NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 211

# CARCINOGENESIS STUDIES OF C.I. ACID ORANGE 10

## (CAS NO. 1936-15-8)

# IN F344/N RATS AND B6C3F$_1$ MICE

# (FEED STUDIES)

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 STUDIES
# OF
# C.I. ACID ORANGE 10

## (CAS NO. 1936-15-8)

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


NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709

October 1987

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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 Studies should be directed to the National Toxicology Program, located at Research Triangle Park, NC 27709 (919-541-3780).**

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.

*Special Note:* This Technical Report was peer reviewed in public session in June and October 1980 and approved in February 1981. Thereafter, the NTP adopted the policy that the experimental data and laboratory records from all NTP Toxicology and Carcinogenesis studies not yet printed and distributed would be audited. [A summary of the data audit is presented in Appendix I.] Consequently, printing and distribution of this Technical Report have been delayed and the format differs from that of Technical Reports peer reviewed more recently. Also, this Technical Report does not utilize the levels of evidence of carcinogenicity adopted for the interpretative conclusions in June 1983. This final Technical Report supersedes all previous drafts of this report that have been distributed.

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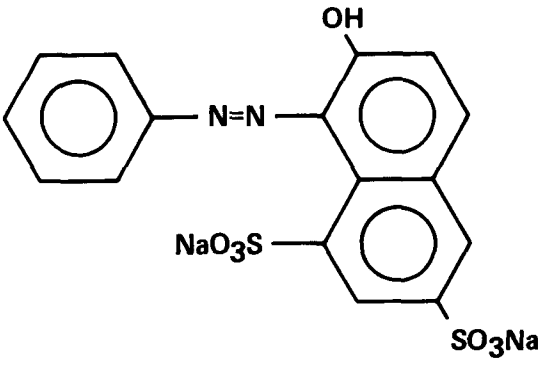


## C.I. ACID ORANGE 10

(7-hydroxy-8-(phenylazo)-1,3-naphthalenedisulfonic acid, disodium salt)

CAS NO. 1936-15-8

Colour Index No. 16230

$C_{16}H_{10}N_2O_7S_2 \cdot 2Na$ Mol. Wt. 452.37

## ABSTRACT

Carcinogenesis studies of 80% pure C.I. Acid Orange 10 (a monoazo textile dye) were conducted by feeding to groups of 50 male and 50 female F344/N rats diets containing 1,000 or 3,000 ppm C.I. Acid Orange 10 for 103 weeks. Groups of 50 male and 50 female B6C3F$_1$ mice were fed diets containing 3,000 or 6,000 ppm for 103 weeks. Groups of 90 male and 90 female untreated rats and 50 male and 50 female untreated mice served as controls.

Mean body weights and clinical signs of control and dosed rats and mice were comparable. Because no toxic effects or consistent weight differences were observed, the rats and mice may have been able to tolerate higher doses.

In male rats with neoplastic nodules of the liver, the dose response trend was positive ($P<0.05$) and the incidence in the 3,000 ppm group was increased ($P<0.05$) compared to controls (control, 5/90, 6%; low dose, 3/50, 6%; high dose, 8/50, 16%). One male rat in the high dose group had both a neoplastic nodule and a carcinoma of the liver. This marginal increase in liver cell neoplasms may have been associated with the dietary administration of C.I. Acid Orange 10.

For both dose groups of male and female rats, leukemia was significantly ($P<0.05$) decreased in a dose related ($P<0.005$) trend (male: 22/90, 24%; 4/50, 8%; 3/50, 6%; female: 16/88,18%; 2/50, 4%; 0/50).

No compound-related nonneoplastic or neoplastic lesions were observed in the female rats or in mice of either sex.

For 103 weeks C.I. Acid Orange 10 was given in the diets of male and female F344/N rats (0, 0.1%, or 0.3%) and of male and female B6C3F$_1$ mice (0, 0.3%, or 0.6%). Under these conditions, there was no evidence of carcinogenicity for male and female F344/N rats or for male and female B6C3F$_1$ mice.

# CONTRIBUTORS

The carcinogenesis studies of C.I. Acid Orange 10 were conducted at Battelle Columbus Laboratories under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the Carcinogenesis Testing Program. The two-year studies were begun in December 1976 for rats, January 1977 for male mice, and February 1977 for female mice. The studies concluded in December 1978 for rats and January 1979 for mice.

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*(a)* Did not attend 27 June 1980 meeting.
*(b)* Did not attend 15 October 1980 meeting.
*(c)* Did not attend 18 February 1981 meeting.

# SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF C.I. ACID ORANGE 10

On 27 June and 15 October 1980 and on 18 February 1981 this technical report on the carcinogenesis studies of C.I. Acid Orange 10 underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and Associated Panel of Experts. The public review meetings began at 9:00 a.m. in the Switzer Building, 330 C Street, S.W., Washington, DC (27 June) or in Conference Room 6, Building 31, National Institutes of Health, Bethesda, MD (15 October and 18 February). The following precis represents the critiques made by the principal reviewers, as well as comments from and discussion by the Peer Review Panel, NTP staff, and attendees.

*Peer Review Meeting of 27 June 1980*

Dr. Nielsen, a principal reviewer for the report on the carcinogenesis studies of C.I. Acid Orange 10, pointed out discrepancies in the reporting of neoplastic nodules in male rats in various sections of the report, which needed to be resolved before any conclusions could be reached. He also commented that the doses selected for rats in the two-year studies (1,000 ppm and 3,000 ppm) appeared to be too low and that in a previous NCI study, a metabolite of C.I. Acid Orange 10 (aniline) had been shown to be carcinogenic at doses 2 to 3 times higher than the doses of C.I. Acid Orange 10 in the present study. In the 13-week studies, he felt that a better description and more consistent terminology were needed for the pigment observed in the renal proximal tubules of the rats and mice, particularly since it was associated with tubular degeneration in male rats.

Dr. Whittemore, a second principal reviewer, agreed with Dr. Nielsen's conclusions. A motion that the report be returned to NTP for clarification of the discrepancies noted above was approved unanimously.

*Peer Review Meeting of 15 October 1980*

Dr. Nielsen, a principal reviewer, stated that the interpretation of the significance of the hepatic and mesothelial tumors which occurred in male rats was difficult since it did not appear that the compound was tested at its maximum tolerated dose (MTD). He also indicated that a better description, chemical characterization, and consistent terminology were needed for the pigment observed in the renal proximal tubules of both rats and mice in the 13-week studies.

Dr. Harper, a second principal reviewer, agreed with Dr. Nielsen's conclusions, adding that the absence of the splenic and renal lesions in the two-year studies (observed in both species in the 13-week studies) supported the opinion that the doses used in the two-year studies were below the MTD. It was also agreed that a comment should be added to the discussion section concerning the marked reduction from controls in lymphocytic leukemia in both male and female rats at both doses.

A motion to return the report to NTP for review of the pathology slides and clarification of the renal tubular pigmentation in the 13-week study was unanimously approved. Dr. Nielsen also recommended that NTP consider retesting C.I. Acid Orange 10 in male rats at doses of 3,000 ppm and 6,000 ppm for two years.

*Peer Review Meeting of 18 February 1981*

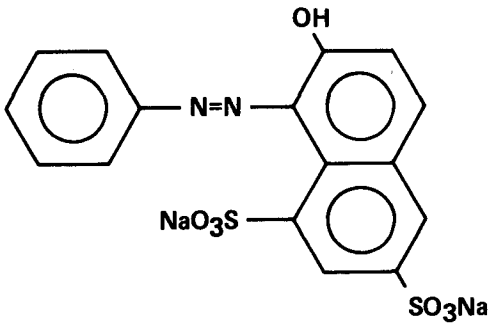
Dr. Nielsen, a principal reviewer, stated that the doses chosen for the two-year studies were based on the splenic and renal lesions observed in the 13-week studies at the next highest dose. The splenic lesions, characterized by subsequent examination as splenic hemosiderosis, erythroid metaplasia, and capsular fibrosis, were considered life-threatening. Upon reexamination, the renal tubular pigment noted in the original report was not considered life-threatening. He said the report was now acceptable and agreed that C.I. Acid Orange 10 was not carcinogenic for male or female F344/N rats or B6C3F$_1$ mice. He stressed that a more complete description of microscopic lesions observed in the 13-week studies is needed in the reports to provide reviewers with a better understanding of the dose criteria for the two-year studies. Dr. Harper, another principal reviewer, agreed with Dr. Nielsen.

Dr. McConnell, NTP, said that important lesions in 13-week studies would be more adequately described in the future to better assist reviewers in judging the adequacy of dose selection for the two-year studies. Dr. Williams requested that the discussion section be expanded so as to become similar to that for other monoazo dyes in relation to possible correlations between lipid solubility, metabolism, and carcinogenicity or non-carcinogenicity.

A motion by Dr. Nielsen, seconded by Dr. Harper, to accept the report on the carcinogenicity studies of C.I. Acid Orange 10 was approved by a vote of 9 to 0, with one abstention.

# I. INTRODUCTION

# I. INTRODUCTION




**C.I. ACID ORANGE 10**

**(7-hydroxy-8-(phenylazo)-1,3-naphthalenedisulfonic acid, disodium salt)**

**CAS NO. 1936-15-8**

**Colour Index No. 16230**

**$C_{16}H_{10}N_2O_7S_2 \cdot 2Na$ Mol. Wt. 452.37**

C.I. Acid Orange 10 (Acid Orange 10, Orange 10, Orange G) is a monoazo dye used to stain biological materials, paper, and wood and to dye leather, wool, and silk; it is also used in inks and pencil coatings (Society for Dyers and Colourists, 1971). First synthesized in 1878 by Baum, C.I. Acid Orange 10 can be made by diazotizing aniline and coupling the resulting diazonium salt with 2-naphthol-6,8-disulfonic acid (IARC, 1975). Production in the U.S. was first reported in 1914, and in 1921 about 42,000 kg were produced. C.I. Acid Orange 10 (yellowish-red crystals or leaflets) was used as a drug and cosmetic additive in the United States until October 1966, when its use for those applications was cancelled (CFR, 1974). In 1978 65,000 kg were produced in the United States (USITC, 1979) and in 1981, 67,000 kg were produced (USITC, 1982).

*Toxicity*

Enlarged spleens were observed in male and female albino rats fed diets containing 2,500, 5,000, 10,000, or 20,000 ppm C.I. Acid Orange 10 for 90 days (Hansen et al., 1960). Heinz bodies in the erythrocytes accompanied by anemia, methemoglobinemia, reticulocytosis, and splenomegaly were detected in CFE rats fed diets containing 5,000 ppm for 105 days (Gaunt et al., 1971).

*Metabolism*

In rats, the azo linkage of C.I. Acid Orange 10 is reduced both by liver enzymes (Daniel, 1967) and by intestinal bacteria (Ryan et al., 1968). When rats were given single oral doses of C.I. Acid Orange 10 (250 mg/kg body weight), 61% of the dose was excreted in the urine as p-aminophenol and 6% was excreted in urine and 22% in feces as aniline (Walker et al., 1972). In rabbits given 500 mg/kg Orange G in the diet, 40% was excreted in urine as p-aminophenol, 3% as o-aminophenol, and 0.6% as aniline (Daniel, 1962). In humans receiving C.I. Acid Orange 10 (20 mg/kg body weight), 95% of the dose was excreted in the urine as p-aminophenol, 0.5% as aniline, and 1.3% as unmodified dye (Walker et al., 1972). Humans convert aniline to urinary conjugates of p-aminophenol (IARC, 1982). Figure 1 shows the comparative metabolic pathways.

*Mutagenicity*

C.I. Acid Orange 10 was not mutagenic in *Salmonella typhimurium* TA1538 with or without metabolic activation; the major metabolite of the dye in rats and humans, p-aminophenol, was also not mutagenic in this test system (Garner and Nutman, 1977). C.I. Acid Orange 10 was tested for mutagenic activity in *Salmonella* TA98, TA100, TA1535, and TA1537 (with and without exogenous metabolic activation supplied by 9000 × g microsomal fractions from Aroclor 1254®-induced Sprague-Dawley rat or Syrian golden hamster liver). Samples were preincubated prior to plating in triplicate, and each series was repeated. The results were negative (NTP, unpublished data). Three other azo dyes (Sudan yellow, Ponceau R, and Ponceau de

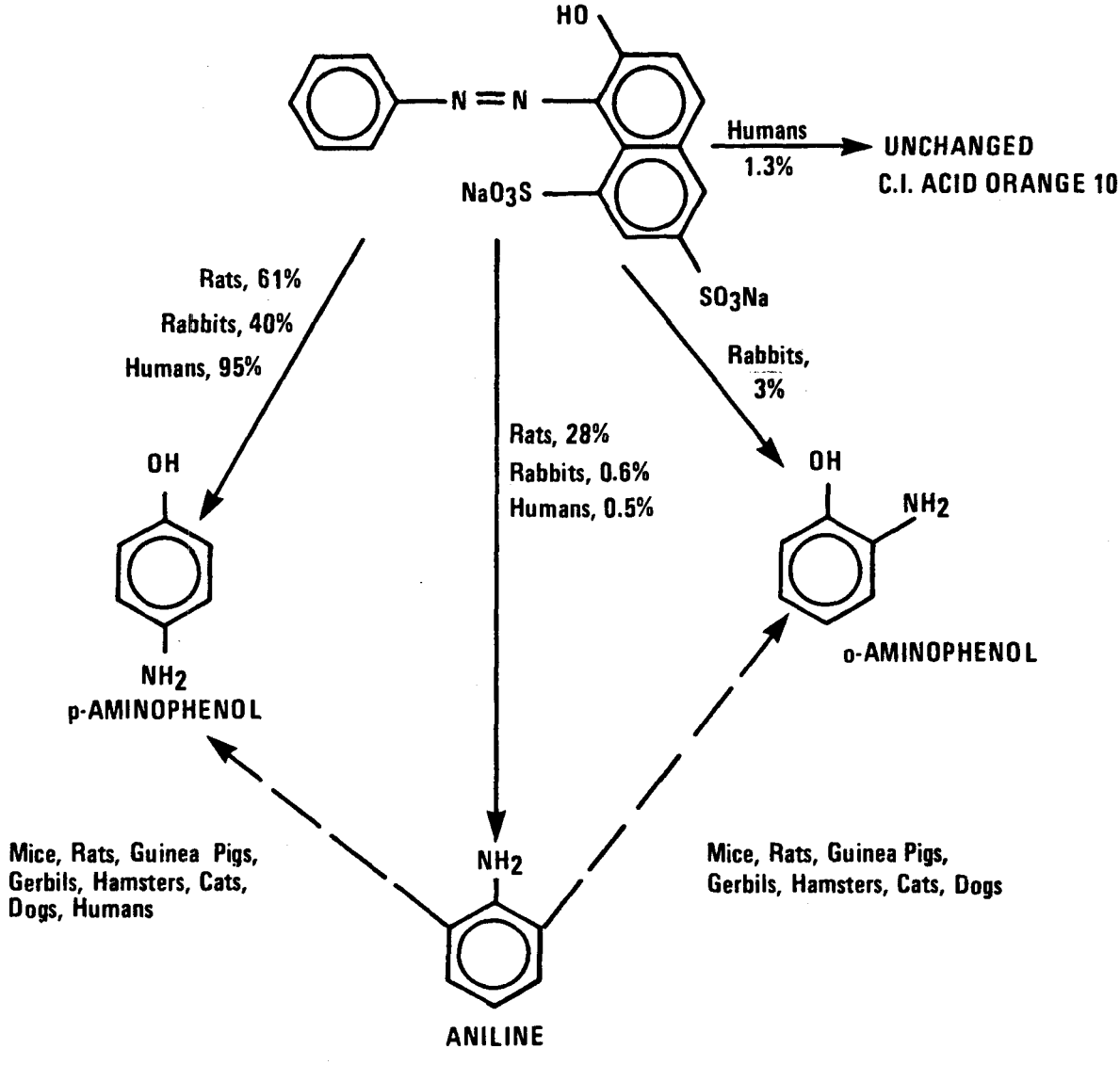



Figure 1. C.I. Acid Orange 10 Metabolism in Rats, Rabbits, and Humans

Xylidine), considered to be carcinogenic in animals, were not mutagenic for *S. typhimurium* TA1538 (Garner and Nutman, 1977).

*Carcinogenicity*

Other azo dyes structurally similar to C.I. Acid Orange 10 [those having at least the hydroxyphenylazo (or naphthalenylazo) naphthalene disulfonic acid moiety] have been tested for carcinogenicity (IARC, 1975): *amaranth*—studies could not be evaluated; *carmoisine*—one 80-week diet study (100-12,500 ppm) in mice gave no evidence of carcinogenicity; *Evans blue*—intraperitoneal injection caused sarcomas of the reticuloendothelial system in the liver; *ponceau MX*—caused liver cell tumors in mice (2,000-50,000 ppm diet for 19 months) and rats (2,500-10,000 ppm diet for two years); *ponceau 3R*—induced liver cell tumors in rats (40,000 ppm diet for 19 months or 5,000-50,000 ppm diet for two years); *ponceau SX*—no carcinogenic response in mice (up to 20,000 ppm diet for two years) or rats (up to 50,000 ppm diet for two years); *sunset yellow FCF*—no evidence of carcinogenicity in mice (up to 20,000 ppm diet for two years) or in rats (up to 50,000 ppm for unspecified period); *trypan blue*—caused reticulum-cell sarcomas of the liver in rats after intraperitoneal or subcutaneous injection.

*D&C Red No. 9* (CAS No. 5160-02-1)—5-chloro-2-[(2-hydroxy-1naphthalenyl)azo]-4-methylbenzene sulfonic acid, barium salt—was given in the diet to groups of 50 male and female F344/N rats at doses of 0, 1,000, or 3,000 ppm and to groups of 50 male and female B6C3F$_1$ mice at concentrations of 0, 1,000, or 2,000 ppm for 103 weeks. Splenic sarcomas (male rats) and neoplastic nodules of the liver (male and female rats) were increased in treated groups compared to controls. No evidence of carcinogenicity was observed in male or female B6C3F$_1$ mice (NTP, 1982).

*Orange G* (C.I. Acid Orange 10) was tested for carcinogenicity in mice (sex and strain not given) by Cook et al. (1940), who gave weekly doses of 15-20 mg in water; in male and female type B heterozygous mice by Waterman and Lignac (1958), who gave 1 mg per day by diet for 500-700 days; and in rats (strain and sex not specified) by Klinke (1957), who administered 2,000 ppm in the diet for 245 days or 1,000 ppm in the diet for 400 days. As recorded by IARC (1975), no liver tumors were seen by Cook et al. (1940) and no tumors were observed by Klinke (1957); Waterman and Lignac (1958) found these tumor incidence rates: male controls, 7/109 (6.4%); female controls, 11/59 (18.6%); treated males, 12/113 (10.6%); and treated females, 15/78 (19.2%). None of these studies was considered adequate for evaluation (IARC, 1975).

*Aniline hydrochloride*—a metabolite of C.I. Acid Orange 10 in rats (28%), rabbits (0.6%), and in humans (0.5%)—was fed to groups of 50 male and female F344 rats and B6C3F$_1$ mice for 103 weeks at concentrations of 0 (25 controls of each sex), 3,000, or 6,000 ppm for rats and 0, 6,000, or 12,000 ppm for mice (NCI, 1978). No chemically related neoplastic effects were observed in B6C3F$_1$ mice. In male F344 rats, aniline hydrochloride induced hemangiosarcomas, fibrosarcomas, and sarcomas of the spleen. In male and female F344 rats, chemically caused fibrosarcomas or sarcomas were found in multiple organs of the body cavity.

In humans aniline produces dose-dependent increases in methemoglobin formation (IARC, 1982); short-term exposures cause headache, vertigo, and mental confusion, whereas chronic exposures result in anemia, anorexia, weight loss, and cutaneous lesions (NCI, 1978). Aniline has been produced commercially since 1847. As stated by the IARC (1982): "The high risk of bladder cancer observed originally in workers in the aniline dye industry was probably due to exposure to chemicals other than aniline. Studies of individuals exposed to aniline but to no other known bladder carcinogens have shown little evidence of increased risk. The best of these reported one death from bladder cancer in 1,223 men producing or using aniline, with 0.83 deaths expected from population rates. The degree of confidence which can be placed in the negative results obtained in the other studies is difficult to assess because of the absence of estimates of expected numbers of bladder cancers and the presumed lack of follow-up of workers who had left the industry." The available epidemiological data were considered insufficient to allow a conclusion about the carcinogenicity of aniline to humans (IARC, 1982).

C.I. Acid Orange 10 was tested because of its moderately large production volume and widespread use, and because previous studies for carcinogenicity (Cook et al., 1940; Klinke, 1957; Waterman and Lignac, 1958) were considered to be inadequate.

# II. MATERIALS AND METHODS

## CHEMICAL ANALYSES

## PREPARATION OF THE TEST DIETS

## SOURCE AND SPECIFICATIONS OF TEST ANIMALS

## ANIMAL MAINTENANCE

## SHORT-TERM STUDIES

### Single-Dose and Fourteen-Day Studies

### Thirteen-Week Studies

## TWO-YEAR STUDIES

### Clinical Examinations and Pathology

### Data Recording and Statistical Analyses

## CHEMICAL ANALYSES

C.I. Acid Orange 10—7-hydroxy-8-(phenylazo)-1,3-naphthalenedisulfonic acid, disodium salt—was obtained in two batches from Abbey Color and Chemical Co., Inc., Philadelphia, Pennsylvania. According to the manufacturer, the salt contained $Na_2SO_4 \cdot 10H_2O$, anhydrous $Na_2SO_4$, and NaCl as diluents, and deodorized mineral oil as a non-dusting agent. Lot No. 1112 was used for the prechronic studies and for the first 6 months of the 2-year rat study and the first 5 months of the 2-year mouse study. Lot No. 2735 was used for the remainder of the 2-year studies.

Purity and identity analyses are recorded in Appendix G. The composition of the two batches was similar.

Titration of reducible groups with titanous chloride indicated that both batches contained 80% ± 2% dye, and results of elemental analyses and Karl Fischer water analyses were consistent with a composition of approximately 80% dye, 4% water, and 12%-13% sodium chloride. Lot No. 2735 was found to contain 1.5% carbonate. One minor and three trace impurities were detected with thin-layer chromatography. One unidentified impurity (4.3% in Lot No. 1112, 2.6% in Lot No. 2735) was detected with high-pressure liquid chromatography. The infrared, ultraviolet, visible, and nuclear magnetic resonance spectra were consistent with the structure.

