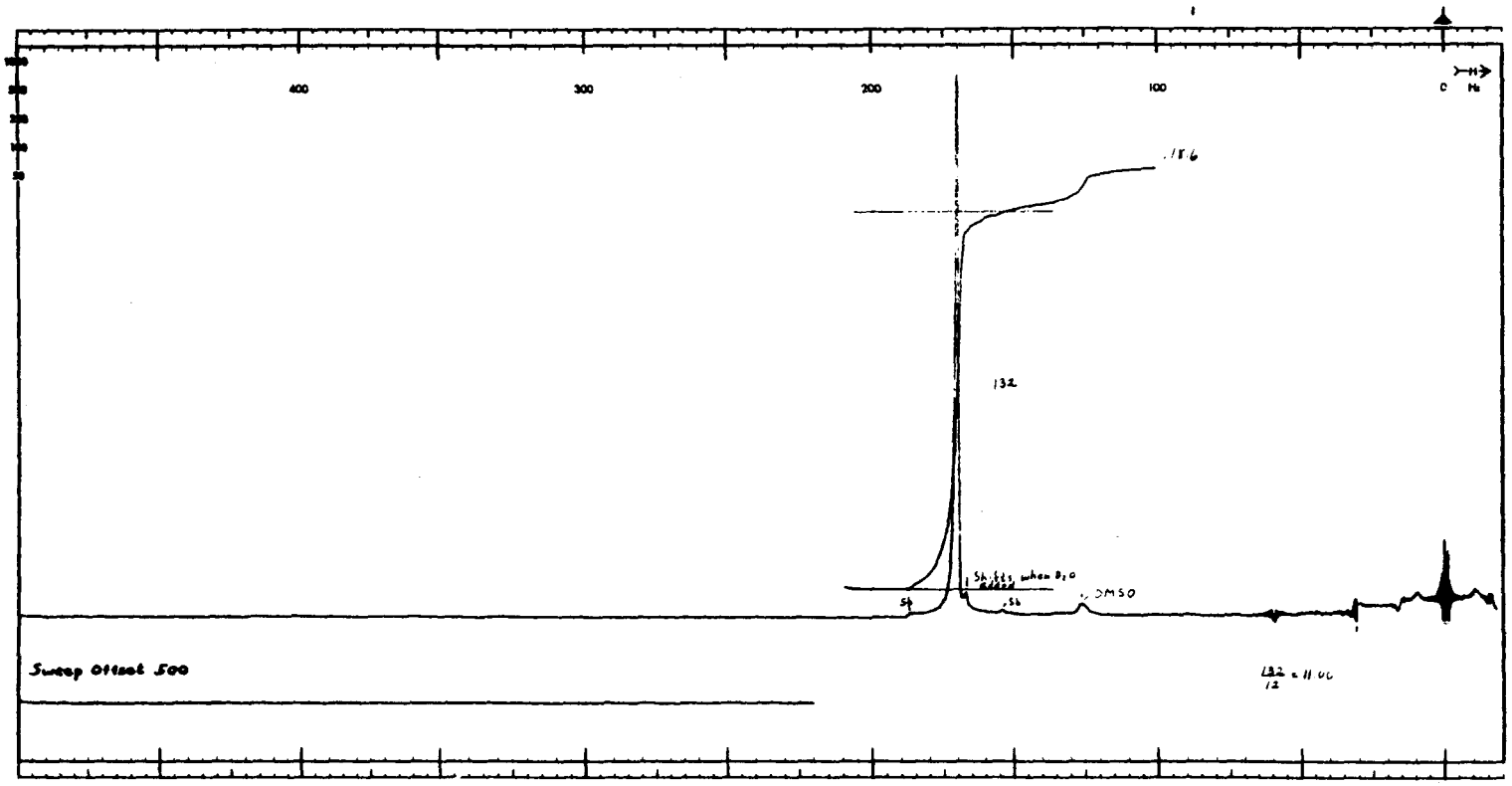

Figure 6. Nuclear Magnetic Resonance Spectrum of Ziram (Lot No. 319400)

APPENDIX F

ANALYSIS OF FORMULATED DIETS FOR STABILITY OF ZIRAM MIDWEST RESEARCH INSTITUTE

APPENDIX F

A. MIXING AND STORAGE: Ziram (2.4118 g) and Wayne Lab-Blox® Rodent Feed (21.8276 g) were mixed in a mortar. Samples of the mixture were removed and stored for 2 weeks at -20°, 5°, 25°, and 45°C, respectively.