C.I. Acid Orange 10 was stored at 23° ± 1°C. The bulk chemical was reanalyzed periodically and results were compared with those for samples stored at -20°C and analyzed concurrently. Analyses indicated that the test material remained stable throughout the period of storage at the laboratory.

## PREPARATION OF THE TEST DIETS

A 1-week supply of each diet was formulated no more than 4 days before use by mixing weighed amounts of Purina Laboratory Chow animal meal (Ralston Purina Co., Richmond, IN) and C.I. Acid Orange 10 in a Patterson-Kelly twin shell blender for 15 minutes. Formulated diets were stored at 23°C for no longer than 10 days.

Spectrophotometric analysis of water extracts of diets formulated with 100,000 ppm dye and stored for 2 weeks at -20°, 5°, 25°, or 45°C indicated that C.I. Acid Orange 10 was stable in feed for 2 weeks at 45°C. Selected batches of formulated diets were analyzed at approximately 2-month intervals during the 2-year studies (Appendix H). Results of these analyses indicated that the analyzed mixtures were properly formulated.

## SOURCE AND SPECIFICATIONS OF TEST ANIMALS

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N × C3H/HeN MTV$^-$) mice used in this study were produced under barrier conditions at the NCI Frederick Cancer Research Center, Frederick, Maryland. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Four-week-old male F344/N rats, 3-week-old female F344/N rats, and 5-week-old B6C3F$_1$ mice were shipped to the testing laboratory, acclimated for 2 weeks, and assigned to control or dosed groups according to a table of random numbers.

## ANIMAL MAINTENANCE

The rats and mice were housed five per cage in solid-bottom polycarbonate cages (Lab Products, Inc., Garfield, NJ) equipped with DuPont 2024 spun-bonded polyester filters and supplied with Absorb-Dri hardware chips (Lab Products, Inc.). Cages and bedding were changed twice weekly.

Tap water, supplied by an automatic watering system (Edstrom Industries, Waterford, WI), and Ralston Purina Laboratory Chow Meal for the controls and the test diet described previously for the dosed animals were available *ad libitum*. Feed hoppers were changed once per week.

The temperature in the animal rooms was maintained between 21° and 23° C, and the relative humidity was 40%-60%. Incoming air was passed through a filter equipped with an electrostatic precipitator at a volume equivalent to 15 changes per hour. Fluorescent lighting was provided 12 hours per day.

Rats and mice fed C.I. Acid Orange 10 were housed in the same room as animals of the same species on feeding studies of FD & C Yellow No. 6 (CAS 2783-94-0) and C.I. Acid Red 14 (CAS 3567-69-9).

## SHORT-TERM STUDIES

### Single-Dose and Fourteen-Day Studies

Acute toxicity and 14-day repeated-dose studies were conducted on F344/N rats and B6C3F$_1$ mice to determine the concentration of C.I. Acid Orange 10 to be used in the 13-week studies.

In the acute toxicity studies, groups of five males and five females of each species were given feed containing 6,000, 12,500, 25,000, 50,000, 100,000, or 200,000 ppm C.I. Acid Orange 10 for 24 hours and were killed after 14 days. The animals that received the highest dose (200,000 ppm) were necropsied. All rats and mice survived to the end of the dosing and observation period, and no chemical-related effects were seen at necropsy for either rats or mice.

In the 14-day studies, groups of five males and five females of each species were fed diets containing 6,000, 12,500, 25,000, 50,000, or 100,000 ppm C.I. Acid Orange 10 for 14 days and then killed and necropsied on day 15.

All rats and mice survived to the end of the study. The spleens of male and female rats in all dosed groups were dark red and enlarged up to 1.5 times normal size, and the splenic enlargement was dose related. The spleens of male and female mice receiving dosed food were also dark red, congested, and enlarged up to 2 times normal size.

### Thirteen-Week Studies

These studies were conducted to evaluate the cumulative toxicity of the test material, to identify organs affected, and to determine the most appropriate doses for the two-year studies. Groups of 10 males and 10 females of each species were given feed containing 0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm C.I. Acid Orange 10 for 13 weeks. Animals were observed twice daily and weighed weekly. At the end of the 91-day period, all animals were anesthetized with $CO_2$, killed, and necropsied.

*Rats:* No deaths occurred. Final body weights were more than 25% lower in male and female rats receiving the 50,000 ppm dose compared to controls. Doses, survivals, and body weights are summarized in Table 1.

A dose-associated splenomegaly was observed in male and female rats fed diets containing 6,000 ppm or more. Myeloid metaplasia of the spleen was present in all dosed animals, and the red pulp was engorged in all dosed animals when compared with controls. The severity of all these effects was dose related. Capsular fibrosis of the spleen, often considered life-threatening, was found in all dosed animals. The effects of this lesion were considered minimal at 3,000 ppm and moderate at 6,000 ppm.

Pigmentation in the epithelial cells was found in renal tubules of all rats receiving 6,000 ppm or more; no significant degenerative changes were associated with the pigmentation. Although some of the pigment in each kidney was iron positive, much of it was iron negative, and no further attempt at identification was made.

Because of the observed splenic effects, doses selected for rats for the two-year studies were 0, 1,000, and 3,000 ppm.

*Mice:* One death occurred among male mice receiving 50,000 ppm. Two of 10 control female mice, 2/10 female mice receiving 12,500 ppm, and 1/10 female mice receiving 50,000 ppm also died.

In male mice mean body weights were decreased about 10% compared to controls in all dosed groups except 3,000 ppm. Final body weights of dosed and control female mice were similar. Doses, survivals, and body weights are summarized in Table 2.

Spleens from male and female mice receiving the highest dose (50,000 ppm) were slightly enlarged. Myeloid metaplasia in the spleen was found in all male and female mice from all dosage groups. Granular pigment was present in epithelial cells of the proximal tubules of the kidneys from both male and female mice receiving 25,000 or 50,000 ppm. Because of the recognized splenic effects, doses selected for mice for the two-year studies were 0, 3,000, and 6,000 ppm.

**TABLE 1. DOSES, SURVIVALS, AND MEAN BODY WEIGHTS OF RATS FED C.I. ACID ORANGE 10 FOR 13 WEEKS**

| Dose (ppm) | Survival *(a)* | Mean Body Weights (grams) | | | Final Body Weight Relative to Controls *(b)* (%) |
|---|---|---|---|---|---|
| | | Initial | Final | Change | |
| **Male** | | | | | |
| 0 | 10/10 | 116.1 | 296.1 | 180.0 | — |
| 3,000 | 10/10 | 107.2 | 307.8 | 200.6 | + 4 |
| 6,000 | 10/10 | 108.3 | 306.7 | 198.4 | + 4 |
| 12,500 | 10/10 | 95.5 | 293.3 | 197.8 | - 1 |
| 25,000 | 10/10 | 103.2 | 268.3 | 165.1 | - 9 |
| 50,000 | 10/10 | 99.7 | 209.1 | 109.4 | -29 |
| **Female** | | | | | |
| 0 | 10/10 | 106.2 | 178.8 | 72.6 | — |
| 3,000 | 10/10 | 103.5 | 185.9 | 82.4 | + 4 |
| 6,000 | 10/10 | 103.2 | 183.4 | 80.2 | + 3 |
| 12,500 | 10/10 | 98.8 | 183.0 | 84.2 | + 2 |
| 25,000 | 10/10 | 99.5 | 183.6 | 84.1 | + 3 |
| 50,000 | 10/10 | 92.1 | 133.0 | 40.9 | -26 |

*(a)* Number surviving/number per group

*(b)* Weight relative to controls =

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

TABLE 2. DOSES, SURVIVALS, AND MEAN BODY WEIGHTS OF MICE FED C.I. ACID ORANGE 10 FOR 13 WEEKS

| Dose (ppm) | Survival *(a)* (Week of Death) | Mean Body Weights (grams) Initial | Final | Change | Final Body Weight Relative to Controls *(b)* (%) |
|---|---|---|---|---|---|
| **Male** | | | | | |
| 0 | 10/10 | 18.2 | 31.6 | 13.4 | — |
| 3,000 | 10/10 | 18.0 | 29.6 | 11.6 | - 6 |
| 6,000 | 10/10 | 18.1 | 28.0 | 9.9 | -11 |
| 12,500 | 10/10 | 18.3 | 28.8 | 10.5 | - 9 |
| 25,000 | 10/10 | 19.1 | 28.5 | 9.4 | -10 |
| 50,000 | 9/10 (2) | 19.0 | 28.7 | 9.2 | - 9 |
| **Female** | | | | | |
| 0 | 8/9 (2) | 15.4 | 22.4 | 7.0 | — |
| 3,000 | 10/10 | 15.7 | 21.4 | 5.7 | - 4 |
| 6,000 | 10/10 | 16.0 | 22.9 | 6.9 | + 2 |
| 12,500 | 8/10 (2,3) | 16.1 | 23.0 | 6.9 | + 3 |
| 25,000 | 10/10 | 16.0 | 21.9 | 5.9 | - 2 |
| 50,000 | 9/10 (2) | 15.8 | 21.9 | 6.1 | - 2 |

*(a)* Number surviving/number per group

*(b)* Weight relative to controls =

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

# TWO-YEAR STUDIES

The numbers of animals in test groups, doses administered, and times of the chronic studies in rats and mice are shown in Table 3.

## Clinical Examinations and Pathology

All animals were observed twice daily, and observations of sick, tumor-bearing, and moribund animals were recorded. Clinical examination and palpation for masses were performed each month, and the animals were weighed at least once per month. Moribund animals and animals that survived to the end of the bioassay were killed with carbon dioxide and necropsied.

Gross and microscopic examinations were performed on major tissues, major organs, and all gross lesions from killed animals and from animals found dead. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin (abdominal), lungs and bronchi, trachea, bone, bone marrow (femur), thigh muscle, spleen, lymph nodes, thymus, heart, salivary glands, liver, gallbladder (mice), pancreas, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, mammary gland, uterus, ovary, brain, epididymis, eye, and all tissue masses.

Necropsies were performed on all animals, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

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 were verified, and histotechniques were evaluated. All tumor diagnoses, target tissues, and tissues from a randomly selected 10% 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 in a blind fashion by the PWG's pathologists, who reached a consensus and compared their findings with the original diagnoses. When conflicts were found, the PWG sent the appropriate slides and its comments to the original pathologist for review. (This procedure has been described by Maronpot and Boorman, 1982). The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group.

TABLE 3. EXPERIMENTAL DESIGN OF THE TWO-YEAR FEEDING STUDIES WITH C.I. ACID ORANGE 10 IN RATS AND MICE

| Test Group | Initial No. of Animals | C.I. Acid Orange 10 in Diet (ppm) | Time on Study | |
|---|---|---|---|---|
| | | | Dosed (weeks) | Not Dosed (weeks) |
| **Male Rats** | | | | |
| Matched Control | 90 *(a)* | 0 | 0 | 104 |
| Low Dose | 50 | 1,000 | 103 | 1 |
| High Dose | 50 | 3,000 | 103 | 1 |
| **Female Rats** | | | | |
| Matched Control | 90 *(a)* | 0 | 0 | 104 |
| Low Dose | 50 | 1,000 | 103 | 1 |
| High Dose | 50 | 3,000 | 103 | 1 |
| **Male Mice** | | | | |
| Matched Control | 50 | 0 | 0 | 104 |
| Low Dose | 50 | 3,000 | 103 | ½ (3 days) |
| High Dose | 50 | 6,000 | 103 | ½ (3 days) |
| **Female Mice** | | | | |
| Matched Control | 50 | 0 | 0 | 104 |
| Low Dose | 50 | 3,000 | 103 | 1 |
| High Dose | 50 | 6,000 | 103 | 1 |

*(a)* Controls were shared with feeding studies of FD&C Yellow 6 and C.I. Acid Red 14.

## Data Recording and Statistical Analyses

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).

*Survival Analyses*—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. All reported P-values for the survival analysis are two-sided.

*Incidence Data*—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 is 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 dose groups with controls and tests for overall dose-response trends.

*Life Table Analyses*—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).

*Incidental Analyses*—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, 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. The computational details of both methods are presented in Peto et al. (1980).

*Trends and Pairwise Comparisons*—In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher 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 for the tumor incidence analyses 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.

# III. RESULTS

## RATS

## TWO-YEAR STUDIES

### Body Weights and Clinical Signs

### Survival

### Pathology and Statistical Analyses of Results

## MICE

## TWO-YEAR STUDIES

### Body Weights and Clinical Signs

### Survival

### Pathology and Statistical Analyses of Results

# RATS

# TWO-YEAR STUDIES

## Body Weights and Clinical Signs

Mean body weights of dosed rats of both sexes were comparable with those of controls (Table 4 and Figure 2). No compound-related clinical signs were observed.

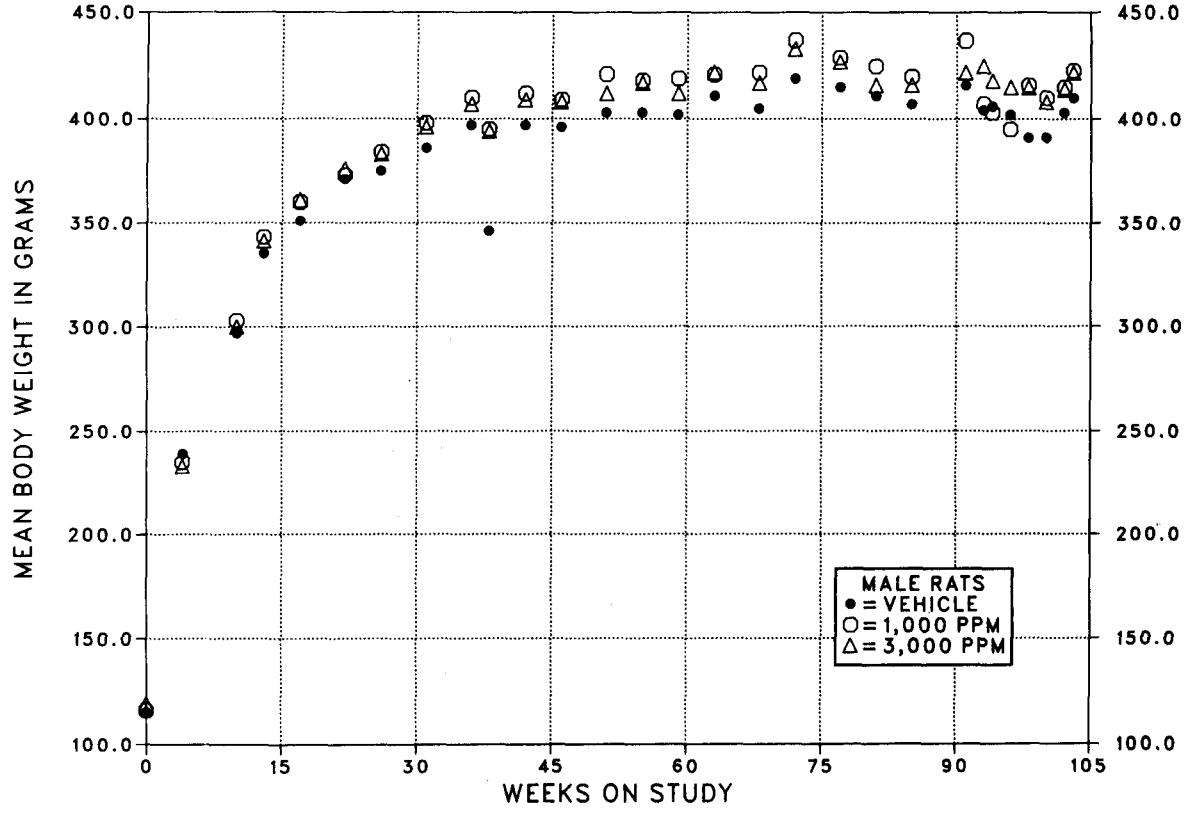
## Survival

Estimates of the probabilities of survival for male and female rats administered C.I. Acid Orange 10 in feed at the doses used in these studies, and those of the controls, are shown by the Kaplan and Meier curves in Figure 3. The results of Tarone's tests indicate comparable survival among all three groups of either sex.

In male rats, 70/90 (78%) of the matched control group, 42/50 (84%) of the low dose group, and 39/50 (78%) of the high dose group lived to the end of the study at week 104. In females, 66/88 (75%) of the control group, 46/50 (92%) of the low dose group, and 44/50 (88%) of the high dose group were alive at the end of the study at 104-105 weeks.

TABLE 4. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) AND SURVIVAL OF RATS FED DIETS CONTAINING C.I. ACID ORANGE 10 FOR TWO YEARS

| Weeks on Study | Vehicle Control Av. Wt. (grams) | Vehicle Control No. of Survivors | Low Dose Av. Wt. (grams) | Low Dose Wt. (percent of veh. controls) | Low Dose No. of Survivors | High Dose Av. Wt. (grams) | High Dose Wt. (percent of veh. controls) | High Dose No. of Survivors |
|---|---|---|---|---|---|---|---|---|
| **MALE** | | | | | | | | |
| 0 | 115 | 90 | 116 | 101 | 50 | 119 | 103 | 50 |
| 4 | 239 | 90 | 235 | 98 | 50 | 233 | 97 | 50 |
| 10 | 297 | 90 | 303 | 102 | 50 | 300 | 101 | 50 |
| 13 | 335 | 90 | 343 | 102 | 50 | 341 | 102 | 50 |
| 17 | 351 | 90 | 360 | 103 | 50 | 361 | 103 | 50 |
| 22 | 371 | 89 | 373 | 101 | 50 | 376 | 101 | 50 |
| 26 | 375 | 89 | 384 | 102 | 50 | 383 | 102 | 50 |
| 31 | 386 | 89 | 398 | 103 | 50 | 396 | 103 | 50 |
| 36 | 397 | 89 | 410 | 103 | 50 | 407 | 103 | 50 |
| 38 | 346 | 89 | 395 | 114 | 50 | 394 | 114 | 50 |
| 42 | 397 | 88 | 412 | 104 | 50 | 409 | 103 | 50 |
| 46 | 396 | 88 | 409 | 103 | 49 | 408 | 103 | 50 |
| 51 | 403 | 88 | 421 | 104 | 49 | 412 | 102 | 50 |
| 55 | 403 | 88 | 418 | 104 | 49 | 417 | 103 | 50 |
| 59 | 402 | 88 | 419 | 104 | 49 | 412 | 102 | 50 |
| 63 | 411 | 87 | 421 | 102 | 49 | 422 | 103 | 50 |
| 68 | 405 | 87 | 422 | 104 | 48 | 417 | 103 | 50 |
| 72 | 419 | 87 | 437 | 104 | 48 | 433 | 103 | 49 |
| 77 | 415 | 86 | 429 | 103 | 48 | 427 | 103 | 49 |
| 81 | 411 | 85 | 425 | 103 | 48 | 416 | 101 | 48 |
| 85 | 407 | 85 | 420 | 103 | 46 | 416 | 102 | 46 |
| 91 | 416 | 81 | 437 | 105 | 45 | 422 | 101 | 44 |
| 93 | 404 | 79 | 407 | 101 | 45 | 425 | 105 | 41 |
| 94 | 406 | 78 | 403 | 99 | 45 | 418 | 103 | 41 |
| 96 | 402 | 77 | 395 | 98 | 45 | 415 | 103 | 41 |
| 98 | 391 | 77 | 416 | 106 | 44 | 415 | 106 | 40 |
| 100 | 391 | 76 | 410 | 105 | 43 | 408 | 104 | 39 |
| 102 | 403 | 73 | 415 | 103 | 43 | 414 | 103 | 39 |
| 103 | 410 | 73 | 423 | 103 | 42 | 422 | 103 | 39 |
| **FEMALE** | | | | | | | | |
| 0 | 104 | 90 | 106 | 102 | 50 | 105 | 101 | 50 |
| 4 | 149 | 90 | 149 | 100 | 50 | 150 | 101 | 50 |
| 9 | 175 | 88 | 174 | 99 | 50 | 176 | 101 | 50 |
| 12 | 189 | 88 | 188 | 99 | 50 | 189 | 100 | 50 |
| 16 | 199 | 87 | 204 | 103 | 50 | 205 | 103 | 50 |
| 21 | 212 | 87 | 213 | 100 | 50 | 213 | 100 | 50 |
| 26 | 215 | 87 | 217 | 101 | 50 | 216 | 100 | 50 |
| 30 | 221 | 87 | 220 | 100 | 50 | 223 | 101 | 50 |
| 35 | 228 | 87 | 227 | 100 | 50 | 228 | 100 | 50 |
| 37 | 218 | 87 | 233 | 107 | 50 | 233 | 107 | 50 |
| 42 | 230 | 87 | 234 | 102 | 50 | 235 | 102 | 50 |
| 45 | 234 | 87 | 233 | 100 | 50 | 234 | 100 | 50 |
| 50 | 239 | 87 | 245 | 103 | 50 | 243 | 102 | 50 |
| 54 | 241 | 87 | 242 | 100 | 50 | 241 | 100 | 50 |
| 58 | 255 | 87 | 250 | 98 | 50 | 253 | 99 | 50 |
| 62 | 256 | 87 | 252 | 98 | 50 | 252 | 98 | 50 |
| 67 | 265 | 87 | 259 | 98 | 50 | 259 | 98 | 50 |
| 71 | 267 | 87 | 268 | 100 | 50 | 270 | 101 | 49 |
| 76 | 275 | 86 | 270 | 98 | 50 | 272 | 99 | 49 |
| 80 | 269 | 84 | 272 | 101 | 50 | 274 | 102 | 49 |
| 84 | 272 | 81 | 271 | 100 | 50 | 268 | 99 | 49 |
| 90 | 285 | 78 | 284 | 100 | 50 | 278 | 98 | 49 |
| 92 | 282 | 76 | 280 | 99 | 50 | 281 | 100 | 47 |
| 93 | 276 | 75 | 278 | 101 | 50 | 280 | 101 | 46 |
| 95 | 280 | 75 | 278 | 99 | 50 | 284 | 101 | 46 |
| 97 | 285 | 72 | 285 | 100 | 49 | 290 | 102 | 45 |
| 99 | 288 | 69 | 283 | 98 | 48 | 287 | 100 | 45 |
| 101 | 297 | 68 | 290 | 98 | 48 | 298 | 100 | 44 |
| 103 | 305 | 68 | 295 | 97 | 48 | 300 | 98 | 44 |



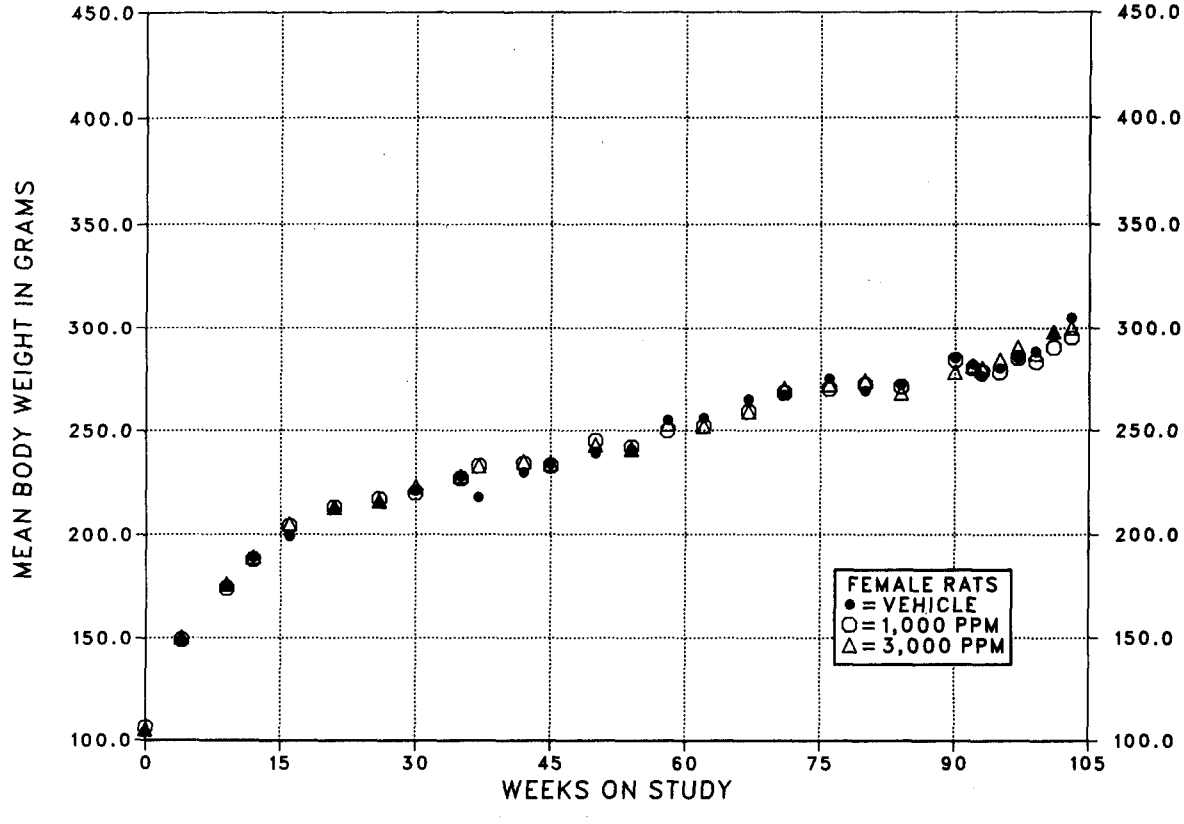




**Figure 2. Growth Curves for Rats Fed Diets Containing C.I. Acid Orange 10**

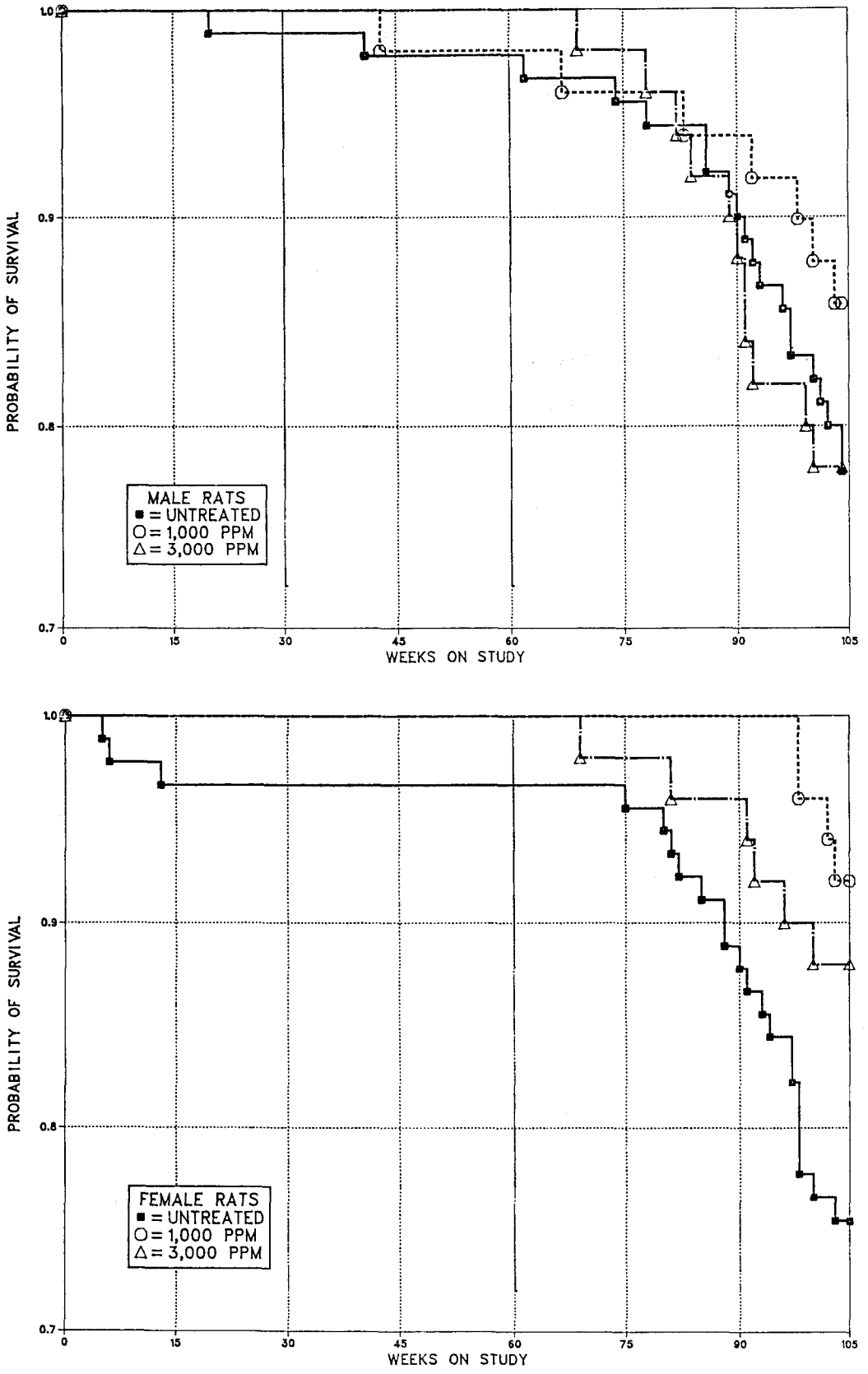



**Figure 3. Kaplan-Meier Survival Curves for Rats Fed Diets Containing C.I. Acid Orange 10**

## Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Appendix F, Tables F1 and F2, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one or more than one group. Significant increases or decreases in the occurrence of particular neoplasms are presented below.

A significant ($P<0.03$) dose-related trend was observed in the incidence of neoplastic nodules in the liver of male rats, and the incidence in the high dose group was higher ($P<0.05$) than that in the controls (5/90, 6%; 3/50, 6%; 8/50, 16%) (Table 5). The 16% rate found in the 3,000 ppm group is greater than the mean rate of 3% (78/2306) observed historically in the Program (Table E1), and is more than that seen in the upper range in controls (6/49, 12%). One hepatocellular carcinoma was also found in a high dose male (an incidence of 2%). These hepatic tumors were consistent with those described by Squire and Levitt (1975). There was no increased incidence of foci of cellular alteration in male rats. In female rats, neoplastic nodules of the liver occurred in 3/88 (3%) controls and 1/50 (2%) high dose animals. Hepatocellular carcinomas occurred in 2/50 (4%) females in the low dose group.

The incidence of male rats with mesotheliomas in the tunica vaginalis was higher ($P<0.05$) in the low dose group than in the controls (0/90; 3/50, 6%; 2/50, 4%). However, when the incidence of males with mesotheliomas at any site is considered, no significant difference is observed (3/90, 3%; 3/50, 6%; 2/50, 4%). The historical rates are shown in Table E3.

Negative trends ($P<0.01$) and significantly lower incidences ($P<0.03$) of leukemia in the hematopoietic system were observed in both dose groups of male and female rats (males: 22/90, 4/50, 3/50; females: 16/88, 2/50, 0/50) (Table 6; Table E2).

TABLE 5. INCIDENCES OF MALE RATS WITH NEOPLASTIC NODULES OF THE LIVER

| | Control | 1,000 ppm | 3,000 ppm |
|---|---|---|---|
| Overall Incidence | 5/90 (6%) | 3/50 (6%) | 8/50 (16%) *(a)* |
| Adjusted Incidence | 6.9% | 7.1% | 20.5% |
| Terminal Incidence | 5/72 (7%) | 3/42 (7%) | 8/39 (21%) |
| Life Table Test | P=0.022 | P=0.633 | P=0.036 |
| Incidental Tumor Test | P=0.022 | P=0.633 | P=0.036 |
| Cochran-Armitage Trend Test | P=0.026 | | |
| Fisher Exact Test | | P=0.593 | P=0.044 |
| Weeks to First Observed Tumor | 104 | 104 | 104 |

*(a)* One male rat in the 3,000 ppm dose group had both a neoplastic nodule and a carcinoma of the liver.

TABLE 6. INCIDENCES OF RATS WITH LYMPHOCYTIC LEUKEMIA

| | Control | 1,000 ppm | 3,000 ppm |
|---|---|---|---|
| **Males** | | | |
| Overall Incidence | 22/90 (24%) | 4/50 (8%) | 3/50 (6%) |
| Adjusted Incidence | 26.7% | 8.6% | 6.4% |
| Terminal Incidence | 13/72 (18%) | 1/42 (2%) | 0/39 (0%) |
| Life Table Test | P=0.006N | P=0.018N | P=0.011N |
| Incidental Tumor Test | P=0.002N | P=0.021N | P=0.002N |
| Cochran-Armitage Trend Test | P=0.003N | | |
| Fisher Exact Test | | P=0.013N | P=0.005N |
| Weeks to First Observed Tumor | 74 | 43 | 84 |
| **Females** | | | |
| Overall Incidence | 16/88 (18%) | 2/50 (4%) | 0/50 (0%) |
| Adjusted Incidence | 21.4% | 4.2% | 0.0% |
| Terminal Incidence | 10/66 (15%) | 1/46 (2%) | 0/44 (0%) |
| Life Table Test | P<0.001N | P=0.009N | P=0.001N |
| Incidental Tumor Test | P=0.002N | P=0.026N | P=0.004N |
| Cochran-Armitage Trend Test | P<0.001N | | |
| Fisher Exact Test | | P=0.014N | P<0.001N |
| Weeks to First Observed Tumor | 5 | 102 | — |

# MICE

# TWO-YEAR STUDIES

## Body Weights and Clinical Signs

Mean body weights of the dosed male and female mice were comparable with those of the controls (Table 7 and Figure 4). No compound-related clinical signs were observed.

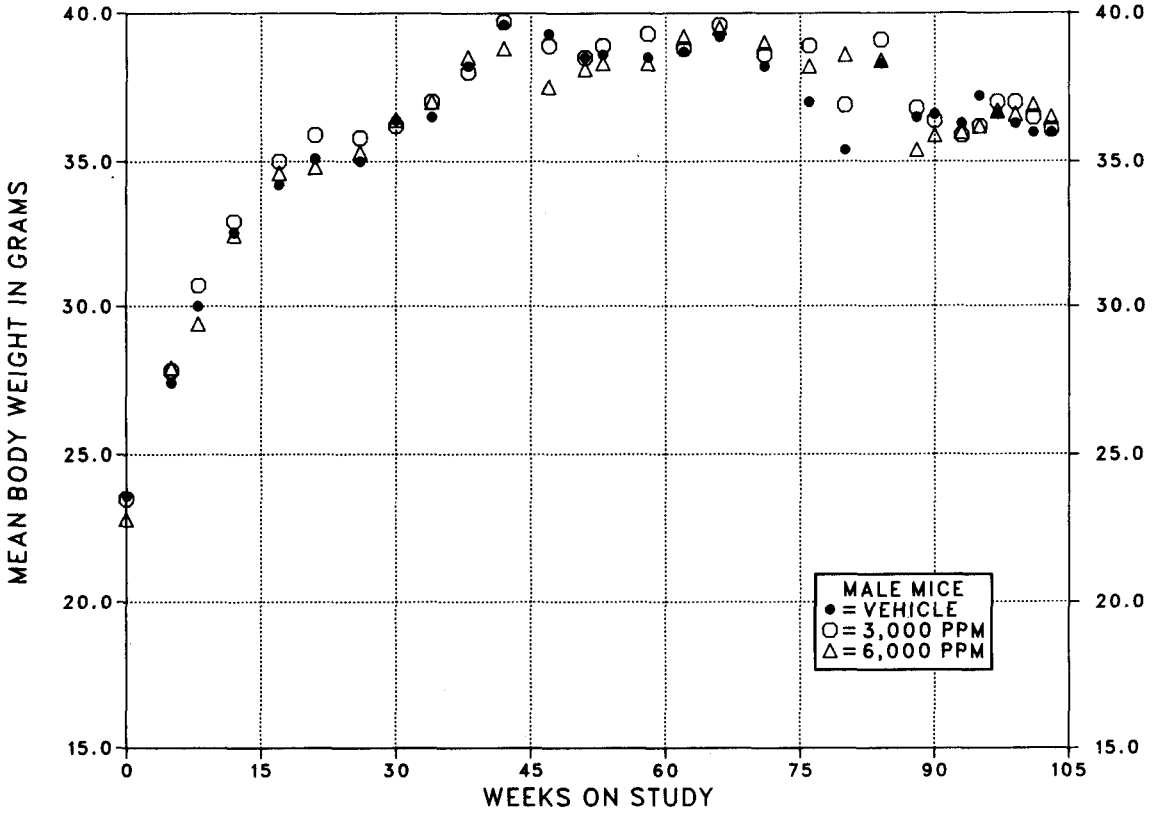
## Survival

Estimates of the probabilities of survival for male and female mice administered C.I. Acid Orange 10 in feed at the doses used in these studies, and those of the controls, are shown by the Kaplan and Meier curves in Figure 5. No significant life-shortening effects were observed in dosed groups relative to controls.

In male mice, 32/50 (64%) of the controls, 33/50 (66%) of the low dose group, and 42/50 (84%) of the high dose group lived to the end of the study at week 103. In females, 40/50 (80%) of the control group, 37/50 (74%) of the low dose group, and 41/50 (82%) of the high dose group lived to the end of the study at 103-104 weeks.

TABLE 7. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) AND SURVIVAL OF MICE FED DIETS CONTAINING C.I. ACID ORANGE 10 FOR TWO YEARS

| Weeks on Study | Vehicle Control | | Low Dose | | | High Dose | | |
|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (grams) | No. of Survivors | Av. Wt. (grams) | Wt. (percent of veh. controls) | No. of Survivors | Av. Wt. (grams) | Wt. (percent of veh. controls) | No. of Survivors |
| **MALE** | | | | | | | | |
| 0 | 23.6 | 50 | 23.5 | 100 | 50 | 22.8 | 97 | 50 |
| 5 | 27.4 | 50 | 27.8 | 101 | 47 | 27.9 | 102 | 50 |
| 8 | 30.0 | 50 | 30.7 | 102 | 47 | 29.4 | 98 | 50 |
| 12 | 32.5 | 50 | 32.9 | 101 | 47 | 32.4 | 100 | 50 |
| 17 | 34.2 | 49 | 35.0 | 102 | 45 | 34.6 | 101 | 50 |
| 21 | 35.1 | 49 | 35.9 | 102 | 45 | 34.8 | 99 | 50 |
| 26 | 35.0 | 49 | 35.8 | 102 | 44 | 35.3 | 101 | 50 |
| 30 | 36.4 | 49 | 36.2 | 99 | 44 | 36.4 | 100 | 50 |
| 34 | 36.5 | 49 | 37.0 | 101 | 43 | 37.0 | 101 | 50 |
| 38 | 38.2 | 49 | 38.0 | 99 | 42 | 38.5 | 101 | 50 |
| 42 | 39.6 | 49 | 39.7 | 100 | 42 | 38.8 | 98 | 50 |
| 47 | 39.3 | 49 | 38.9 | 99 | 41 | 37.5 | 95 | 50 |
| 51 | 38.5 | 49 | 38.5 | 100 | 41 | 38.1 | 99 | 50 |
| 53 | 38.6 | 49 | 38.9 | 101 | 41 | 38.3 | 99 | 50 |
| 58 | 38.5 | 48 | 39.3 | 102 | 41 | 38.3 | 99 | 50 |
| 62 | 38.7 | 47 | 38.8 | 100 | 41 | 39.2 | 101 | 50 |
| 66 | 39.2 | 46 | 39.6 | 101 | 41 | 39.5 | 101 | 50 |
| 71 | 38.2 | 46 | 38.6 | 101 | 41 | 39.0 | 102 | 50 |
| 76 | 37.0 | 46 | 38.9 | 105 | 40 | 38.2 | 103 | 49 |
| 80 | 35.4 | 46 | 36.9 | 104 | 40 | 38.6 | 109 | 48 |
| 84 | 38.3 | 46 | 39.1 | 102 | 38 | 38.4 | 100 | 47 |
| 88 | 36.5 | 44 | 36.8 | 101 | 38 | 35.4 | 97 | 45 |
| 90 | 36.6 | 44 | 36.4 | 99 | 37 | 35.9 | 98 | 45 |
| 93 | 36.3 | 43 | 35.9 | 99 | 37 | 36.0 | 99 | 44 |
| 95 | 37.2 | 42 | 36.2 | 97 | 37 | 36.2 | 97 | 44 |
| 97 | 36.6 | 34 | 37.0 | 101 | 36 | 36.7 | 100 | 44 |
| 99 | 36.3 | 34 | 37.0 | 102 | 36 | 36.6 | 101 | 44 |
| 101 | 36.0 | 33 | 36.5 | 101 | 35 | 36.9 | 103 | 42 |
| 103 | 36.0 | 33 | 36.1 | 100 | 33 | 36.5 | 101 | 42 |
| **FEMALE** | | | | | | | | |
| 0 | 18.0 | 50 | 16.4 | 91 | 50 | 18.4 | 102 | 50 |
| 4 | 20.0 | 50 | 20.8 | 104 | 50 | 20.0 | 100 | 50 |
| 7 | 23.4 | 50 | 22.1 | 94 | 50 | 21.8 | 93 | 50 |
| 11 | 25.8 | 50 | 25.3 | 98 | 50 | 25.4 | 98 | 50 |
| 16 | 27.8 | 50 | 27.6 | 99 | 50 | 27.9 | 100 | 50 |
| 20 | 27.8 | 50 | 27.7 | 100 | 50 | 27.3 | 98 | 50 |
| 25 | 29.1 | 50 | 29.1 | 100 | 50 | 28.9 | 99 | 50 |
| 29 | 30.2 | 50 | 29.5 | 98 | 50 | 29.0 | 96 | 50 |
| 33 | 30.4 | 50 | 29.5 | 97 | 50 | 30.2 | 99 | 49 |
| 37 | 31.4 | 50 | 30.9 | 98 | 50 | 31.8 | 101 | 49 |
| 41 | 32.1 | 50 | 31.7 | 99 | 50 | 31.7 | 99 | 49 |
| 45 | 32.3 | 50 | 32.2 | 100 | 50 | 32.1 | 99 | 49 |
| 49 | 33.2 | 50 | 32.3 | 97 | 50 | 32.6 | 98 | 49 |
| 52 | 34.1 | 50 | 34.0 | 100 | 50 | 33.6 | 99 | 49 |
| 57 | 35.3 | 50 | 35.4 | 100 | 50 | 35.4 | 100 | 49 |
| 61 | 35.8 | 50 | 36.5 | 102 | 50 | 36.4 | 102 | 49 |
| 65 | 36.8 | 50 | 37.6 | 102 | 50 | 37.3 | 101 | 49 |
| 70 | 36.7 | 50 | 37.0 | 101 | 50 | 36.7 | 100 | 49 |
| 75 | 36.7 | 50 | 37.0 | 101 | 49 | 36.5 | 99 | 49 |
| 79 | 35.4 | 49 | 34.8 | 98 | 49 | 36.2 | 102 | 48 |
| 83 | 37.9 | 49 | 37.4 | 99 | 48 | 37.5 | 99 | 48 |
| 87 | 34.9 | 48 | 35.0 | 100 | 48 | 32.9 | 94 | 45 |
| 89 | 34.4 | 44 | 35.2 | 102 | 44 | 34.5 | 100 | 44 |
| 92 | 35.1 | 44 | 34.4 | 98 | 43 | 34.0 | 97 | 44 |
| 94 | 36.4 | 44 | 35.7 | 98 | 41 | 34.1 | 94 | 44 |
| 96 | 37.3 | 43 | 37.5 | 101 | 40 | 35.7 | 96 | 43 |
| 98 | 37.9 | 43 | 38.2 | 101 | 39 | 36.0 | 95 | 42 |
| 100 | 36.6 | 41 | 37.6 | 103 | 39 | 36.2 | 99 | 41 |
| 103 | 37.5 | 40 | 40.0 | 107 | 36 | 36.0 | 96 | 41 |