B. EXTRACTION AND ANALYSIS: Half-gram samples of the chemical/feed mixtures were combined with 50 ml of chloroform in an ultrasonic vibratory bath for 1 minute and then triturated for 1 minute using a Polytron high-speed blender. The resulting mixture was filtered through a fine-pore paper (Whatman No. 42), and the feed residue was reextracted in this same manner with 50 ml fresh chloroform. The combined filtrates were made up to exactly 100 ml with additional chloroform. Five-ml aliquots of these solutions were each mixed with 5 ml of freshly prepared aqueous 0.0024 M cuprous chloride solution, and this was made up to 100 ml with 95% ethanol. The optical absorbance of these final solutions was measured at 395 nm.

Instrument: Cary 118

C. RESULTS:

Sample (°C)	Average Percent Compound Recovered *(a)*
-20	9.9 ± 0.3
5	10.0 ± 0.3
25	10.2 ± 0.3
45	9.9 ± 0.3

(a) Corrected for spiked recovery yield of 92.3%. Theoretical yield, 9.95%.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF ZIRAM SOUTHERN RESEARCH INSTITUTE

Three-gram samples of the chemical/feed mixtures were combined with 50 ml of chloroform and triturated for 1.5 minutes using a Polytron high-speed blender. The resulting mixture was filtered through a fiberglass filter paper and the feed residue was reextracted in this same manner with 50 ml of fresh chloroform. The combined filtrates were made up to exactly 100 ml with additional chloroform. Five-milliliter aliquots* of these solutions were mixed with 5 ml aqueous 0.0024 M cuprous chloride solution** and diluted to 50 ml with 95% ethanol. The optical absorbance of these final solutions was measured at 395 nm.

Plain feed samples were made up in the same manner as the chemical/feed mixtures. Spiked feed references were made by weighing the plain feed and adding an accurately known weight of the pure compound. Plain and spiked feed samples were analyzed with each set of dosage mixture samples.

The method described above was used from June, 1977 until July, 1979 by Southern Research Institute (SoRI) and was originally developed by Midwest Research Institute (MRI) for analysis at the 100,000 ppm level. However, the levels being mixed for the chronic study were only 300-1200 ppm. Due to the insensitivity of this method, most of the analyses performed in this time period produced results that were usually more than 10% lower than the target concentration. A simple modification** was made to attempt to correct this deficiency since the blank values were extremely high. However, it did not appear to help appreciably. MRI reported on a new procedure based on atomic absorption in July, 1979 that was sensitive to 100 ppm. SoRI initiated use of this procedure immediately (August, 1979) and the majority of the analyses conducted between August, 1979 and April, 1980 using this procedure indicated that the samples were formulated properly. This would imply that most of the formulations in this study were properly mixed. The procedure used in the last eight months of the study was as follows:

Two-gram feed samples were weighed into 50 ml, acid-washed, Pyrex beakers. Five ml of acetone was added to each chemical/feed mixture and to the undosed feed blanks. Spiked samples (standard curve) were prepared by adding 5 ml of a ziram stock solution in acetone to undosed feed.

The samples were covered with acid-washed watch glasses and placed in a cold muffle furnace. The temperature was set for approximately 800° F and held constant until samples were completely ashed. The samples were allowed to cool to room temperature and Ultrex (J.T. Baker Chemical Co.) nitric acid (2 ml) and distilled water (8 ml) were added to each sample. The solutions were then refluxed for 1 hour.

The samples were diluted to 25 ml with water. An aliquot (2 ml) of these samples was further diluted to 50 ml with 5% nitric acid in water.

The diluted solutions were then analyzed by atomic absorption spectroscopy using the following instrumental parameters.

Instruments: Perkin-Elmer AA Model 603

Hollow cathode lamp current: 20 mA

Wavelength: 215.2 nm (The instrument was calibrated routinely with a zinc standard before the chemical/vehicle analyses were performed.)

Slit width: 0.2 nm

Flame: Air/acetylene

Gas flows: Air, 30 psi
Acetylene, 12 psi

Background correction: Hydrogen lamp

Results: See Table G1

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* Method Modification by SoRI: 15-ml aliquots of extracts were mixed with 15 ml of the cuprous chloride solution.

** Method Modification:
Aqueous cuprous chloride:
100 mg cuprous chloride + 20 ml 0.3 N hydrochloric acid diluted to 100 ml with 95% ethanol.
This solution was made fresh on each analysis day.

TABLE G1. ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF ZIRAM *(a)*

Date Mixed	Week Used	Concentration *(b)* of Ziram in Feed for target concentration of 300 ppm	600 ppm	1,200 ppm
10/17/77	10/24/77	360	620	1,210
11/18/77	11/25/77	230	540	1,080
12/13/77	12/20/77	280	550	
			510	1,070
12/16/77	12/23/77	230	490	
01/17/78	01/24/78	250	470	
			480	
02/21/78	02/28/78			
02/23/78	02/30/78			1,200
03/14/78	03/21/78		680	
03/15/78	03/22/78			760
03/21/78	03/28/78		490	1,120
04/18/78	04/25/78	170	420	
05/16/78	05/23/78		500	1,140
06/20/78	06/27/78	170	480	1,130
07/11/78	07/18/78	210	480	1,040
08/8/78	08/15/78	230	500	
09/5/78	09/12/78	230	450	1,090
10/3/78	10/10/78	250	440	
11/6/78	11/13/78	240	520	
11/21/78	11/28/78	260	600	1,110
12/19/78	12/26/78		485	
12/21/78	12/26/79	200		1,080
01/23/79	01/30/79		530	1,030
01/25/79	01/30/79	220		
02/20/79	02/27/79	210	490	
03/13/79	03/20/79			1,080
03/15/79	03/20/79	250	620	
04/12/79	04/17/79	220	500	
05/17/79	05/24/79	180	490	
06/13/79	06/19/79	180	440	
07/10/79	07/17/79	200	460	
Mean (ppm)		227	509	1,081
Standard deviation		42.7	61.6	106
Coefficient of variation (%)		18.8	13.9	9.8
Range (ppm)		170-370	420-680	760-1,210
Number of samples		21	26	14
08/7/79 *(c)*	08/14/79	340	740	
09/4/79 *(c)*	09/11/79	300	600	
10/2/79 *(c)*	10/9/79	320	600	
10/30/79 *(c)*	11/6/79	280	660	
11/27/79 *(c)*	12/4/79	300	620	
12/26/79 *(c)*	01/1/80	280	560	
01/22/80 *(c)*	01/29/80	320	540	
02/19/80 *(c)*	02/25/80	300		
02/22/80 *(c)*	02/25/80		540	
03/18/80 *(c)*	03/25/80	370	540	
		370		
Mean (ppm)		318	600	
Standard deviation		32.9	67.1	
Coefficient of variation (%)		10.3	11.2	
Range (ppm)		280-370	540-740	
Number of samples		10	9	

(a) The mouse study began in June 1977 and the rat study in April 1978.
(b) The data presented are the average of the results of duplicate analyses.
(c) New analytical procedure used.

APPENDIX H

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE

TABLE H1. HISTORICAL INCIDENCES OF THYROID TUMORS IN CONTROL MALE F344/N RATS *(a)*

	C-Cell Adenoma	C-Cell Carcinoma	Combined
Battelle	3/238 (1.3%)	11/238 (4.6%)	14/238 (5.9%)
Dow	7/89 (7.8%)	1/89 (1.1%)	8/89 (9.0%)
Frederick	38/462 (8.2%)	8/462 (1.7%)	46/462 (10.0%)
Hazleton	1/192 (0.5%)	9/192 (4.7%)	10/192 (5.2%)
Litton	35/655 (5.3%)	11/655 (1.7%)	46/655 (7.0%)
Mason	33/940 (3.5%)	29/940 (3.1%)	62/940 (6.6%)
Southern (b)	48/584 (8.2%)	18/584 (3.1%)	65/584 (11.1%)
Total	165/3160 (5.2%)	87/3160 (2.8%)	251/3160 (7.9%)
Range			
High	8/49 (16.3%)	4/48 (8.3%)	10/49 (20.4%)
Low	0/89 (0.0%)	0/53 (0.0%)	0/47 (0.0%)

(a) Data as of January 17, 1981. Range is presented for groups in which at least 35 animals were examined microscopically. Interim death (<104 weeks) animals are included.
(b) Southern Research Institute conducted the bioassay described in this report.

TABLE H2. HISTORICAL INCIDENCES OF MAMMARY TUMORS IN CONTROL FEMALE F344/N RATS *(a)*

	Adenocarcinoma	Fibroadenoma
Battelle	2/238 (0.8%)	42/238 (17.7%)
Dow	3/100 (3.0%)	22/100 (22.0%)
Frederick	4/470 (0.9%)	74/470 (15.7%)
Hazleton	2/200 (1.0%)	39/200 (19.5%)
Litton	4/737 (0.5%)	82/737 (11.1%)
Mason	18/1071 (1.7%)	286/1071 (26.7%)
Southern *(b)*	13/591 (2.2%)	157/591 (26.6%)
Total	46/3407 (1.4%)	702/3407 (20.6%)
Range		
High	3/50 (6.0%)	23/50 (46.0%)
Low	0/52 (0.0%)	4/50 (8.0%)

(a) Data as of January 17, 1981. Range is presented for groups in which at least 35 animals were examined microscopically. Interim death (<104 weeks) animals are included.
(b) Southern Research Institute conducted the bioassay described in this report.