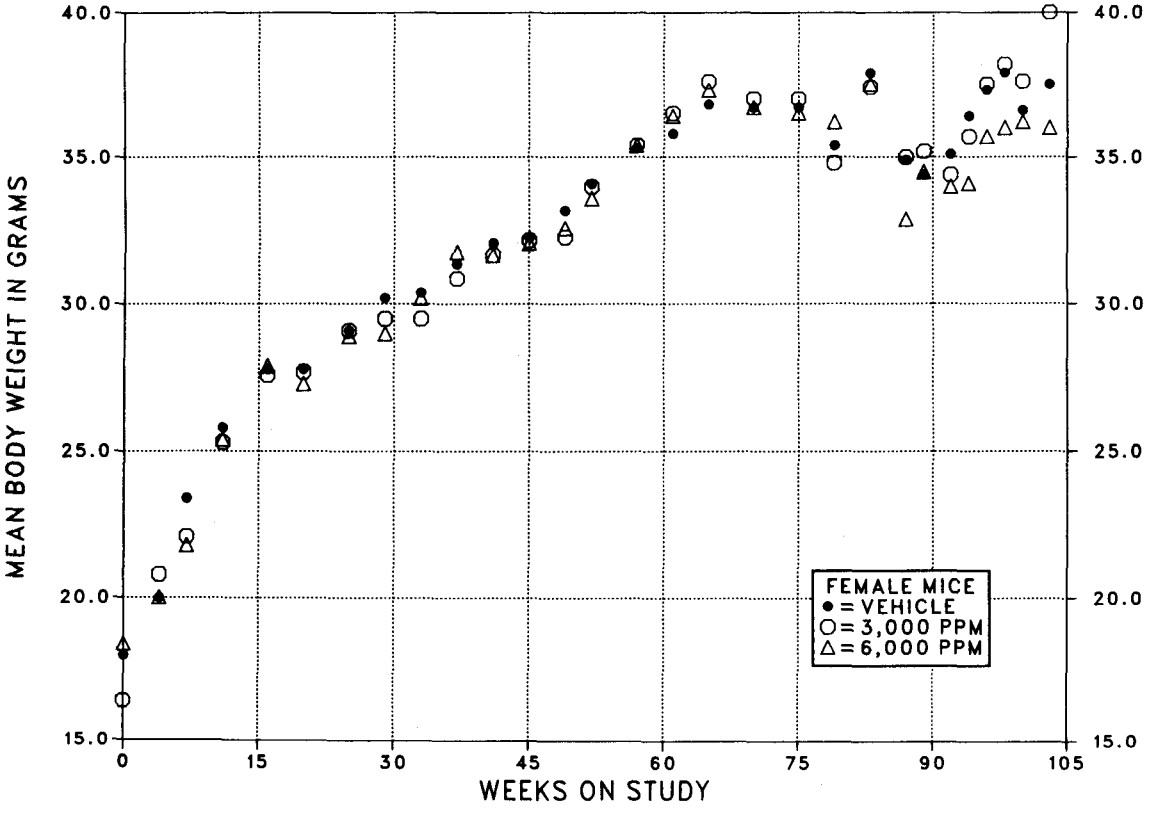




**Figure 4. Growth Curves for Mice Fed Diets Containing C.I. Acid Orange 10**

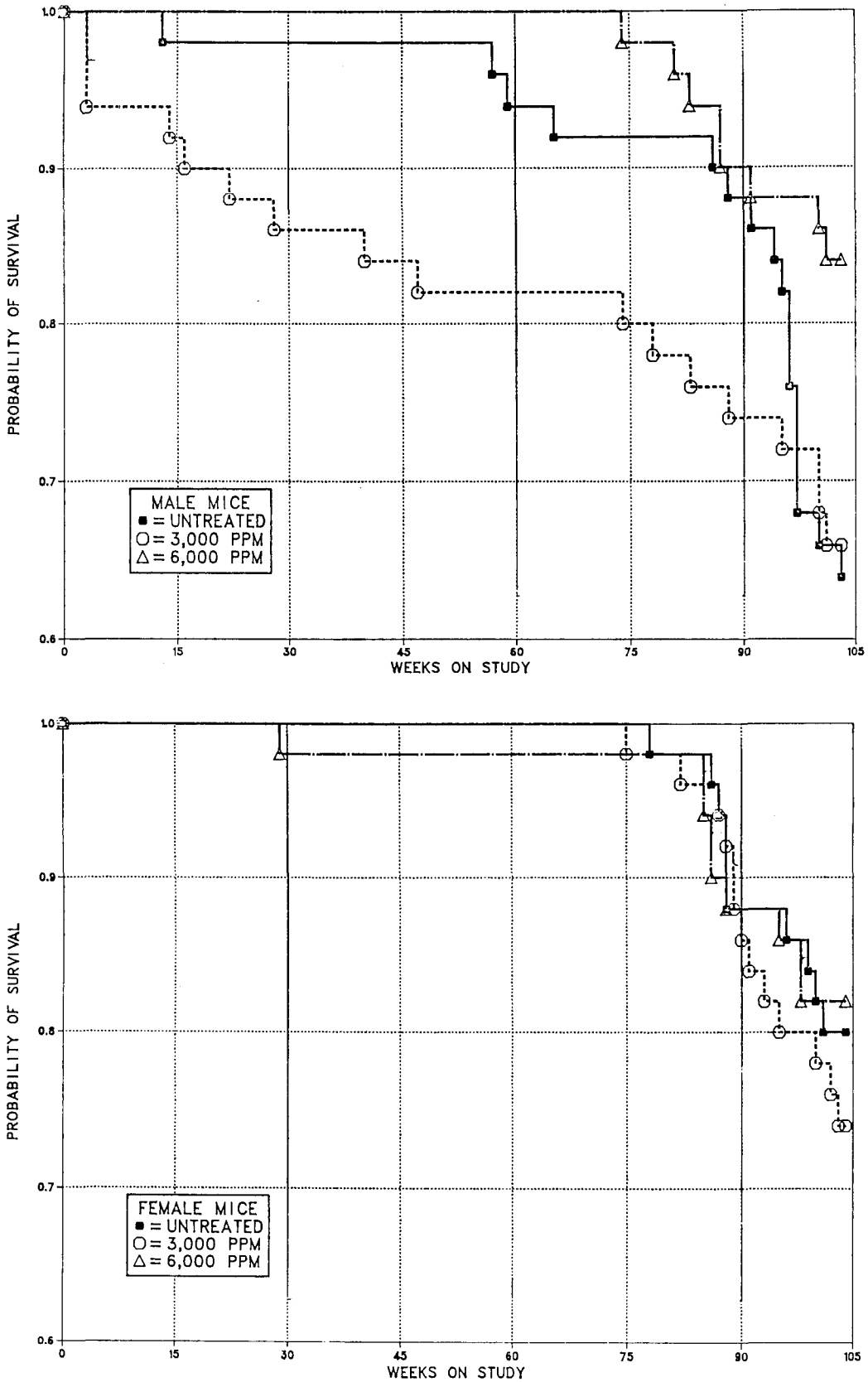



**Figure 5. Kaplan-Meier Survival Curves for Mice Fed Diets Containing C.I. Acid Orange 10**

## Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Appendix F, Tables F3 and F4, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in at least one group. Significant increases or decreases in the occurrence of particular neoplasms are presented below.

At no site was a significant positive increase in tumors observed. In male mice, the incidence of hepatocellular carcinoma in the low dose group was lower ($P<0.05$) than that in the controls (14/50, 28%; 5/49, 10%; 12/50, 24%) (Table 8). When carcinoma and adenoma of the liver are combined, the decrease in the low dose males is significant only by the Fisher exact test (P=0.05). In female mice, hepatocellular adenoma or carcinoma occurred in 3/50 (6%) controls, 3/50 (6%) low dose, and 3/49 (6%) high dose animals.

TABLE 8. INCIDENCES OF MALE MICE WITH LIVER TUMORS

| | Control | 3,000 ppm | 6,000 ppm |
|---|---|---|---|
| **Hepatocellular Carcinoma** | | | |
| Overall Incidence | 14/50 (28%) | 5/49(10%) | 12/50 (24%) |
| Adjusted Incidence | 36.7% | 14.3% | 27.1% |
| Terminal Incidence | 10/33 (30%) | 4/33 (12%) | 10/42 (24%) |
| Life Table Test | P=0.189N | P=0.028N | P=0.208N |
| Incidental Tumor Test | P=0.289N | P=0.046N | P=0.306N |
| Cochran-Armitage Trend Test | P=0.356N | | |
| Fisher Exact Test | | P=0.022N | P=0.410N |
| Weeks to First Observed Tumor | 86 | 78 | 81 |
| **Hepatocellular Carcinoma or Adenoma** | | | |
| Overall Incidence | 15/50 (30%) | 7/49 (14%) | 12/50 (24%) |
| Adjusted Incidence | 39.5% | 20.2% | 27.1% |
| Terminal Incidence | 11/33 (33%) | 6/33 (18%) | 10/42 (24%) |
| Life Table Test | P=0.127N | P=0.057N | P=0.147N |
| Incidental Tumor Test | P=0.201N | P=0.088N | P=0.223N |
| Cochran-Armitage Trend Test | P=0.276N | | |
| Fisher Exact Test | | P=0.050N | P=0.327N |
| Weeks to First Observed Tumor | 86 | 78 | 81 |

# IV. DISCUSSION AND CONCLUSIONS

# IV. DISCUSSION AND CONCLUSIONS

In the 13-week studies, lesions detected in the spleen and to a lesser degree in the kidney influenced the dosage levels selected for the two-year studies. Splenomegaly was observed during the 13-week studies at levels above 3,000 ppm; however, the red pulp of the spleen from animals at all dietary levels was engorged with blood, the extent of engorgement being dose related. Moreover, myeloid metaplasia was present in all animals at all dosage levels. In the kidneys, globular pigments were observed in dose-related quantities in the proximal tubules from animals at all dose levels except 3,000 ppm (these pigments were not identified).

The dietary concentrations used in the two-year studies were 0, 0.1% (1,000 ppm), or 0.3% (3,000 ppm) for male and female F344/N rats and 0, 0.3% (3,000 ppm), or 0.6% (6,000 ppm) for male and female B6C3F1 mice. In these studies, mean body weights of dosed rats and mice were similar to those of the controls throughout the studies. No compound-related clinical signs were observed. Because no compound-related splenic, renal, or toxic effects were observed in the two-year studies, both rats and mice may have been able to tolerate higher doses.

Neoplastic nodules of the liver in high dose male rats occurred at an increased incidence when compared with the controls ($P<0.05$). The 16% rate found in the 3,000 ppm group is greater than the mean rate of 3% (78/2306) observed historically in the Program (Table E1) and is more than that seen in the upper range in controls (6/49, 12%). This marginal increase in liver cell neoplasms may have been associated with the dietary administration of C.I. Acid Orange 10.

Although the incidence of mesotheliomas of the tunica vaginalis was increased in the low dose male rats, there are no significant differences between control and dosed groups when all sites are considered. No apparent compound-related neoplastic or nonneoplastic lesions were seen in the female rats or in mice of either sex.

An as yet unexplained pattern of increasing neoplasms of the liver in F344 rats frequently associates with decreasing hematopoietic lesions, specifically mononuclear cell leukemia (Haseman, 1983). A similar negative association between the incidences of lymphomas and liver tumors in CF-1 mice exposed to DDT was reported by Wahrendorf (1983). C.I. Acid Orange 10 caused a marginal increase in the incidence of neoplastic nodules of the liver in the 3,000 ppm male rats (6% versus 16%: $P<0.05$). Conversely the rate for leukemia was reduced considerably in exposed male rats (24% versus 8% or 6%: $P<0.05$). Female rats also showed a decrease in leukemia (18% versus 4% or 0%: $P<0.05$) yet no increases were seen for neoplasms of the liver. The chemicals reported to cause this pattern of increased liver neoplasms with decreased leukemia (Haseman, 1983) might exert their effects either by direct action on the organ systems to produce both responses simultaneously or by a sequential process affecting first the liver to produce some product or products that, in turn, affect the bone marrow. The reverse sequence (a bone marrow effect resulting in an effect on the liver) seems less likely. The mechanism or mechanisms for this "compensatory biologic reaction" remain unknown.

Aniline, a known metabolite of C.I. Acid Orange 10 in rats (28%), in rabbits (0.6%), and in humans (0.5%) (Figure 1) caused hemangiosarcomas and fibrosarcomas or sarcomas of the spleen and fibrosarcomas or sarcomas of multiple organs in male and female F344 rats (NCI, 1978). The detection of aniline and aniline derivatives as metabolites of C.I. Acid Orange 10 (Walker et al., 1972) suggests that higher dietary levels of this dye might contribute to any adverse effects on the spleen or hematopoietic system. The levels of aniline associated with nonneoplastic and neoplastic involvement were at the 3,000 and 6,000 ppm dietary levels, compared to the no observable effects from the C.I. Acid Orange 10 used in these studies (up to 3,000 ppm for rats or up to 6,000 ppm for mice) and less than one third (28%) of the dye has been reported to be converted to aniline (NCI, 1978). Induction of tumors from aniline liberated as a metabolite therefore seems unlikely.

Rats and mice eating diets containing C.I. Acid Orange 10 were housed in the same room with rats and mice in other studies being fed food containing C.I. Acid Red 14 (NTP, 1982) or FD&C Yellow No. 6 (NTP, 1981). For Yellow 6, no nonneoplastic or neoplastic effects were observed in male and female F344/N rats or in female $B6C3F_1$ mice. Hepatocellular carcinomas were increased in the low dose (12,500 ppm) group of male mice (13/50 versus 22/48: $P<0.05$); the high dose group was increased but not statistically (16/50). C.I. Acid Red 14 did not cause any neoplastic responses in male or female F344/N rats or $B6C3F_1$ mice. Therefore, the marginal increases diagnosed in the C.I. Acid Orange 10 studies were not considered to be influenced by these two other chemicals.

*Conclusion: For 103 weeks C.I. Acid Orange 10 was given in the diets of male and female F344/N rats (0%, 0.1%, or 0.3%) and of male and female $B6C3F_1$ mice (0%, 0.3%, or 0.6%). Under these conditions, there was no evidence of carcinogenicity for male and female F344/N rats or for male and female $B6C3F_1$ mice.*

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## V. REFERENCES


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# APPENDIX A

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED DIETS CONTAINING C.I. ACID ORANGE 10

## TABLE A1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIETS CONTAINING C.I. ACID ORANGE 10

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 90 | 50 | 50 |
| ANIMALS NECROPSIED | 90 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 90 | 50 | 50 |
| **INTEGUMENTARY SYSTEM** | | | |
| *SKIN | (90) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | 3 (3%) | | |
| BASAL-CELL CARCINOMA | | 1 (2%) | |
| SEBACEOUS ADENOMA | 1 (1%) | 1 (2%) | |
| FIBROMA | 1 (1%) | | |
| FIBROSARCOMA | | 1 (2%) | |
| *SUBCUT TISSUE | (90) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| FIBROMA | 4 (4%) | 4 (8%) | 2 (4%) |
| FIBROSARCOMA | 1 (1%) | 1 (2%) | 1 (2%) |
| **RESPIRATORY SYSTEM** | | | |
| #LUNG | (89) | (50) | (50) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | 1 (1%) | | |
| PHEOCHROMOCYTOMA, METASTATIC | 1 (1%) | | |
| FIBROSARCOMA, METASTATIC | 1 (1%) | | |
| **HEMATOPOIETIC SYSTEM** | | | |
| *MULTIPLE ORGANS | (90) | (50) | (50) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (1%) | | |
| LYMPHOCYTIC LEUKEMIA | 21 (23%) | 4 (8%) | 3 (6%) |
| #BONE MARROW | (84) | (48) | (48) |
| OSTEOMA | 1 (1%) | | |
| #SPLEEN | (90) | (50) | (50) |
| LYMPHOCYTIC LEUKEMIA | 1 (1%) | | |
| #CERVICAL LYMPH NODE | (89) | (49) | (49) |
| C-CELL CARCINOMA, METASTATIC | | | 1 (2%) |

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

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #LYMPH NODE OF THORAX | (89) | (49) | (49) |
| INTERSTITIAL-CELL TUMOR, METASTA | 1 (1%) | | |
| #MESENTERIC L. NODE | (89) | (49) | (49) |
| MUCINOUS ADENOCARCINOMA, METASTA | 1 (1%) | | |
| **CIRCULATORY SYSTEM** | | | |
| #SPLEEN | (90) | (50) | (50) |
| HEMANGIOMA | | | 1 (2%) |
| #HEART | (90) | (49) | (50) |
| ADENOCARCINOMA, NOS, UNC PRIM OR | | 1 (2%) | |
| ALVEOLAR/BRONCHIOLAR CA, INVASIV | 1 (1%) | | |
| NONCHROMAFFIN PARAGANGLIOMA | 1 (1%) | | |
| #ENDOCARDIUM | (90) | (49) | (50) |
| NEURILEMOMA, MALIGNANT | | 1 (2%) | |
| **DIGESTIVE SYSTEM** | | | |
| *INTESTINAL TRACT | (90) | (50) | (50) |
| MUCINOUS ADENOCARCINOMA | 1 (1%) | | |
| #SALIVARY GLAND | (89) | (49) | (47) |
| MIXED TUMOR, MALIGNANT | 1 (1%) | | |
| #LIVER | (90) | (50) | (50) |
| NEOPLASTIC NODULE | 5 (6%) | 3 (6%) | 8 (16%) |
| HEPATOCELLULAR CARCINOMA | | | 1 (2%) |
| FIBROSARCOMA, METASTATIC | 1 (1%) | | |
| *OROPHARYNX | (90) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | | 1 (2%) |
| #CARDIAC STOMACH | (87) | (50) | (49) |
| SQUAMOUS CELL PAPILLOMA | 1 (1%) | | |
| #JEJUNUM | (87) | (48) | (47) |
| LEIOMYOSARCOMA | | 1 (2%) | |
| #COLON | (87) | (47) | (49) |
| ADENOMATOUS POLYP, NOS | 1 (1%) | | |

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

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| URINARY SYSTEM | | | |
| NONE | | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (84) | (47) | (46) |
| ADENOMA, NOS | 1 (1%) | | |
| CHROMOPHOBE ADENOMA | 4 (5%) | 2 (4%) | |
| CHROMOPHOBE CARCINOMA | 1 (1%) | 4 (9%) | 2 (4%) |
| ACIDOPHIL ADENOMA | 2 (2%) | | |
| #ADRENAL | (89) | (49) | (50) |
| CORTICAL ADENOMA | 3 (3%) | | 2 (4%) |
| CORTICAL CARCINOMA | | 1 (2%) | |
| PHEOCHROMOCYTOMA | 11 (12%) | 4 (8%) | 8 (16%) |
| PHEOCHROMOCYTOMA, MALIGNANT | 3 (3%) | | 1 (2%) |
| #THYROID | (89) | (50) | (49) |
| FOLLICULAR-CELL ADENOMA | 2 (2%) | 1 (2%) | |
| FOLLICULAR-CELL CARCINOMA | 2 (2%) | | |
| C-CELL ADENOMA | | | 1 (2%) |
| C-CELL CARCINOMA | 2 (2%) | 5 (10%) | 2 (4%) |
| #PANCREATIC ISLETS | (88) | (47) | (46) |
| ISLET-CELL CARCINOMA | 3 (3%) | 1 (2%) | 3 (7%) |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (90) | (50) | (50) |
| FIBROADENOMA | 2 (2%) | 3 (6%) | |
| *PREPUTIAL GLAND | (90) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | |
| SEBACEOUS ADENOMA | | | 2 (4%) |
| SEBACEOUS ADENOCARCINOMA | 1 (1%) | | 1 (2%) |
| #TESTIS | (90) | (50) | (50) |
| INTERSTITIAL-CELL TUMOR | 86 (96%) | 49 (98%) | 49 (98%) |
| INTERSTITIAL-CELL TUMOR, MALIGNA | 1 (1%) | | |
| NERVOUS SYSTEM | | | |
| #CEREBRUM | (90) | (50) | (50) |
| ASTROCYTOMA | 1 (1%) | | |

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

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #BRAIN | (90) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA, INVASIV | | | 1 (2%) |
| ASTROCYTOMA | 1 (1%) | 2 (4%) | 1 (2%) |
| OLIGODENDROGLIOMA | 1 (1%) | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *INTERCOSTAL MUSCLE | (90) | (50) | (50) |
| ALVEOLAR/BRONCHIOLAR CA, INVASIV | 1 (1%) | | |
| BODY CAVITIES | | | |
| *PERITONEUM | (90) | (50) | (50) |
| MESOTHELIOMA, MALIGNANT | 1 (1%) | | 1 (2%) |
| *MESENTERY | (90) | (50) | (50) |
| LEIOMYOSARCOMA, METASTATIC | | 1 (2%) | |
| *TUNICA VAGINALIS | (90) | (50) | (50) |
| MESOTHELIOMA, NOS | | 2 (4%) | 1 (2%) |
| MESOTHELIOMA, MALIGNANT | | 1 (2%) | 1 (2%) |
| ALL OTHER SYSTEMS | | | |
| *MULTIPLE ORGANS | (90) | (50) | (50) |
| MESOTHELIOMA, NOS | 1 (1%) | | |
| MESOTHELIOMA, MALIGNANT | 1 (1%) | | |
| THORACIC CAVITY | | | |
| CORTICAL CARCINOMA, METASTATIC | | 1 | |

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

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 90 | 50 | 50 |
| NATURAL DEATH@ | 9 | 5 | 6 |
| MORIBUND SACRIFICE | 11 | 2 | 5 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | 1 | |
| TERMINAL SACRIFICE | 70 | 42 | 39 |
| ANIMAL MISSING | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 90 | 50 | 50 |
| TOTAL PRIMARY TUMORS | 175 | 94 | 94 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 86 | 49 | 49 |
| TOTAL BENIGN TUMORS | 124 | 65 | 66 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 40 | 19 | 17 |
| TOTAL MALIGNANT TUMORS | 45 | 23 | 19 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 4 | 2 | 2 |
| TOTAL SECONDARY TUMORS | 7 | 2 | 2 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | 6 | 4 | 9 |
| TOTAL UNCERTAIN TUMORS | 6 | 5 | 9 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | 1 | |
| TOTAL UNCERTAIN TUMORS | | 1 | |

@ INCLUDES AUTOLYZED ANIMALS

* 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 C.I. ACID ORANGE 10

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 90 | 50 | 50 |
| ANIMALS MISSING | 2 | | |
| ANIMALS NECROPSIED | 88 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 88 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (88) | (50) | (50) |
| FIBROSARCOMA | | 1 (2%) | |
| *SUBCUT TISSUE | (88) | (50) | (50) |
| BASAL-CELL TUMOR | | 1 (2%) | |
| FIBROMA | 2 (2%) | 2 (4%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (88) | (50) | (49) |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (88) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 2 (2%) | | 1 (2%) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | 1 (2%) | |
| LYMPHOCYTIC LEUKEMIA | 14 (16%) | 2 (4%) | |
| #SPLEEN | (88) | (50) | (50) |
| LYMPHOCYTIC LEUKEMIA | 2 (2%) | | |
| #RENAL LYMPH NODE | (86) | (49) | (50) |
| TRANSITIONAL-CELL CARCINOMA, MET | 1 (1%) | | |
| #THYMUS | (70) | (41) | (36) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | 1 (2%) | |
| CIRCULATORY SYSTEM | | | |
| #HEART | (88) | (50) | (49) |
| NEURILEMOMA, MALIGNANT | 1 (1%) | | |

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

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| **DIGESTIVE SYSTEM** | | | |
| *TONGUE | (88) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | |
| #LIVER | (88) | (50) | (50) |
| NEOPLASTIC NODULE | 3 (3%) | | 1 (2%) |
| HEPATOCELLULAR CARCINOMA | | 2 (4%) | |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | |
| **URINARY SYSTEM** | | | |
| #KIDNEY/PELVIS | (88) | (50) | (50) |
| TRANSITIONAL-CELL CARCINOMA | 1 (1%) | | |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (83) | (44) | (46) |
| CHROMOPHOBE ADENOMA | 25 (30%) | 13 (30%) | 11 (24%) |
| CHROMOPHOBE CARCINOMA | 5 (6%) | 1 (2%) | 1 (2%) |
| GANGLIONEUROMA | | | 1 (2%) |
| #ADRENAL | (86) | (50) | (50) |
| CORTICAL ADENOMA | 6 (7%) | 4 (8%) | 2 (4%) |
| CORTICAL CARCINOMA | 1 (1%) | | |
| PHEOCHROMOCYTOMA | 3 (3%) | 4 (8%) | |
| PHEOCHROMOCYTOMA, MALIGNANT | 1 (1%) | | |
| #THYROID | (86) | (50) | (49) |
| FOLLICULAR-CELL ADENOMA | 1 (1%) | | 2 (4%) |
| C-CELL CARCINOMA | 3 (3%) | | 1 (2%) |
| #PARATHYROID | (69) | (35) | (37) |
| ADENOMA, NOS | | 1 (3%) | |
| #PANCREATIC ISLETS | (83) | (50) | (48) |
| ISLET-CELL CARCINOMA | 1 (1%) | 1 (2%) | |
| **REPRODUCTIVE SYSTEM** | | | |
| *MAMMARY GLAND | (88) | (50) | (50) |
| ADENOMA, NOS | 2 (2%) | 2 (4%) | 1 (2%) |

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

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ADENOCARCINOMA, NOS | 2 (2%) | 1 (2%) | |
| FIBROMA | | | 1 (2%) |
| FIBROADENOMA | 18 (20%) | 7 (14%) | 6 (12%) |
| *PREPUTIAL GLAND | (88) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | 1 (1%) | | |
| *CLITORAL GLAND | (88) | (50) | (50) |
| SEBACEOUS ADENOMA | | | 1 (2%) |
| *VAGINA | (88) | (50) | (50) |
| FIBROMA | 1 (1%) | | |
| #UTERUS | (87) | (50) | (49) |
| SARCOMA, NOS | | | 1 (2%) |
| FIBROMA | | | 1 (2%) |
| FIBROSARCOMA | | | 1 (2%) |
| LEIOMYOSARCOMA | | | 1 (2%) |
| ENDOMETRIAL STROMAL POLYP | 9 (10%) | 7 (14%) | 6 (12%) |
| #OVARY | (86) | (50) | (48) |
| GRANULOSA-CELL TUMOR | | | 1 (2%) |
| GRANULOSA-CELL CARCINOMA | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| #BRAIN | (88) | (50) | (50) |
| EPENDYMOMA | 1 (1%) | | |
| ASTROCYTOMA | | 1 (2%) | |
| #MEDULLA OBLONGATA | (88) | (50) | (50) |
| ASTROCYTOMA | | 1 (2%) | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| NONE | | | |

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

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ALL OTHER SYSTEMS | | | |
| *MULTIPLE ORGANS | (88) | (50) | (50) |
| SARCOMA, NOS | 1 (1%) | | |
| LEIOMYOSARCOMA | | 1 (2%) | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 90 | 50 | 50 |
| NATURAL DEATH@ | 11 | 1 | 4 |
| MORIBUND SACRIFICE | 11 | 3 | 2 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 66 | 46 | 44 |
| ANIMAL MISSING | 2 | | |

@ INCLUDES AUTOLYZED ANIMALS

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 68 | 33 | 31 |
| TOTAL PRIMARY TUMORS | 106 | 55 | 41 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 50 | 26 | 28 |
| TOTAL BENIGN TUMORS | 67 | 42 | 32 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 33 | 10 | 6 |
| TOTAL MALIGNANT TUMORS | 36 | 13 | 7 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | 1 | |
| TOTAL SECONDARY TUMORS | 1 | 2 | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | 3 | | 2 |
| TOTAL UNCERTAIN TUMORS | 3 | | 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 A3.

# INDIVIDUAL ANIMAL TUMOR PATHOLOGY IN MALE RATS IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

## CONTROL

| 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 | 104 | 104 | 090 | 104 | 104 | 096 | 101 | 104 | 104 | 104 | 104 | 104 | 104 | 097 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 086 | 104 | 104 | 104 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | N | + | + | + | + | + | + | N | + | + | N | + | + | N | + | + | + | + | + | N | + | + |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SEBACEOUS ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | N | + | + | + | + | + | + | N | + | + | N | + | + | N | + | + | + | + | + | N | + | + |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | X | | |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | X | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | - | + | + | + | + | + | + | + | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OSTEOMA | | | | | | | | | | | | | | | | | | | | | | X | | | |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MUCINOUS ADENOCARCINOMA, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | |
| INTERSTITIAL-CELL TUMOR, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | + | + | + | + | + | - | - | + | + | + | + | - | - | + | + | + | + | + | + | + | + | - | + | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR CA, INVASIVE | | | | | | | | | | | | | | | | | | | | | | | | | |
| NONCHROMAFFIN PARAGANGLIOMA | | | | | | | | | | | | | | | | | | | | | | | X | | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| MIXED TUMOR, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASTIC NODULE | | | | | | | | | | | | | | | | | | | X | | | | | | |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| 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 | | | | | | | | | | | | | | | | | | | | | | | | | |
| SMALL INTESTINE | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ADENOMATOUS POLYP, NOS | | X | | | | | | | | | | | | | | | | | | | | | | | |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| ADENOMA, NOS | | | | | | | | | | | X | | X | | | | | | | | | | | | |
| CHROMOPHOBE ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ACIDOPHIL ADENOMA | | | | | | | | | | | | | | | | | | X | | | | | | | |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | | X | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | | | | | X | | | | | | | | | | | | | | X | X | | | |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | | | | X | | | | | | | | | | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | X | | | | | | | | | | | | |
| FOLLICULAR-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | X | | | | |
| C-CELL CARCINOMA | | | | | | | | | X | | | | | | | | | | | | | | | | |
| PARATHYROID | + | - | + | + | + | + | + | - | + | - | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| PANCREATIC ISLETS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | + | N | N | + | N | + | N | N | N | 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 | X | X |
| INTERSTITIAL-CELL TUMOR, MALIGNAN | | | | | | | | | | | | | | | | | | | | | | | | | |
| 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 |
| SEBACEOUS ADENOCARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ASTROCYTOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| OLIGODENDROGLIOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MUSCLE | 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 |
| ALVEOLAR/BRONCHIOLAR CA, INVASIVE | | | | | | | | | | | | | | | | | | | | | | | | | |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PERITONEUM | 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, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| **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 | | | | | | | | | | | | | | X | | | | | | | | | | | |
| MESOTHELIOMA, MALIGNANT | X | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPHOCYTIC LEUKEMIA | | | X | X | | X | X | | | | X | X | | | | | | | | | | X | X | | |
| INTESTINAL TRACT | | | | | | | | | | | | | | | | | | | | | | | | | |
| MUCINOUS ADENOCARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |

+: 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 | 026 | 027 | 028 | 029 | 030 | 031 | 032 | 033 | 034 | 035 | 036 | 037 | 038 | 039 | 040 | 041 | 042 | 043 | 044 | 045 | 046 | 047 | 048 | 049 | 058 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 104 | 104 | 104 | 104 | 104 | 104 | 097 | 104 | 089 | 091 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 092 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | N | + | + | + | + |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | X | | | | | | X | | | | | | | |
| SEBACEOUS ADENOMA | | | | | | | | | | | | | | | | | | | | | | X | | | |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | N | + | + | + | + |
| FIBROMA | | | | | | | | | | | | | | X | | | | | | X | | | | | |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OSTEOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MUCINOUS ADENOCARCINOMA, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | |
| INTERSTITIAL-CELL TUMOR, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | + | + | + | + | + | + | - | + | - | - | + | + | - | + | - | - | + | + | + | + | + | + | + | + | - |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR CA, INVASIVE | | | | | | | | | | | | | | | | | | | | | | | | | |
| NONCHROMAFFIN PARAGANGLIOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MIXED TUMOR, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | X |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASTIC NODULE | | | | | | | | | | | | | | | | | | | | | | | | X | |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| 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 | | | | | | | | | | | | | | | | | | | | | | | | | |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| ADENOMATOUS POLYP, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | - | + | + | + | - |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| CHROMOPHOBE ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ACIDOPHIL ADENOMA | | | | | | | | | | | | | | X | | | | | | | | | | | |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | | X | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | X | | X | | | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | X | X | | | | | | | | | | | | | | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | X | | | | | | | | | | |
| FOLLICULAR-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| C-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PARATHYROID | + | + | + | + | + | - | - | - | - | - | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| PANCREATIC ISLETS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | X | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | + | N | + | N | + | N | + | + | N | N | N | + | + | + | + | N | N | + | + | 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 | X | X |
| INTERSTITIAL-CELL TUMOR, MALIGNAN | | | | | | | | | | | | | | | | | | | | | | | | | |
| 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 |
| SEBACEOUS ADENOCARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ASTROCYTOMA | | | | | | | | | | X | | | | | | | | | | | | | | | |
| OLIGODENDROGLIOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MUSCLE | 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 |
| ALVEOLAR/BRONCHIOLAR CA, INVASIVE | | | | | | | | | | | | | | | | | | | | | | | | | |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PERITONEUM | 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, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| **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 | | | | | | | | | | | | | | | | | | | | | | | | | |
| MESOTHELIOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPHOCYTIC LEUKEMIA | | | | | | | X | X | | X | | | | X | X | | | | | | | | | | |
| INTESTINAL TRACT | | | | | | | | | | | | | | | | | | | | | | | | | |
| MUCINOUS ADENOCARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |

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

: 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 | 051171 | 052141 | 053141 | 054112 | 055514 | 056114 | 057714 | 058814 | 059114 | 060104 | 061104 | 062104 | 063104 | 064104 | 065104 | 066104 | 067104 | 068804 | 069704 | 070104 | 071104 | 072104 | 073104 | 074104 | 075104 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 104 | 104 | 104 | 102 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 097 | 104 | 104 | 104 | 104 | 104 | 104 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | N | + | + | + | + | N | + | + | N | + | + | + | + | + | + | + | + | + | + |
| SQUAMOUS CELL PAPILLOMA | | | | | | X | | | | | | | | | | | | | | | | | | | |
| SEBACEOUS ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROMA | | X | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | N | + | + | + | + | N | + | + | N | + | + | + | + | + | + | + | + | + | + |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | X |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | X | | | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OSTEOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | | | X | | | |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + |
| MUCINOUS ADENOCARCINOMA, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | |
| INTERSTITIAL-CELL TUMOR, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | + | + | - | + | - | - | + | - | + | - | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR CA, INVASIVE | | | | | X | | | | | | | | | | | | | | | | | | | | |
| NONCHROMAFFIN PARAGANGLIOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MIXED TUMOR, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASTIC NODULE | | | | | | | | | | X | | X | | | | | | | | | | X | | | |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| 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 | | | | | | | | | | | | | | | | | | | | | | | | | |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ADENOMATOUS POLYP, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + |
| ADENOMA, NOS | | | | | | | | | | | | | X | | | | | | | | | | | | |
| CHROMOPHOBE ADENOMA | | | | | | | | | | | | | | | | | | | | X | | | | | |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | X | | | | | | | | | | | |
| ACIDOPHIL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADRENAL | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | | X | X | | | | | | | | | X | X | X | | | X | | | | | | |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| FOLLICULAR-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| C-CELL CARCINOMA | | | | | X | | | | | | | | | | | | | | | | | | | | |
| PARATHYROID | + | + | - | + | - | - | + | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PANCREATIC ISLETS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | N | + | + | + | + | N | N | + | N | N | + | N | + | + | N | + | + | N | + | + | N | N | + | N | + |
| 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 | X | X | X |
| INTERSTITIAL-CELL TUMOR, MALIGNAN | | | | | | | | | | | | | | | | | | | | | | | | | |
| 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 | N |
| SEBACEOUS ADENOCARCINOMA | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ASTROCYTOMA | | | | | | | | | | | | X | | | | | | | | | | | | | |
| OLIGODENDROGLIOMA | | | | | | | | | | | | | | | | | | | X | | | | | | |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MUSCLE | N | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | N | + | N | N | N | N | N | N |
| ALVEOLAR/BRONCHIOLAR CA, INVASIVE | | | | | X | | | | | | | | | | | | | | | | | | | | |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PERITONEUM | 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, MALIGNANT | | | 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 | | | | | | | | | | | | | | | | | | | | | | | | | |
| MESOTHELIOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPHOCYTIC LEUKEMIA | | X | | | | | | | | | | X | | X | | | | X | | | | | | | |
| INTESTINAL TRACT | | | | | | | | | | | | | | | | | | | | | | | | | |
| MUCINOUS ADENOCARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |

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

: 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 | 07603 | 07704 | 07804 | 07904 | 08004 | 08101 | 08204 | 08304 | 08406 | 08504 | 08604 | 08704 | 08804 | 08902 | 09004 | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 093 | 104 | 104 | 104 | 120 | 100 | 104 | 104 | 086 | 104 | 104 | 104 | 104 | 062 | 104 | |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | N | + | N | + | + | + | + | N | + | 90* |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | 3 |
| SEBACEOUS ADENOMA | | | | | | | | | | | | | | | | 1 |
| FIBROMA | | | | | | | | | | | | | | | | 1 |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | N | + | N | + | + | + | + | N | + | 90* |
| FIBROMA | | | | | | | | | | | | | | | | 4 |
| FIBROSARCOMA | | | | | | | | | X | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 89 |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | | | | 1 |
| PHEOCHROMOCYTOMA, METASTATIC | | | | | | | | | | | | | | | | 1 |
| FIBROSARCOMA, METASTATIC | | | | | | | | | X | | | | | | | 1 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 84 |
| OSTEOMA | | | | | | | | | | | | | | | | 1 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 90 |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | 1 |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 89 |
| MUCINOUS ADENOCARCINOMA, METASTATI | | | | | | | | | | | | | | X | | 1 |
| INTERSTITIAL-CELL TUMOR, METASTAT | | | | | | | | | X | | | | | | | 1 |
| THYMUS | + | + | + | + | - | + | + | + | - | + | + | + | + | - | + | 69 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 90 |
| ALVEOLAR/BRONCHIOLAR CA, INVASIVE | | | | | | | | | | | | | | | | 1 |
| NONCHROMAFFIN PARAGANGLIOMA | | | | | | | | | | | | | | | | 1 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 89 |
| MIXED TUMOR, MALIGNANT | | | | | | | | | | | | | | | | 1 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 90 |
| NEOPLASTIC NODULE | | | | | | | | | | | | | | | | 5 |
| FIBROSARCOMA, METASTATIC | | | | | | | | | X | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 90 |
| GALLBLADDER & COMMON BILE DUCT | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 90* |
| PANCREAS | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 88 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 89 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | 87 |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | X | 1 |
| SMALL INTESTINE | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + | 87 |
| LARGE INTESTINE | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 87 |
| ADENOMATOUS POLYP, NOS | | | | | | | | | | | | | | | | 1 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 90 |
| URINARY BLADDER | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 82 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | - | + | + | + | + | + | + | + | - | + | + | 84 |
| ADENOMA, NOS | | | | | | | | | | | | X | | | | 1 |
| CHROMOPHOBE ADENOMA | | | | | | | | | | | | | | | | 4 |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | | 1 |
| ACIDOPHIL ADENOMA | | | | | | | | | | | | | | | | 2 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 89 |
| CORTICAL ADENOMA | | | | | | | | | | | X | | | | | 3 |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | 11 |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | | | | | | | 3 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 89 |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | X | | | | | | 2 |
| FOLLICULAR-CELL CARCINOMA | | | | | | | | | | | | | | | | 2 |
| C-CELL CARCINOMA | | | | | | | | | | | | | | | | 2 |
| PARATHYROID | + | + | + | + | - | + | + | + | + | + | - | - | + | + | - | 70 |
| PANCREATIC ISLETS | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 88 |
| ISLET-CELL CARCINOMA | | | | X | | | | | | | | | | | | 3 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | + | N | N | N | N | N | N | N | + | N | N | N | N | 90* |
| FIBROADENOMA | | | | | | | | | | | | | | | | 2 |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 90 |
| INTERSTITIAL-CELL TUMOR | X | X | X | X | | X | X | X | | X | X | X | X | | X | 86 |
| INTERSTITIAL-CELL TUMOR, MALIGNAN | | | | | | | | | X | | | | | | | 1 |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | 84 |
| PREPUTIAL/CLITORAL GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 90* |
| SEBACEOUS ADENOCARCINOMA | | | | | | | | | | | | | | | | 1 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 90 |
| ASTROCYTOMA | | | | | | | | | | | | | | | | 2 |
| OLIGODENDROGLIOMA | | | | | | | | | | | | | | | | 1 |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | |
| MUSCLE | N | N | N | N | N | N | N | N | + | N | N | N | N | N | N | 90* |
| ALVEOLAR/BRONCHIOLAR CA, INVASIVE | | | | | | | | | | | | | | | | 1 |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | |
| PERITONEUM | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 90* |
| MESOTHELIOMA, MALIGNANT | | | | | | | | | | | | | | | | 1 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 90* |
| MESOTHELIOMA, NOS | | | | | | | | | | | | | | | | 1 |
| MESOTHELIOMA, MALIGNANT | | | | | | | | | | | | | | | | 1 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | X | | | | | | | | | | | 1 |
| LYMPHOCYTIC LEUKEMIA | X | | | X | | X | | | | | | X | | | | 21 |
| INTESTINAL TRACT | | | | | | | | | | | | | | | | |
| MUCINOUS ADENOCARCINOMA | | | | | | | | | | | | | | X | | 1 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 IN MALE RATS IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

### LOW 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 | 067 | 090 | 093 | 098 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 083 | 104 | 043 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | N | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + |
| BASAL-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | X |
| SEBACEOUS ADENOMA | | | | | | | | | | | | | | | | | | | | | X | | | | |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | N | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FIBROMA | | | | | | | X | | | | | | | | | | | | | X | | | | | |
| FIBROSARCOMA | | | X | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYMUS | - | - | - | + | + | + | + | - | + | + | + | + | + | + | - | - | - | + | + | + | + | + | + | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ADENOCARCINOMA, NOS, UNC PRIM OR NEURILEMOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASTIC NODULE | | | | | | | | 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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LEIOMYOSARCOMA | | | | | | | | | | | | | | | X | | | | | | | | | | |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | - | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | - | + | + | + | + |
| CHROMOPHOBE ADENOMA | | | | | | | | | X | | | | | | | | | | | | | | | | |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | X | | | | | | | | | | | X | | |
| ADRENAL | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | | | | | | | X | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | X | | | | | | | | | | | | | | | | | | | |
| C-CELL CARCINOMA | | | | | | X | | | X | | | | | | | | | | | | | | | | |
| PARATHYROID | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PANCREATIC ISLETS | - | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | X | | | | | | | | | | | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | + | N | + | N | + | + | + | N | N | N | + | + | N | N | N | + | + | N | N | + | + | N | + |
| 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 | 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 |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ASTROCYTOMA | | | | | | | | | | | | | | | X | | | | | | | | | | |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PLEURA | 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 |
| CORTICAL CARCINOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| TUNICA VAGINALIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MESOTHELIOMA, NOS | X | | | | | | | | | | | | | | X | | | | | | | | | | |
| MESOTHELIOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| 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 |
| LEIOMYOSARCOMA, METASTATIC | | | | | | | | | | | | | | | 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 |
| LYMPHOCYTIC LEUKEMIA | | 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) LOW DOSE

| 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 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 092 | 104 | 104 | 104 | 104 | 104 | 082 | 104 | 104 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | N | + | + | + | + | + | + | + | 50M |
| BASAL-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SEBACEOUS ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| FIBROSARCOMA | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | N | + | + | + | + | + | + | + | 50M |
| FIBROMA | | | | | | | | X | | | | | | | | | | X | | | | | | | | 4 |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | 49 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| THYMUS | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - | - | - | - | + | + | + | - | + | 37 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| ADENOCARCINOMA, NOS, UNC PRIM OR | | | | | | | | | | | | X | | | | | | X | | | | | | | | 1 |
| NEURILEMOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| NEOPLASTIC NODULE | | | | | | | | | | X | | | | | | | | | | X | | | | | | 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 | 50M |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | 47 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | - | + | + | 48 |
| LEIOMYOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | 47 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | 47 |
| CHROMOPHOBE ADENOMA | | X | | | | | | | | | X | | | | | | | | | | | | | | | 2 |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | | | | | | X | | | | | | 4 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | X | + | + | + | + | + | + | + | 49 |
| CORTICAL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| PHEOCHROMOCYTOMA | | | | | X | X | | | | | | | | | | | | X | | | | | | | | 4 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| C-CELL CARCINOMA | | | | | X | | | | | | X | | | | | X | | | | | | | | | | 5 |
| PARATHYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | 48 |
| PANCREATIC ISLETS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | 47 |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | + | + | + | N | N | + | N | N | N | + | N | N | N | + | N | + | N | + | + | N | N | N | + | + | 50M |
| FIBROADENOMA | | | | | | | | | | | | | | | X | | | | | | | | | | | 3 |
| 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 | 49 |
| PROSTATE | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | 45 |
| 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 |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ASTROCYTOMA | | | | | | | | | | | | | | | | | X | | | | | | | | | 2 |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PLEURA | 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 |
| CORTICAL CARCINOMA, METASTATIC | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| TUNICA VAGINALIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50M |
| MESOTHELIOMA, NOS | | | | | | | | | | | | | | | | | | | | X | | | | | | 2 |
| MESOTHELIOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | | 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 | N | 50M |
| LEIOMYOSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 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 |
| LYMPHOCYTIC LEUKEMIA | | | | | | X | | | | | | | | | | | | | | | | | | | | 4 |