TABLE H3. HISTORICAL INCIDENCES OF LUNG TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE *(a)*

	Alveolar/Bronchiolar		Adenoma or Carcinoma Combined
	Adenoma	Carcinoma	
Battelle	13/349 (3.7%)	5/349 (1.4%)	18/349 (5.2%)
Dow	5/95 (5.3%)	1/95 (1.1%)	6/95 (6.3%)
Frederick	18/428 (4.2%)	11/428 (2.6%)	29/428 (6.8%)
Hazleton	5/99 (5.1%)	1/99 (1.0%)	6/99 (6.1%)
Litton	25/502 (5.0%)	4/502 (0.8%)	29/502 (5.8%)
Mason	50/814 (6.1%)	21/814 (2.6%)	71/814 (8.7%)
Southern *(b)*	18/501 (3.6%)	8/501 (1.6%)	25/501 (5.0%)
Total	134/2788 (4.8%)	51/2788 (1.8%)	184/2788 (6.6%)
Range:			
High	7/50 (14.0%)	3/50 (6.0%)	8/50 (16.0%)
Low	0/50 (0.0%)	0/50 (0.0%)	0/50 (0.0%)

(a) Data as of January 17, 1981. Range is presented for groups in which at least 35 animals were examined microscopically. Interim death (<104 weeks) animals are included.
(b) Southern Research Institute conducted the bioassay described in this report.

TABLE H4. HISTORICAL INCIDENCES OF LIVER TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE *(a)*

	Adenoma	Carcinoma	Combined
Battelle	5/348 (1.4%)	21/348 (6.0%)	25/348 (7.2%)
Dow	3/98 (3.1%)	5/98 (5.1%)	7/98 (7.1%)
Frederick	10/431 (2.3%)	13/431 (3.0%)	22/431 (5.1%)
Hazleton	1/100 (1.0%)	4/100 (4.0%)	5/100 (5.0%)
Litton	21/511 (4.1%)	11/511 (2.2%)	32/511 (6.3%)
Mason	35/809 (4.3%)	39/809 (4.8%)	73/809 (9.0%)
Southern *(b)*	14/498 (2.8%)	18/498 (3.6%)	31/498 (6.2%)
Total	89/2795 (3.2%)	111/2795 (4.0%)	195/2795 (7.0%)
Range			
High	9/49 (18.4%)	7/48 (14.6%)	10/49 (20.4%)
Low	0/50 (0.0%)	0/50 (0.0%)	0/50 (0.0%)

(a) Data as of January 17, 1981. Range is presented for groups in which at least 35 animals were examined microscopically. Interim death (<104 weeks) animals are included.
(b) Southern Research Institute conducted the bioassay described in this report.

TABLE H5. HISTORICAL INCIDENCES OF LIVER TUMORS IN CONTROL MALE B6C3F$_1$ MICE *(a)*

	Adenoma	Carcinoma	Combined
Battelle	30/347 (8.7%)	75/347 (21.6%)	102/347 (29.4%)
Dow	13/98 (13.3%)	33/98 (33.7%)	46/98 (46.9%)
Frederick	31/407 (7.6%)	100/407 (24.5%)	131/407 (32.2%)
Hazleton	3/49 (6.1%)	17/49 (34.7%)	20/49 (40.8%)
Litton	47/499 (9.4%)	85/499 (17.0%)	132/499 (26.5%)
Mason	71/800 (8.9%)	198/800 (24.8%)	264/800 (33.0%)
Southern *(b)*	42/490 (8.6%)	94/490 (19.2%)	134/490 (27.3%)
Total	237/2690 (8.8%)	602/2690 (22.4%)	829/2690 (30.8%)
Range			
High	11/50 (22.0%)	24/54 (44.4%)	29/50 (58.0%)
Low	0/49 (0.0%)	4/50 (8.0%)	8/50 (16.0%)

(a) Data as of January 17, 1981. Range is presented for groups in which at least 35 animals were examined microscopically. Interim death (<104 weeks) animals are included.

(b) Southern Research Institute conducted the bioassay described in this report.

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