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 IN MALE RATS IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

## HIGH DOSE

| ANIMAL NUMBER | 0011 | 0023 | 0034 | 0045 | 0056 | 0067 | 0078 | 0089 | 0101 | 0110 | 0121 | 0132 | 0143 | 0154 | 0165 | 0176 | 0187 | 0198 | 0210 | 0221 | 0232 | 0243 | 0254 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 0 4 | 0 9 | 0 4 | 0 4 | 0 4 | 0 4 | 0 4 | 0 4 | 0 4 | 0 6 | 0 4 | 0 2 | 0 4 | 0 8 | 0 4 | 0 2 | 0 4 | 0 4 | 0 4 | 0 4 | 0 4 | 0 1 | 0 4 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + | + | + | + | N | + |
| SQUAMOUS CELL CARCINOMA | | | | | | | | | | | | | | X | | X | | | X | | | | |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | - | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEMANGIOMA | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPH NODES | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-CELL CARCINOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | X | | | |
| THYMUS | + | + | + | + | - | + | + | + | - | + | - | - | + | + | + | - | - | + | + | + | - | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **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 |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | X | | | | | | | |
| SALIVARY GLAND | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASTIC NODULE | | | | | | | | | | | X | | X | | | | | | | X | | | X |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | |
| 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 | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SMALL INTESTINE | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| CHROMOPHOBE CARCINOMA | | | | | | | | X | | | | | | | | | | | | | X | | |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | X | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | X | | | X | | | | | | | | | | | | | | | X | | |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | X | | | | | | | | | | | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + |
| C-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | |
| C-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | X | | |
| PARATHYROID | - | + | - | + | + | + | + | + | + | - | - | + | + | - | + | + | + | - | + | + | - | + | + |
| PANCREATIC ISLETS | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | - | + | + |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | X |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | + | + | + | + | N | N | + | N | N | N | + | N | N | N | N | + | + | + | N | N | + | + | N | N |
| 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 | 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 |
| SEBACEOUS ADENOMA | | | | | | | | X | | | | | | | | | | | | | | | |
| SEBACEOUS ADENOCARCINOMA | | | | | | | | | | | | | | | | | | | | | | | |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SQUAMOUS CELL CARCINOMA, INVASIVE | | | | | | | | | | | | X | | X | | | | | | | | | |
| ASTROCYTOMA | | | | | | | | | | | | | | | | | | | | | | | |
| OLIGODENDROGLIOMA | | | | | | | | | | | | | | | | | | | | | | | |
| **BODY CAVITIES** | | | | | | | | | | | | | | | | | | | | | | | |
| PERITONEUM | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| MESOTHELIOMA, MALIGNANT | | | | | | | | | | | | | | | | X | | | | | | | |
| TUNICA VAGINALIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MESOTHELIOMA, NOS | | | | | | | | | | | | | | | | X | | | | | | | |
| MESOTHELIOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | |
| **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 |
| LYMPHOCYTIC LEUKEMIA | | 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) HIGH DOSE

| ANIMAL NUMBER / WEEKS ON STUDY | TOTAL TISSUES TUMORS |
|---|---|
| **INTEGUMENTARY SYSTEM** | |
| SUBCUTANEOUS TISSUE | 50* |
| SQUAMOUS CELL CARCINOMA | 1 |
| FIBROMA | 2 |
| FIBROSARCOMA | 1 |
| **RESPIRATORY SYSTEM** | |
| LUNGS AND BRONCHI | 50 |
| TRACHEA | 48 |
| **HEMATOPOIETIC SYSTEM** | |
| BONE MARROW | 48 |
| SPLEEN | 50 |
| HEMANGIOMA | 1 |
| LYMPH NODES | 49 |
| C-CELL CARCINOMA, METASTATIC | 1 |
| THYMUS | 38 |
| **CIRCULATORY SYSTEM** | |
| HEART | 50 |
| **DIGESTIVE SYSTEM** | |
| ORAL CAVITY | 50* |
| SQUAMOUS CELL PAPILLOMA | 1 |
| SALIVARY GLAND | 47 |
| LIVER | 50 |
| NEOPLASTIC NODULE | 8 |
| HEPATOCELLULAR CARCINOMA | 1 |
| BILE DUCT | 50 |
| GALLBLADDER & COMMON BILE DUCT | 50* |
| PANCREAS | 46 |
| ESOPHAGUS | 49 |
| STOMACH | 49 |
| SMALL INTESTINE | 47 |
| LARGE INTESTINE | 49 |
| **URINARY SYSTEM** | |
| KIDNEY | 50 |
| URINARY BLADDER | 46 |
| **ENDOCRINE SYSTEM** | |
| PITUITARY | 46 |
| CHROMOPHOBE CARCINOMA | 2 |
| ADRENAL | 50 |
| CORTICAL ADENOMA | 2 |
| PHEOCHROMOCYTOMA | 8 |
| PHEOCHROMOCYTOMA, MALIGNANT | 1 |
| THYROID | 49 |
| C-CELL ADENOMA | 1 |
| C-CELL CARCINOMA | 2 |
| PARATHYROID | 37 |
| PANCREATIC ISLETS | 46 |
| ISLET-CELL CARCINOMA | 3 |
| **REPRODUCTIVE SYSTEM** | |
| MAMMARY GLAND | 50* |
| TESTIS | 50 |
| INTERSTITIAL-CELL TUMOR | 49 |
| PROSTATE | 45 |
| PREPUTIAL/CLITORAL GLAND | 50* |
| SEBACEOUS ADENOMA | 2 |
| SEBACEOUS ADENOCARCINOMA | 1 |
| **NERVOUS SYSTEM** | |
| BRAIN | 50 |
| *SQUAMOUS CELL CARCINOMA, INVASIVE* | 1 |
| ASTROCYTOMA | 1 |
| OLIGODENDROGLIOMA | 1 |
| **BODY CAVITIES** | |
| PERITONEUM | 50* |
| MESOTHELIOMA, MALIGNANT | 1 |
| TUNICA VAGINALIS | 50* |
| MESOTHELIOMA, NOS | 1 |
| MESOTHELIOMA, MALIGNANT | 1 |
| **ALL OTHER SYSTEMS** | |
| MULTIPLE ORGANS NOS | 50* |
| LYMPHOCYTIC LEUKEMIA | 3 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 IN FEMALE RATS IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

## CONTROL

| 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 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 075 | 104 | 088 | 104 | 103 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 088 | 104 | 104 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE<br>FIBROMA | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN<br>LYMPHOCYTIC LEUKEMIA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +<br>X |
| LYMPH NODES<br>*TRANSITIONAL-CELL CARCINOMA, META* | + | + | + | + | + | + | + | + | + | + | +<br>X | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYMUS | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART<br>NEURILEMOMA, MALIGNANT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER<br>NEOPLASTIC NODULE | + | + | + | + | + | + | + | + | + | + | +<br>X | + | +<br>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<br>TRANSITIONAL-CELL CARCINOMA | + | + | + | + | + | + | + | + | + | + | +<br>X | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | - | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY<br>CHROMOPHOBE ADENOMA<br>CHROMOPHOBE CARCINOMA | + | +<br>X | +<br>X | + | - | +<br>X | + | + | + | +<br>X | + | +<br>X | + | + | +<br>X | + | + | + | + | + | +<br>X | +<br>X | + | + | +<br>X |
| ADRENAL<br>CORTICAL ADENOMA<br>CORTICAL CARCINOMA<br>PHEOCHROMOCYTOMA<br>PHEOCHROMOCYTOMA, MALIGNANT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +<br>X | + | + | + | + | + | + | + | + | + |
| THYROID<br>FOLLICULAR-CELL ADENOMA<br>C-CELL CARCINOMA | + | +<br>X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PARATHYROID | + | + | - | + | + | + | + | + | - | + | + | + | + | - | + | + | - | + | + | - | - | + | + | + | + |
| PANCREATIC ISLETS<br>ISLET-CELL CARCINOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND<br>ADENOMA, NOS<br>ADENOCARCINOMA, NOS<br>FIBROADENOMA | N | + | +<br>X | + | + | + | N | N | + | + | +<br>X | + | + | N | + | N | N | + | + | + | + | + | + | + | +<br>X |
| PREPUTIAL/CLITORAL GLAND<br>SQUAMOUS CELL CARCINOMA | N | N<br>X | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| VAGINA<br>FIBROMA | 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 |
| UTERUS<br>ENDOMETRIAL STROMAL POLYP | + | + | + | + | + | + | +<br>X | + | + | + | +<br>X | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN<br>EPENDYMOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS<br>SARCOMA, NOS<br>MALIGNANT LYMPHOMA, NOS<br>LYMPHOCYTIC LEUKEMIA | N | N | N | N | N | N | N | N | X | N | N | N | N | X | N | X | N | N | N | N | N | X | 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) 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 094 | 104 | 104 | 104 | 098 | 085 | 097 | 104 | 090 | 104 | 091 | 104 | 104 | 082 | 104 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + |
| FIBROMA | | | | | X | | | | | | | | | X | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPHOCYTIC LEUKEMIA | | | | X | | | | | | | | | | | | | | | | | | | | | |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRANSITIONAL-CELL CARCINOMA, META | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | + | + | - | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | - | + | + | - | + | + | |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEURILEMOMA, MALIGNANT | | X | | | | | | | | | | | | | | | | | | | | | | | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASTIC NODULE | | | | | | | | | | | | | | | | | | | | | | | 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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + |
| CHROMOPHOBE ADENOMA | X | | | | X | | X | | | | | | | | X | | X | | X | | | | | | |
| CHROMOPHOBE CARCINOMA | | | | X | | | | X | | | | | | | | | | X | | | | | | | |
| ADRENAL | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | X | | | | | | | | | | | X | | | | | | | | | | | |
| CORTICAL CARCINOMA | | | | | | | | | | | | | X | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | X | | | | | | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYROID | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | X | | | | | | | | | | | | | | | | |
| C-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PARATHYROID | + | + | + | + | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | - | |
| PANCREATIC ISLETS | - | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | + | + | N | + | + | + | N | + | N | + | N | + | + | + | + | + | + | + | + | + | + | N | + | + |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADENOCARCINOMA, NOS | | | | | X | | | | | | | | | | | | | | | X | X | | | | |
| FIBROADENOMA | | | | | | | 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 |
| SQUAMOUS CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| VAGINA | 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 |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | X |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + |
| ENDOMETRIAL STROMAL POLYP | X | | | | | | | | | | | | | | | | | | | | | X | X | | |
| OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| EPENDYMOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **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 | | | | | | | | | | |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPHOCYTIC LEUKEMIA | | | X | | | | | | X | | X | | | | | X | | | | X | | | | | |

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 | 051 | 052 | 053 | 054 | 055 | 056 | 057 | 058 | 059 | 060 | 061 | 062 | 063 | 064 | 065 | 066 | 067 | 068 | 069 | 070 | 071 | 072 | 073 | 074 | 075 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 098 | 104 | 104 | 080 | 104 | 104 | 104 | 104 | 098 | 104 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 100 | 105 | 105 | 105 | 093 | 081 | 105 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPH NODES | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRANSITIONAL-CELL CARCINOMA, META | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | + | M | – | – | M | + | + | + | – | + | – | + | + | + | + | – | + | + | – | – | – | + | – | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEURILEMOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | M | + | – | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASTIC NODULE | | | | | | | | | | | | | | | | | | | | | | | | | |
| BILE DUCT | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | N | M | N | N | M | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| PANCREAS | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | ~ | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SMALL INTESTINE | + | M | + | – | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | M | – | – | M | + | + | + | + | + | + | – | – | + | + | + | + | + | – | + | – | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| KIDNEY/PELVIS | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRANSITIONAL-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| URINARY BLADDER | – | M | + | + | M | + | – | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | – | + | + | – | + | + | + | + | + | + |
| CHROMOPHOBE ADENOMA | | | | | | | | X | X | | | | | | X | | | | | | X | | | X | |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | | | X | | | | | | | | |
| ADRENAL | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | | | | | | | | | + | | | | | | | | | | | |
| CORTICAL CARCINOMA | | | | | | | | | | | | | | X | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | | | | | X | | | | | |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYROID | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | X | | | | | | | | | | | | |
| C-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PARATHYROID | – | M | + | + | M | + | + | – | + | + | – | + | + | + | – | – | + | – | + | + | + | + | + | – | + |
| PANCREATIC ISLETS | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + |
| ISLET-CELL CARCINOMA | | | X | | | | | | | | | | | | | | | | | | | | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | M | + | N | M | + | + | + | N | + | + | + | + | + | + | N | N | N | + | + | N | + | + | N | + |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROADENOMA | X | | | | | | X | | | | X | | | | X | | | | X | | | | | X | X |
| PREPUTIAL/CLITORAL GLAND | N | M | N | N | M | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| SQUAMOUS CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| VAGINA | N | M | N | N | M | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| UTERUS | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ENDOMETRIAL STROMAL POLYP | | | | | | | | | | | | X | | | | | | | | | X | | | | |
| OVARY | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| EPENDYMOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | M | N | N | M | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | X | | | | | | | |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | X | | | X | | |

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 | 07761 | 07778 | 07799 | 07800 | 08811 | 08212 | 08533 | 08544 | 08855 | 08866 | 08877 | 08888 | 08899 | 09000 | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 105 | 105 | 105 | 105 | 098 | 097 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 006 | |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | N | 88* |
| FIBROMA | | | | | | | | | | | | | | | 2 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 86 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 86 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | 2 |
| LYMPH NODES | + | + | - | + | + | + | + | + | + | + | + | + | + | + | 86 |
| TRANSITIONAL-CELL CARCINOMA, META | | | | | | | | | | | | | | | 1 |
| THYMUS | + | + | + | + | + | + | + | + | - | + | + | + | + | - | 70 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| NEURILEMOMA, MALIGNANT | | | | | | | | | | | | | | | 1 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 87 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| NEOPLASTIC NODULE | | | | | | | | | | | | | | | 3 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| GALLBLADDER & COMMON BILE DUCT | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 88* |
| PANCREAS | + | + | + | + | + | + | - | + | + | + | + | + | + | + | 83 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 87 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | - | + | + | + | 86 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 85 |
| LARGE INTESTINE | - | + | - | - | + | + | + | + | + | + | - | + | + | + | 72 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| KIDNEY/PELVIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| TRANSITIONAL-CELL CARCINOMA | | | | | | | | | | | | | | | 1 |
| URINARY BLADDER | + | + | - | + | + | + | + | + | + | - | + | + | + | + | 80 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 83 |
| CHROMOPHOBE ADENOMA | | X | | | X | | X | X | | X | | | X | | 25 |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | 5 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 86 |
| CORTICAL ADENOMA | | | | | X | | | | X | | | | | | 6 |
| CORTICAL CARCINOMA | | | | | | | | | | | | | | | 1 |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | 3 |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | | | | | | 1 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 86 |
| FOLLICULAR-CELL ADENOMA | | | | | | | | X | | | | | | | 1 |
| C-CELL CARCINOMA | | | | | | | | | | | | | | | 3 |
| PARATHYROID | + | + | + | + | + | + | + | - | - | + | + | + | + | + | 69 |
| PANCREATIC ISLETS | + | + | + | + | + | + | - | + | + | + | + | + | + | + | 83 |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | | 1 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | + | + | + | + | N | + | + | N | N | + | + | + | N | 88* |
| ADENOMA, NOS | | | | | | | | | | | | | X | | 2 |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | 2 |
| FIBROADENOMA | | | | | X | | | X | | | X | | | | 18 |
| PREPUTIAL/CLITORAL GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 88* |
| SQUAMOUS CELL CARCINOMA | | | | | | | | | | | | | | | 1 |
| VAGINA | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 88* |
| FIBROMA | | | | | | | | | | | | | | | 1 |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 87 |
| ENDOMETRIAL STROMAL POLYP | X | | | | | | X | | | | | | | | 9 |
| OVARY | + | + | + | + | + | + | - | + | + | + | + | + | + | + | 86 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 88 |
| EPENDYMOMA | | | | | | X | | | | | | | | | 1 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 88* |
| SARCOMA, NOS | | | | | | | | | | | | | | | 1 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | X | 2 |
| LYMPHOCYTIC LEUKEMIA | | | | | | | X | X | | | | | | | 14 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
5: ANIMAL MIS-SEXED
: 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 IN FEMALE RATS IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

### LOW 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 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 102 | 098 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + |
| FIBROSARCOMA | | | X | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + |
| BASAL-CELL TUMOR | | | | | | | | | | | | | X | | | | | | | | | | | | |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FIBROSARCOMA, METASTATIC | | | X | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| THYMUS | + | + | + | + | + | + | + | + | + | + | + | - | - | + | - | + | + | + | + | + | + | + | + | + | - |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **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 |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROSARCOMA, METASTATIC | | | 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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + |
| CHROMOPHOBE ADENOMA | | | | | | X | | X | | X | | | X | X | | | | | | | | | | X | |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | | | X | | | | | X | X | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | | | | | | | | X | | | | | | | | | | | | | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PARATHYROID | - | - | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | + | + | + | + |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| PANCREATIC ISLETS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | X | | | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | N | + | + | N | + | N | + | + | + | + | + | + | + | + | + | + | + | N | + | N | + | + | N | + | + |
| ADENOMA, NOS | | | | X | | | | | | | X | | | | | | | | | | | | | | |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | X | | | | | | | | | | | | |
| FIBROADENOMA | | | | | | | | X | | X | | X | | | | | | | | | | | | | |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ENDOMETRIAL STROMAL POLYP | | X | | | | | | | | | | | | | | | X | | | | | | X | X | |
| OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ASTROCYTOMA | | | | | | | | | | | | | | | | | | | | 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 |
| LEIOMYOSARCOMA | | | | | | | | | | | | | | | | | | | | | | X | | | |
| MALIG.LYMPHOMA, LYMPHOCYTIC 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 A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

| 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 | 104 | 104 | 104 | 098 | 041 | 104 | 104 | 104 | 104 | 104 | 104 | 106 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 103 | 104 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + | + | + | + | + | 50 M |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + | + | + | + | + | 50 M |
| BASAL-CELL TUMOR | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | X | | | | 2 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| THYMUS | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | – | – | + | + | + | + | – | – | 41 |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| **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 M |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | X | | | | | | | X | 2 |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 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 M |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 44 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | – | + | – | + | + | + | 44 |
| CHROMOPHOBE ADENOMA | | X | | | | | | | X | | | X | | | | | | X | X | | X | | | | X | 13 |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| CORTICAL ADENOMA | | | | | | | | | | | | | | | X | | | | | | | | | | | 4 |
| PHEOCHROMOCYTOMA | | X | | | | | | | X | | | | | | | | | | | | | X | | | | 4 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| PARATHYROID | – | + | + | – | – | + | – | + | + | + | – | + | + | – | + | – | + | + | + | – | + | + | + | – | + | 35 |
| ADENOMA, NOS | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| PANCREATIC ISLETS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ISLET-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| ***REPRODUCTIVE SYSTEM*** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | N | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | N | + | N | + | 50 M |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| FIBROADENOMA | | | | | | X | | | X | | X | X | | | | | | | | | | | | | | 7 |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ENDOMETRIAL STROMAL POLYP | X | | | | | | | | X | | | | | | | | | | | | | X | | | | 7 |
| OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ASTROCYTOMA | | | | X | | | | | | | | | | | | | | | | | | | | | | 2 |
| **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 M |
| LEIOMYOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | | | | | X | | 2 |

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

: 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 IN FEMALE RATS IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

## 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 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 096 | 104 | 104 | 104 | 104 | 104 | 104 | 091 | 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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASTIC NODULE | | | | | 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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | - | + | + |
| CHROMOPHOBE ADENOMA | | | | | | | X | | X | | | | | | X | | | | | | | | | | |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | | | | X | | | | | | | |
| GANGLIONEUROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | X | | | | | | | | | | | X | | | | | | | | | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | X | | | | | | | | | | | X | | | | | | | | | |
| C-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | X | | | | |
| PARATHYROID | + | + | + | + | + | + | + | + | + | + | - | + | + | - | + | + | - | - | + | - | + | - | + | + | + |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | N | + | N | + | + | + | + | + | N | + | N | + | N | + | + | N | + | N | + | + | + | + | + | N |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | X | | | |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROADENOMA | | | | | 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 |
| SEBACEOUS ADENOMA | | | | | | | | | | | | | | | | | | | | | | | X | | |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROSARCOMA | | | | | | | | | | | | X | | | | | | | | | | | | | |
| LEIOMYOSARCOMA | | | | | | | | | X | | | | | | | | | | | | | | | | |
| ENDOMETRIAL STROMAL POLYP | | | | | | | | | | | | | | | | X | | | | | | | | | |
| OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| GRANULOSA-CELL TUMOR | | | | | | | | | | | | | | X | | | | | | | | | | | |
| GRANULOSA-CELL CARCINOMA | | | | | | | | | 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 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |

+: 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 | 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 | 104 | 081 | 104 | 092 | 096 | 104 | 104 | 100 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| THYMUS | + | + | + | - | - | + | - | + | - | + | + | + | + | + | - | + | + | + | + | + | + | + | - | - | 36 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| NEOPLASTIC NODULE | | | | | | | | | | | | | | | | | | | | | | | | | 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 | 50* |
| PANCREAS | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| ESOPHAGUS | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| STOMACH | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SMALL INTESTINE | + | + | + | + | - | + | + | + | - | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | 47 |
| LARGE INTESTINE | - | - | + | - | - | - | + | + | + | + | + | + | - | + | - | - | + | + | - | + | + | + | + | + | 31 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | - | + | 45 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | 46 |
| CHROMOPHOBE ADENOMA | | | X | X | | | | | | | | | X | X | X | X | X | | | | | | | | 11 |
| CHROMOPHOBE CARCINOMA | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| GANGLIONEUROMA | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| CORTICAL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| THYROID | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| C-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| PARATHYROID | + | - | + | - | - | + | - | + | - | + | + | + | - | + | + | + | + | + | - | + | + | + | + | + | 37 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | + | + | + | + | N | N | + | + | + | + | N | + | + | N | + | + | + | + | + | + | N | + | N | 50* |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| FIBROMA | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| FIBROADENOMA | | | | | | | | | X | | | | | X | | | | | | | | | | | 6 |
| 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 | 50* |
| SEBACEOUS ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| UTERUS | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SARCOMA, NOS | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| FIBROMA | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| LEIOMYOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| ENDOMETRIAL STROMAL POLYP | | | | | | | | | X | X | X | | | X | | | | X | | | | | | | 6 |
| OVARY | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| GRANULOSA-CELL TUMOR | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| GRANULOSA-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | 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* |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 C.I. ACID ORANGE 10

## TABLE B1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIETS CONTAINING C.I. ACID ORANGE 10

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 49 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 49 | 50 |
| **INTEGUMENTARY SYSTEM** | | | |
| *SKIN | (50) | (49) | (50) |
| SARCOMA, NOS | | 3 (6%) | |
| FIBROMA | | 1 (2%) | 3 (6%) |
| FIBROUS HISTIOCYTOMA | 1 (2%) | | |
| *SUBCUT TISSUE | (50) | (49) | (50) |
| SARCOMA, NOS | 2 (4%) | 1 (2%) | 2 (4%) |
| FIBROSARCOMA | 4 (8%) | | |
| RHABDOMYOSARCOMA | 1 (2%) | | |
| **RESPIRATORY SYSTEM** | | | |
| #LUNG | (49) | (49) | (50) |
| HEPATOCELLULAR CARCINOMA, METAST | 3 (6%) | | 1 (2%) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 1 (2%) | 2 (4%) | 2 (4%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | 1 (2%) | |
| SARCOMA, NOS, METASTATIC | | 1 (2%) | |
| FIBROSARCOMA, METASTATIC | 1 (2%) | | |
| RHABDOMYOSARCOMA, METASTATIC | 1 (2%) | | |
| **HEMATOPOIETIC SYSTEM** | | | |
| *MULTIPLE ORGANS | (50) | (49) | (50) |
| MALIGNANT LYMPHOMA, NOS | 2 (4%) | 4 (8%) | 4 (8%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 2 (4%) | | |
| MALIGNANT LYMPHOMA, MIXED TYPE | | | 1 (2%) |
| LYMPHOCYTIC LEUKEMIA | 1 (2%) | | |
| #MEDIASTINAL L.NODE | (37) | (34) | (42) |
| MALIGNANT LYMPHOMA, NOS | | 1 (3%) | |
| #AXILLARY LYMPH NODE | (37) | (34) | (42) |
| SARCOMA, NOS, METASTATIC | 1 (3%) | | |

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

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #LIVER | (50) | (49) | (50) |
| KUPFFER-CELL SARCOMA | | 1 (2%) | |
| **CIRCULATORY SYSTEM** | | | |
| #SPLEEN | (48) | (46) | (50) |
| HEMANGIOSARCOMA | | 1 (2%) | |
| #MESENTERIC L. NODE | (37) | (34) | (42) |
| HEMANGIOSARCOMA, METASTATIC | | | 1 (2%) |
| #HEART | (48) | (49) | (50) |
| RHABDOMYOSARCOMA, METASTATIC | 1 (2%) | | |
| #LIVER | (50) | (49) | (50) |
| HEMANGIOSARCOMA | | | 1 (2%) |
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (50) | (49) | (50) |
| HEPATOCELLULAR ADENOMA | 1 (2%) | 2 (4%) | |
| HEPATOCELLULAR CARCINOMA | 14 (28%) | 5 (10%) | 12 (24%) |
| RHABDOMYOSARCOMA, METASTATIC | 1 (2%) | | |
| *GALLBLADDER | (50) | (49) | (50) |
| ADENOMA, NOS | | | 1 (2%) |
| *RECTUM | (50) | (49) | (50) |
| ADENOCARCINOMA, NOS | | | 1 (2%) |
| **URINARY SYSTEM** | | | |
| NONE | | | |
| **ENDOCRINE SYSTEM** | | | |
| #ADRENAL | (49) | (46) | (48) |
| CORTICAL ADENOMA | | 2 (4%) | 1 (2%) |
| PHEOCHROMOCYTOMA | | 1 (2%) | 1 (2%) |
| PHEOCHROMOCYTOMA, MALIGNANT | 1 (2%) | | |

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

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #THYROID | (48) | (40) | (48) |
| FOLLICULAR-CELL ADENOMA | 1 (2%) | | 1 (2%) |
| REPRODUCTIVE SYSTEM | | | |
| #TESTIS | (50) | (48) | (49) |
| INTERSTITIAL-CELL TUMOR | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *SKELETAL MUSCLE | (50) | (49) | (50) |
| SARCOMA, NOS | | | 1 (2%) |
| BODY CAVITIES | | | |
| *MESENTERY | (50) | (49) | (50) |
| SARCOMA, NOS | 1 (2%) | | |
| ALL OTHER SYSTEMS | | | |
| *MULTIPLE ORGANS | (50) | (49) | (50) |
| SARCOMA, NOS, METASTATIC | | | 1 (2%) |
| ADIPOSE TISSUE | | | |
| SARCOMA, NOS | | | 1 |

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

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| NATURAL DEATH@ | 15 | 15 | 4 |
| MORIBUND SACRIFICE | 3 | 2 | 4 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 32 | 33 | 42 |
| ANIMAL MISSING | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 30 | 19 | 25 |
| TOTAL PRIMARY TUMORS | 32 | 25 | 33 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 4 | 8 | 10 |
| TOTAL BENIGN TUMORS | 4 | 8 | 10 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 26 | 14 | 21 |
| TOTAL MALIGNANT TUMORS | 28 | 17 | 23 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 6 | 1 | 3 |
| TOTAL SECONDARY TUMORS | 8 | 1 | 3 |
| 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 C.I. ACID ORANGE 10

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (50) | (50) | (49) |
| SARCOMA, NOS | 1 (2%) | | |
| FIBROSARCOMA | | 2 (4%) | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (50) | (50) | (49) |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 (2%) | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 2 (4%) | 1 (2%) | |
| SARCOMA, NOS, METASTATIC | 1 (2%) | | |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (50) | (50) | (49) |
| MALIGNANT LYMPHOMA, NOS | 6 (12%) | 9 (18%) | 7 (14%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (2%) | 1 (2%) | 1 (2%) |
| LYMPHOCYTIC LEUKEMIA | 1 (2%) | 1 (2%) | |
| #SPLEEN | (50) | (50) | (49) |
| MALIGNANT LYMPHOMA, NOS | | | 1 (2%) |
| #LYMPH NODE | (35) | (38) | (41) |
| MALIGNANT LYMPHOMA, NOS | | 1 (3%) | |
| #LYMPH NODE OF THORAX | (35) | (38) | (41) |
| FIBROSARCOMA, METASTATIC | | | 1 (2%) |
| #LUMBAR LYMPH NODE | (35) | (38) | (41) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | 1 (2%) |
| #LIVER | (50) | (50) | (49) |
| MALIGNANT LYMPHOMA, NOS | | 1 (2%) | |

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

## TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (2%) | | |
| #KIDNEY | (50) | (50) | (49) |
| MALIGNANT LYMPHOMA, NOS | | 1 (2%) | |
| #OVARY | (44) | (48) | (42) |
| MALIGNANT LYMPHOMA, NOS | 1 (2%) | | |
| **CIRCULATORY SYSTEM** | | | |
| *SKIN | (50) | (50) | (49) |
| HEMANGIOSARCOMA | 1 (2%) | | |
| #SPLEEN | (50) | (50) | (49) |
| HEMANGIOSARCOMA | | 1 (2%) | |
| *MESENTERY | (50) | (50) | (49) |
| HEMANGIOMA | 1 (2%) | | |
| #UTERUS | (48) | (50) | (48) |
| HEMANGIOMA | 1 (2%) | 1 (2%) | 1 (2%) |
| #OVARY | (44) | (48) | (42) |
| HEMANGIOMA | 1 (2%) | 1 (2%) | |
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (50) | (50) | (49) |
| HEPATOCELLULAR ADENOMA | | 2 (4%) | |
| HEPATOCELLULAR CARCINOMA | 3 (6%) | 1 (2%) | 3 (6%) |
| #STOMACH | (50) | (48) | (47) |
| OSTEOSARCOMA | 1 (2%) | | |
| **URINARY SYSTEM** | | | |
| #KIDNEY | (50) | (50) | (49) |
| TUBULAR-CELL ADENOCARCINOMA | | 1 (2%) | |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (47) | (42) | (41) |
| ADENOMA, NOS | | 1 (2%) | |

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

## TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| CHROMOPHOBE ADENOMA | 3 (6%) | 4 (10%) | 1 (2%) |
| #ADRENAL | (46) | (47) | (47) |
| PHEOCHROMOCYTOMA | | | 1 (2%) |
| #THYROID | (49) | (45) | (47) |
| FOLLICULAR-CELL ADENOMA | 1 (2%) | 1 (2%) | |
| #PARATHYROID | (30) | (32) | (25) |
| ADENOMA, NOS | | | 1 (4%) |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (50) | (50) | (49) |
| ADENOMA, NOS | 3 (6%) | 2 (4%) | |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| #UTERUS | (48) | (50) | (48) |
| LEIOMYOMA | 1 (2%) | 1 (2%) | |
| LEIOMYOSARCOMA | | | 1 (2%) |
| ENDOMETRIAL STROMAL POLYP | | | 2 (4%) |
| #OVARY | (44) | (48) | (42) |
| PAPILLARY CYSTADENOMA, NOS | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE/LACRIMAL GLAND | (50) | (50) | (49) |
| ADENOMA, NOS | 1 (2%) | 1 (2%) | 2 (4%) |
| PAPILLARY ADENOMA | 1 (2%) | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *VERTEBRA | (50) | (50) | (49) |
| SARCOMA, NOS, INVASIVE | 1 (2%) | | |
| BODY CAVITIES | | | |
| *MEDIASTINUM | (50) | (50) | (49) |
| SARCOMA, NOS, 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 |
|---|---|---|---|
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| NATURAL DEATHa | 9 | 10 | 9 |
| MORIBUND SACRIFICE | 1 | 3 | |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 40 | 37 | 41 |
| ANIMAL MISSING | | | |
| a INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 25 | 27 | 19 |
| TOTAL PRIMARY TUMORS | 31 | 35 | 24 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 14 | 15 | 6 |
| TOTAL BENIGN TUMORS | 15 | 15 | 9 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 14 | 18 | 15 |
| TOTAL MALIGNANT TUMORS | 16 | 20 | 15 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | 2 | 1 |
| TOTAL SECONDARY TUMORS | 3 | 2 | 2 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

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

# TABLE B3.

# INDIVIDUAL ANIMAL TUMOR PATHOLOGY IN MALE MICE IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

## CONTROL

| 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 | 088 | 103 | 106 | 096 | 065 | 100 | 105 | 097 | 093 | 103 | 057 | 059 | 097 | 103 | 103 | 103 | 097 | 103 | 097 | 103 | 113 | 103 | 103 | 103 | 103 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + |
| FIBROUS HISTIOCYTOMA | | | | X | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + |
| SARCOMA, NOS | | | | | | | | | | X | | | | | | | | | | | | | | | |
| FIBROSARCOMA | | | | | | X | | | | | | | X | | | | | X | | | | | X | | |
| RHABDOMYOSARCOMA | | | | | X | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR CARCINOMA, METASTA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | X | | | | | | | | | | | | | | | | | | | |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| *RHABDOMYOSARCOMA, METASTATIC* | | | | | X | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | − | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | − | + | + | + |
| LYMPH NODES | + | + | − | − | − | + | + | + | − | + | + | + | + | − | + | + | + | + | + | − | + | + | + | + | + |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | − | + | + | − | − | − | − | − | − | + | − | − | + | − | + | + | − | + | − | + | − | + | + | − | |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| RHABDOMYOSARCOMA, METASTATIC | | | | | X | | | | | | | | | | | | | | | | | | | | |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR ADENOMA | | | | | | | | | | | | | | | | | | | | X | | | | | |
| HEPATOCELLULAR CARCINOMA | | X | | | | | | | | | | | | | X | | | | X | | + | | | | |
| RHABDOMYOSARCOMA, METASTATIC | | | | | X | | | | | | | | | | | | | | | | | | | | |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | N | N | N | + | + | + | + | N | + | + | + | + | + | + | N | + | + | N | + | N | + |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SMALL INTESTINE | + | + | + | + | − | − | + | + | − | + | + | + | + | + | + | + | − | + | − | + | − | + | − | − | − |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | − | + | + | + | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | − | + | − | + | + | + | − | + | + | + | + | − | + | − | + | − | − | − | + | + | + | − | − | + | − |
| ADRENAL | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | | | | | | X | | | | | | | | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | | X | | | | | | | | | | | | | | | | | | |
| PARATHYROID | − | − | + | − | + | − | + | − | + | − | + | − | − | + | + | + | − | − | + | + | + | − | − | + | + |
| **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 | + | + | + | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **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 | | | | | | | | | | | | | | | | | | | | | | | | | |
| **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 | | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | X | | | | | | | | | | | | | | | | | | | | | | | | 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 B3. MALE 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 TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 103 | 103 | 103 | 096 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 086 | 103 | 103 | 103 | 103 | 103 | 103 | 091 | 103 | 096 | 094 | 095 | 103 | |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | 50* |
| FIBROUS HISTIOCYTOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | 50* |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | X | | | | | | | | | 2 |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| RHABDOMYOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | 49 |
| HEPATOCELLULAR CARCINOMA, METASTA | | | | | | | | | | | | | X | X | | | | | | X | | | | | | 3 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| RHABDOMYOSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| TRACHEA | + | - | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | 46 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | - | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - | + | + | + | + | - | + | 43 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| LYMPH NODES | + | + | + | + | + | + | + | - | - | - | - | - | + | + | + | - | + | + | + | + | + | + | + | - | + | 37 |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| THYMUS | + | - | + | + | + | + | + | + | + | + | + | + | - | + | - | + | - | + | - | - | + | - | - | - | - | 27 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + | 48 |
| RHABDOMYOSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| HEPATOCELLULAR CARCINOMA | X | | | X | X | | X | | | X | | | X | X | | | | | | X | X | | | | | 14 |
| RHABDOMYOSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | + | + | N | + | + | + | + | + | + | N | + | + | N | + | + | + | + | + | + | N | + | + | N | + | + | 50* |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | 49 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + | - | + | 38 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - | + | + | + | - | 46 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | - | - | + | - | - | + | + | + | + | - | - | - | - | + | + | - | - | + | - | + | + | + | - | + | - | 27 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| PHEOCHROMOCYTOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | 48 |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| PARATHYROID | + | + | - | - | - | + | - | - | + | - | - | + | - | + | + | - | - | - | - | + | - | - | + | - | + | 23 |
| **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 | N | 50* |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **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 | | | | | | | | | | | | | | | | | | | | | | | | 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 | X | N | X | 50* |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: 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 IN MALE MICE IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

## LOW 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 | 103 | 103 | 116 | 028 | 022 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 100 | 047 | 048 | 103 | 095 | 104 | 103 | 074 | 103 | 103 | 103 |
| INTEGUMENTARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + X | A | + | + | + X | + | + | + | + | + | + |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| FIBROMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | A | + | + | + | + | + | + | + | + | + X |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| RESPIRATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | X | | | | | | | | | | | | | | | | | | |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | X | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | − | − | + | + | + | A | + | + | + | + | + | − | + | + | + |
| HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | − | + | − | + | + | + | + | + | + |
| SPLEEN | + | + | + | − | + | + | + | + | + | + | + | + | − | + | + | A | + | + | + | + | − | + | + | + | + |
| HEMANGIOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPH NODES | + | + | + | − | + | + | + | + | + | − | − | − | − | + | + | A | − | + | − | + | − | + | + | + | + |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | + | + | − | + | − | − | + | + | + | − | − | − | − | + | − | A | − | − | − | − | + | − | + | + | + |
| CIRCULATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | − | − | + | + | + | A | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR ADENOMA | | | | | | | | | | | | | | | X | | | | X | | | | | | |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| KUPFFER-CELL SARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | + | + | N | + | N | N | + | + | + | + | N | N | N | + | N | A | N | + | + | N | + | N | + | + | + |
| PANCREAS | + | + | − | − | + | + | + | + | + | + | + | + | + | + | + | A | − | + | + | + | − | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | − | − | − | + | + | A | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | − | + | + | + | + | + | + | + | + | − | + | + | A | − | + | + | + | + | + | + | + | + |
| SMALL INTESTINE | + | + | + | − | − | − | + | + | + | + | − | + | − | + | + | A | − | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | − | + | + | + | + | + | + | + | + | − | + | + | A | + | + | + | + | + | − | + | + | + |
| URINARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | − | + | + | + | + | + | + | + | − | + | + | + | + | A | − | + | + | + | + | + | + | + | + |
| ENDOCRINE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | − | − | − | + | + | + | + | − | − | − | − | + | − | A | − | + | − | − | − | − | − | + | + |
| ADRENAL | + | + | − | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | − | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | | | | X | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYROID | + | + | + | + | − | + | + | + | + | + | − | − | + | + | + | A | − | + | + | + | + | + | + | + | + |
| PARATHYROID | + | + | + | + | − | − | − | + | − | − | − | − | − | − | − | A | − | − | − | − | + | + | + | + | + |
| REPRODUCTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | A | N | N | N | N | N | N | N | N | N |
| TESTIS | + | + | + | + | + | + | + | + | + | + | − | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | − | + | − | + | + | A | + | + | − | − | + | + | + | + | + |
| ALL OTHER SYSTEMS | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | A | N | N | N | N | N | N | N | N | N |
| MALIGNANT LYMPHOMA, NOS | | | | | | | 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 B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

| 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 | 103 | 103 | 103 | 103 | 103 | 101 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | 49* |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | X | | | | | | | | | 3 |
| FIBROMA | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | 49* |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | | | | | | | | | | | | X | | | | | X | | | 2 |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | - | + | 44 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | - | + | + | + | + | - | + | 44 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| HEMANGIOSARCOMA | | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |
| LYMPH NODES | + | - | + | + | + | + | - | + | + | + | + | - | - | - | + | + | - | + | + | + | + | + | - | + | + | 34 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| THYMUS | + | + | + | - | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | - | - | + | 30 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| HEPATOCELLULAR ADENOMA | X | | | | | | | | | | | | | | | | X | | | | | | | | | 2 |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | X | | | | | | | | X | X | | 5 |
| KUPFFER-CELL SARCOMA | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| GALLBLADDER & COMMON BILE DUCT | N | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | N | + | + | + | + | N | + | + | 49* |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | 44 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| STOMACH | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| SMALL INTESTINE | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | - | + | + | 39 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | 45 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | - | + | - | + | + | + | - | + | + | + | + | + | + | + | - | - | + | - | + | 29 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | 46 |
| CORTICAL ADENOMA | | | | | | | | X | | | | X | | | | | | | | | | | | | | 2 |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | - | + | - | + | - | - | + | 40 |
| *PARATHYROID* | - | + | + | - | + | + | - | + | - | - | + | + | - | - | - | - | + | + | - | - | + | - | - | - | - | 20 |
| **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 | N | 49* |
| *TESTIS* | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | - | + | + | + | + | + | 43 |
| **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* |
| MALIGNANT LYMPHOMA, NOS | | | | | | X | | | | X | | | | | | | | | | | | | | | | 4 |

* *ANIMALS NECROPSIED*

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: *TUMOR INCIDENCE*
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: 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 IN MALE MICE IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

### 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 | 103 | 103 | 100 | 087 | 103 | 103 | 103 | 103 | 103 | 081 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 087 | 103 | 103 | 074 | 103 | 103 | 103 | 103 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | N | + | + | |
| FIBROMA | | | | | | | | | | | | | X | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | N | + | + | |
| SARCOMA, NOS | | | | | | | | | | | | | X | | | | | X | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR CARCINOMA, METASTA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | X |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | – | + | – | + | + | + | + | – | – | + | + | – | + | + | + | |
| HEMANGIOSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | X | | | | | |
| THYMUS | – | + | – | – | + | – | + | + | + | – | + | + | + | – | + | + | – | – | + | – | – | + | – | – | – |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR CARCINOMA | | | X | | | | | | | | | | | | | X | | | | | | | | X | X |
| HEMANGIOSARCOMA | | | | | | | | | | | | | | | | | | | | | X | | | | |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| GALLBLADDER & COMMON BILE DUCT | N | + | N | + | + | + | + | + | + | N | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SMALL INTESTINE | + | + | – | + | + | + | + | + | + | – | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| RECTUM | 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 |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | X | | | | | | | | |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | – | + | + | + | – | – | + | + | – | + | + | – | + | + | + | + | + | + | + | + | + | + | + |
| ADRENAL | + | + | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | | X | | | | | | | | | | | | | | | | | | |
| PARATHYROID | + | – | + | + | + | – | – | + | + | – | – | + | + | + | + | + | – | – | – | + | + | – | – | – | + |
| **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 | N |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| INTERSTITIAL-CELL TUMOR | | | | | | | | | | X | | | | | | | | | | | | | | | |
| PROSTATE | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – |
| **MUSCULOSKELETAL SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MUSCLE | 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 |
| SARCOMA, NOS, METASTATIC | | | X | | | | | | | | | | | | | | | | | | | | | | |
| MALIGNANT LYMPHOMA, NOS | | | | | | X | | | | | | | | | | | | | | | | | | | |
| MALIGNANT LYMPHOMA, MIXED TYPE | | | | | | | | | | X | | | | | | | | | | | | | | | |
| ADIPOSE TISSUE | | | | | | | | | | | | | | | | | | | | | | | | | |
| SARCOMA, NOS | | | 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 26 | 02 27 | 02 28 | 02 29 | 03 01 | 03 11 | 03 32 | 03 33 | 03 34 | 03 35 | 03 36 | 03 37 | 03 38 | 03 39 | 04 01 | 04 02 | 04 03 | 04 04 | 04 45 | 04 46 | 04 47 | 04 48 | 04 49 | 05 00 | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 09 1 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 10 1 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 10 3 | 08 1 | 10 3 | 10 3 | 10 3 | 10 3 | |
| INTEGUMENTARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + | + | + | + | + | + | + | + | 50M |
| FIBROMA | | | X | | | | | | | | | | | | | | | | | | X | | | | 3 |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + | + | + | + | + | + | + | + | 50M |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| RESPIRATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR CARCINOMA, METASTA | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | X | | | | | | | | | | | | | | | | | | | | | | | 2 |
| TRACHEA | + | + | + | + | ~ | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | - | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LYMPH NODES | + | + | + | + | ~ | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | 42 |
| HEMANGIOSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| THYMUS | - | + | - | + | + | + | + | + | + | + | - | + | + | + | - | - | + | + | + | + | + | - | + | + | 31 |
| CIRCULATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR CARCINOMA | | | X | | | | | | X | | | X | | | | | | X | | | X | | X | X | 12 |
| HEMANGIOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | N | + | + | + | + | 50M |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ESOPHAGUS | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | 46 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | 49 |
| RECTUM | N | N | N | N | N | N | + | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50M |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| URINARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 48 |
| ENDOCRINE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | - | + | + | - | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 42 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | ~ | + | + | + | + | + | + | 48 |
| CORTICAL ADENOMA | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| THYROID | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | 48 |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| PARATHYROID | - | + | ~ | + | - | + | + | + | - | + | + | - | + | + | + | - | + | + | ~ | + | - | - | + | - | 29 |
| 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 | 50M |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | 49 |
| INTERSTITIAL-CELL TUMOR | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| MUSCULOSKELETAL SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| MUSCLE | 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 |
| 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 |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| MALIGNANT LYMPHOMA, NOS | X | | | | | | | | | | X | | | X | | | | | | | | | | | 4 |
| MALIGNANT LYMPHOMA, MIXED TYPE | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| ADIPOSE TISSUE | | | | | | | | | | | | | | | | | | | | | | | | | |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: 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 IN FEMALE MICE IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

## CONTROL

| ANIMAL NUMBER | 00101 | 00201 | 00301 | 00401 | 00501 | 00601 | 00701 | 00801 | 00901 | 01001 | 01101 | 01201 | 01301 | 01401 | 01501 | 01601 | 01701 | 01801 | 01901 | 02001 | 02101 | 02201 | 02301 | 02401 | 02501 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 088 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 091 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 103 | 101 | 103 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEMANGIOSARCOMA | | | | | | | | | | | | | | | | | | X | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | X | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | | | | | | X | | | | | | | | | | | | | |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | X | |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | - | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES | + | + | + | + | - | + | - | + | + | + | - | + | + | + | - | + | - | + | - | + | + | + | + | + | - |
| THYMUS | - | - | - | + | + | + | + | + | + | + | + | + | + | + | - | + | - | + | - | + | + | + | - | - | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | X | | | | | | X | | | | | | | X |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | X |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | N | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | N | + |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OSTEOSARCOMA | | | | | | | | | | | | | | | X | | | | | | | | | | |
| SMALL INTESTINE | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | - | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | - | + | + | + | + | + | + | - | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | - | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CHROMOPHOBE ADENOMA | | | | | | | | | | X | X | | | | | | | | | | | | | | X |
| ADRENAL | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PARATHYROID | + | - | + | - | - | - | + | + | + | + | - | + | + | + | - | + | - | - | + | + | - | - | + | - | + |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | + | + | + | N | + | + | N | N | + | + | + | + | N | N | + | + | + | N | + | N | + | + | + |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | X | | X | X | |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LEIOMYOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEMANGIOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| OVARY | + | + | + | + | + | - | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| HEMANGIOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LACRIMAL 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 |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| PAPILLARY ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **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 |
| SARCOMA, NOS, INVASIVE | | | | | | | | | | | | | | | | | | | | | | | | 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 |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | 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 | X | N | N | N | N |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPHOCYTIC 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 B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

| ANIMAL NUMBER | 0 2 6 | 0 2 7 | 0 2 8 | 0 2 9 | 0 3 0 | 0 3 1 | 0 3 2 | 0 3 3 | 0 3 4 | 0 3 5 | 0 3 6 | 0 3 7 | 0 3 8 | 0 3 9 | 0 4 0 | 0 4 1 | 0 4 2 | 0 4 3 | 0 4 4 | 0 4 5 | 0 4 6 | 0 4 7 | 0 4 8 | 0 4 9 | 0 5 0 | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 1 0 3 | 1 0 3 | 0 8 3 | 1 0 3 | 1 0 3 | 0 9 6 | 0 7 8 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 0 8 6 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 1 0 3 | 0 8 7 | 0 8 8 | |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEMANGIOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | | | | | | | | | | | | | | X | | | | | | 2 |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| TRACHEA | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | 48 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | – | + | + | + | + | + | + | + | + | + | 46 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LYMPH NODES | + | + | + | + | + | + | – | + | – | + | + | – | + | + | + | + | + | – | – | + | + | + | – | – | – | 35 |
| THYMUS | + | + | – | + | + | – | – | + | + | + | + | + | + | + | + | – | – | + | + | + | + | + | + | – | – | 33 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | 48 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| PANCREAS | + | + | – | + | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | – | – | 46 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| OSTEOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SMALL INTESTINE | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | – | 44 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | 48 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | – | 45 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| CHROMOPHOBE ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| ADRENAL | + | + | + | + | + | + | + | + | + | – | + | + | + | – | + | + | + | + | + | + | + | + | + | + | – | 46 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | 49 |
| FOLLICULAR-CELL ADENOMA | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| PARATHYROID | + | + | – | + | + | + | – | + | – | – | + | + | + | + | + | – | – | + | + | – | + | – | + | + | – | 30 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | + | + | + | + | + | N | + | + | + | N | N | N | + | + | + | + | + | + | N | + | + | + | N | + | 50 |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| UTERUS | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | + | + | 48 |
| LEIOMYOMA | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| HEMANGIOMA | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| OVARY | + | + | – | + | + | + | + | – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | – | – | + | 44 |
| HEMANGIOMA | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LACRIMAL 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 |
| ADENOMA, NOS | | | | X | | | | | | | | | | | | | | | X | | | | | | | 1 |
| PAPILLARY ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **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 | 50 |
| SARCOMA, NOS, INVASIVE | | | | | | | | | | | | | | | | | | | | | | | | | | 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 | N | 50 |
| SARCOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 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 | N | 50 |
| 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 | N | 50 |
| MALIGNANT LYMPHOMA, NOS | | | X | | | | | | | X | | | X | | | X | | | | | | | | | X | 6 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |

N ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
~: *REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY*
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 IN FEMALE MICE IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

## LOW DOSE

| ANIMAL NUMBER | 00111 | 00123 | 00135 | 00147 | 00156 | 00167 | 00178 | 00189 | 00191 | 00201 | 00212 | 00223 | 00234 | 00245 | 00256 | 00267 | 00278 | 00289 | 00290 | 00301 | 00312 | 00323 | 00334 | 00345 | 00356 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 104 | 104 | 104 | 095 | 089 | 093 | 104 | 104 | 104 | 090 | 104 | 102 | 104 | 104 | 104 | 104 | 104 | 104 | 095 | 091 | 104 | 104 | 088 | 082 | 087 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE<br>FIBROSARCOMA | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | X | + | + | + | + | + |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI<br>ADENOCARCINOMA, NOS, METASTATIC<br>ALVEOLAR/BRONCHIOLAR ADENOMA<br>FIBROSARCOMA, METASTATIC | + | + | + | + | + | + | + | + | + | + | + | + | X | + | + | + | X | + | + | X | + | + | + | + | + |
| TRACHEA | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | - | + |
| SPLEEN<br>HEMANGIOSARCOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES<br>MALIGNANT LYMPHOMA, NOS | + | + | + | - | + | - | + | + | + | + | X | + | + | + | + | + | + | - | - | - | + | + | + | + | + |
| THYMUS | - | + | + | - | - | - | + | + | + | + | - | - | - | + | - | - | - | + | - | - | + | + | - | - | - |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | - | + | + | + | + | + | + | - |
| LIVER<br>HEPATOCELLULAR ADENOMA<br>HEPATOCELLULAR CARCINOMA<br>MALIGNANT LYMPHOMA, NOS | + | + | + | + | + | + | + | X | + | + | + | + | + | + | + | + | + | X | + | + | + | + | + | X | + |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + |
| PANCREAS | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | - | + | + |
| SMALL INTESTINE | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | - |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY<br>TUBULAR-CELL ADENOCARCINOMA<br>MALIGNANT LYMPHOMA, NOS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | X | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY<br>ADENOMA, NOS<br>CHROMOPHOBE ADENOMA | + | + | + | + | - | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | - | - |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + |
| THYROID<br>FOLLICULAR-CELL ADENOMA | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | + | - | + |
| PARATHYROID | - | + | + | + | + | + | + | + | + | - | - | + | + | + | + | - | + | - | + | + | - | - | + | - | + |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND<br>ADENOMA, NOS<br>ADENOCARCINOMA, NOS | + | + | + | N | N | + | + | + | N | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + |
| UTERUS<br>LEIOMYOMA<br>HEMANGIOMA | + | + | + | + | + | + | + | + | + | + | X | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OVARY<br>HEMANGIOMA | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LACRIMAL GLAND<br>ADENOMA, NOS | N | N | N | N | N | N | N | N | N<br>X | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS<br>MALIGNANT LYMPHOMA, NOS<br>MALIG.LYMPHOMA, HISTIOCYTIC TYPE<br>LYMPHOCYTIC LEUKEMIA | N | N | N | N<br>X | N | N<br>X | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N<br>X | 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 B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

| 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 | 104 | 104 | 104 | 089 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 100 | 104 | 104 | 104 | 104 | 104 | 104 | 104 | 075 | 104 | 104 | 104 | 104 | 104 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | N | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | X | + | + | + | + | 50* |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ADENOCARCINOMA, NOS, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | ~ | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - | 45 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEMANGIOSARCOMA | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| LYMPH NODES | - | - | + | - | + | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | - | + | + | - | 38 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| THYMUS | - | - | + | - | - | + | + | + | + | + | + | - | + | + | - | - | + | + | - | - | - | + | - | + | + | 24 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | - | + | + | + | 44 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR ADENOMA | | | | | | X | | | | | | | | | | | | | | | | | | | | 2 |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | N | + | + | + | + | 50* |
| PANCREAS | + | + | + | - | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| SMALL INTESTINE | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| LARGE INTESTINE | + | + | + | + | + | - | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| TUBULAR-CELL ADENOCARCINOMA | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| URINARY BLADDER | + | + | + | - | + | + | + | + | + | + | + | + | + | - | + | + | - | + | + | + | + | + | + | + | + | 44 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | - | + | + | + | - | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 42 |
| ADENOMA, NOS | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| CHROMOPHOBE ADENOMA | | | X | | | | | | | | | | | | X | | | | | | X | X | | | | 4 |
| ADRENAL | + | + | + | + | + | + | + | - | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| PARATHYROID | + | ~ | - | + | + | - | + | - | + | + | + | - | - | - | ~ | - | + | + | + | + | + | + | + | + | - | 32 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | N | + | N | + | + | + | + | N | N | + | + | + | + | + | N | + | + | N | + | + | + | + | + | + | 50* |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LEIOMYOMA | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| HEMANGIOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| HEMANGIOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LACRIMAL 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* |
| ADENOMA, 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* |
| MALIGNANT LYMPHOMA, NOS | | | | | X | | | | X | | X | X | | | X | X | | | | | | X | | | | 9 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| LYMPHOCYTIC LEUKEMIA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 IN FEMALE MICE IN THE 2-YEAR STUDY OF C.I. ACID ORANGE 10

### 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 | 104 | 104 | 104 | 104 | 098 | 104 | 104 | 104 | 029 | 104 | 098 | 104 | 088 | 104 | 104 | 104 | 104 | 104 | 095 | 086 | 104 | 104 | 104 | 104 | 104 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE FIBROSARCOMA | + | + | + | + | + | + | + | N | + | + | + X | + | + | + | + | + | + | + | + | + | + | + | + | + | N |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI FIBROSARCOMA, METASTATIC | + | + | + | + | + | + | + | + | + | + | + X | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA | + | + | + | + | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN MALIGNANT LYMPHOMA, NOS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + X | + |
| LYMPH NODES FIBROSARCOMA, METASTATIC MALIG.LYMPHOMA, HISTIOCYTIC TYPE | + | + | + | + | + | + | + | + | + | + | + X | + | + | - | + | + | - | - | + | + | + | + | + | + | - |
| THYMUS | + | + | + | - | - | + | + | + | - | - | - | + | - | - | - | + | - | + | - | - | + | + | + | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER HEPATOCELLULAR CARCINOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + X | + | + | + |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + |
| PANCREAS | + | + | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | - | + | + | + | + | + | + |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | - | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| *ENDOCRINE SYSTEM* | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY CHROMOPHOBE ADENOMA | + | + | + | + | + | + | + X | - | + | + | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + |
| ADRENAL PHEOCHROMOCYTOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| PARATHYROID ADENOMA, NOS | + | + | + | - | + | + | - | - | + | + X | - | + | - | - | - | + | - | - | + | + | - | - | + | + | - |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | + | N | + | N | + | + | N | N | N | + | + | N | + | + | + | + | + | N | N | + | + | + | + | + |
| UTERUS LEIOMYOSARCOMA ENDOMETRIAL STROMAL POLYP HEMANGIOMA | + | + | + | + | + | + | + | + | + | + X | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| OVARY PAPILLARY CYSTADENOMA, NOS | + | + | + | - | + | - | + | + | - | + | + | + | - | + | - | + X | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LACRIMAL GLAND ADENOMA, NOS | N | N | N | N | N | N | N X | N | N | N X | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS MALIG.LYMPHOMA, HISTIOCYTIC TYPE | N | N | N | N X | N X | N | N | N X | N | N | N | N | N | N | N | N X | N | N | N X | N | N | N | N X | 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 B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

| ANIMAL NUMBER | 0126 | 0127 | 0128 | 0129 | 0130 | 0131 | 0132 | 0133 | 0134 | 0135 | 0136 | 0137 | 0138 | 0139 | 0140 | 0141 | 0142 | 0143 | 0144 | 0145 | 0146 | 0147 | 0148 | 0149 | 0150 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 1041 | 1041 | 0841 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 1041 | 0841 | 1041 | 0841 | 0841 | 1041 | 1041 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49* |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49 |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 47 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| LYMPH NODES | - | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | - | + | A | + | + | 41 |
| FIBROSARCOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| THYMUS | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | - | + | + | - | + | A | + | + | 34 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | A | + | + | 47 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49 |
| HEPATOCELLULAR CARCINOMA | | X | | | | | X | | | | | | | | | | | | | | | | | | | 3 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49 |
| GALLBLADDER & COMMON BILE DUCT | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | A | + | + | 49* |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 46 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 47 |
| SMALL INTESTINE | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | A | + | + | 45 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | - | + | A | + | + | 47 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 49 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | - | + | A | + | + | 46 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | - | + | - | + | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | - | + | A | + | + | 41 |
| CHROMOPHOBE ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| ADRENAL | + | + | + | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 47 |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | A | + | + | 47 |
| PARATHYROID | - | + | + | - | + | + | + | - | - | + | - | - | - | + | + | - | - | + | + | - | - | + | A | - | + | 25 |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | + | + | + | + | N | + | + | + | + | N | N | + | + | + | + | + | + | + | N | N | + | + | A | + | N | 49* |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 48 |
| LEIOMYOSARCOMA | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| ENDOMETRIAL STROMAL POLYP | | | | | | | | | | | | | | X | | | | | | | | | | | | 2 |
| HEMANGIOMA | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| OVARY | + | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | A | + | + | 42 |
| PAPILLARY CYSTADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LACRIMAL GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | A | N | N | 49* |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **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 | A | N | N | 49* |
| MALIGNANT LYMPHOMA, NOS | X | | | | | | | | | | | | | | | | | | | | | | | | | 7 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: *TUMOR INCIDENCE*
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: 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 C.I. ACID ORANGE 10

## TABLE C1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIETS CONTAINING C.I. ACID ORANGE 10

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 90 | 50 | 50 |
| ANIMALS NECROPSIED | 90 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 90 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (90) | (50) | (50) |
| EPIDERMAL INCLUSION CYST | 2 (2%) | | 1 (2%) |
| *SUBCUT TISSUE | (90) | (50) | (50) |
| EDEMA, NOS | | | 1 (2%) |
| INFLAMMATION, GRANULOMATOUS | | | 1 (2%) |
| GRANULATION, TISSUE | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (89) | (50) | (50) |
| HEMORRHAGE | 1 (1%) | | |
| INFLAMMATION, INTERSTITIAL | 2 (2%) | 1 (2%) | 1 (2%) |
| PNEUMONIA INTERSTITIAL CHRONIC | | 1 (2%) | |
| NECROSIS, FOCAL | 1 (1%) | | |
| HEMOSIDEROSIS | | | 1 (2%) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 1 (1%) | 1 (2%) | 2 (4%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (84) | (48) | (48) |
| CONGESTION, ACUTE | 1 (1%) | | |
| FIBROSIS, FOCAL | 1 (1%) | | |
| HYPERPLASIA, HEMATOPOIETIC | | 1 (2%) | |
| HYPERPLASIA, RETICULUM CELL | | | 1 (2%) |
| HYPOPLASIA, HEMATOPOIETIC | 4 (5%) | 1 (2%) | 1 (2%) |
| #SPLEEN | (90) | (50) | (50) |
| CONGESTION, NOS | 1 (1%) | | |
| FIBROSIS, FOCAL | | 2 (4%) | |
| FIBROSIS, DIFFUSE | 1 (1%) | | |

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

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| INFARCT, FOCAL | 1 (1%) | | |
| INFARCT, ACUTE | | | 1 (2%) |
| LYMPHOID DEPLETION | | | 2 (4%) |
| #LYMPH NODE | (89) | (49) | (49) |
| EDEMA, NOS | 1 (1%) | | |
| LYMPHOID DEPLETION | 1 (1%) | | |
| #SUBMANDIBULAR L.NODE | (89) | (49) | (49) |
| EDEMA, NOS | | | 1 (2%) |
| HEMORRHAGE | 1 (1%) | | |
| #MANDIBULAR L. NODE | (89) | (49) | (49) |
| PLASMACYTOSIS | | 1 (2%) | |
| #MEDIASTINAL L.NODE | (89) | (49) | (49) |
| EDEMA, NOS | | | 1 (2%) |
| #MESENTERIC L. NODE | (89) | (49) | (49) |
| INFLAMMATION ACTIVE CHRONIC | | | 1 (2%) |
| INFLAMMATION, GRANULOMATOUS | | | 1 (2%) |
| LYMPHOID DEPLETION | 1 (1%) | 1 (2%) | |
| #LUNG | (89) | (50) | (50) |
| HYPERPLASIA, LYMPHOID | 1 (1%) | | |
| #LIVER | (90) | (50) | (50) |
| HEMATOPOIESIS | | 2 (4%) | |
| #THYMUS | (69) | (37) | (38) |
| HYPERPLASIA, EPITHELIAL | | 1 (3%) | |
| CIRCULATORY SYSTEM | | | |
| #MANDIBULAR L. NODE | (89) | (49) | (49) |
| LYMPHANGIECTASIS | | 4 (8%) | 1 (2%) |
| #MESENTERIC L. NODE | (89) | (49) | (49) |
| LYMPHANGIECTASIS | | 6 (12%) | 10 (20%) |
| #HEART | (90) | (49) | (50) |
| MINERALIZATION | 1 (1%) | | |
| FIBROSIS, DIFFUSE | | | 1 (2%) |
| ENDOCARDIOSIS | 1 (1%) | | |

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

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #HEART/ATRIUM | (90) | (49) | (50) |
| THROMBOSIS, NOS | 1 (1%) | 1 (2%) | 1 (2%) |
| #LEFT ATRIUM | (90) | (49) | (50) |
| THROMBOSIS, NOS | 1 (1%) | | |
| #HEART/VENTRICLE | (90) | (49) | (50) |
| FIBROSIS, FOCAL | | | 1 (2%) |
| #MYOCARDIUM | (90) | (49) | (50) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (1%) | | |
| FIBROSIS, FOCAL | 1 (1%) | | 1 (2%) |
| FIBROSIS, MULTIFOCAL | | | 1 (2%) |
| DEGENERATION, NOS | 31 (34%) | 21 (43%) | 12 (24%) |
| #CARDIAC VALVE | (90) | (49) | (50) |
| INFLAMMATION, CHRONIC FOCAL | 1 (1%) | | |
| FIBROSIS | 1 (1%) | 1 (2%) | |
| FIBROSIS, FOCAL | 1 (1%) | | |
| *PANCREATIC ARTERY, | (90) | (50) | (50) |
| FIBROSIS | 1 (1%) | 1 (2%) | 1 (2%) |
| *MESENTERIC ARTERY | (90) | (50) | (50) |
| THROMBOSIS, NOS | 1 (1%) | | |
| INFLAMMATION, ACUTE/CHRONIC | 1 (1%) | | |
| #LIVER | (90) | (50) | (50) |
| THROMBOSIS, NOS | 1 (1%) | | |
| #PANCREAS | (88) | (47) | (46) |
| PERIARTERITIS | | 1 (2%) | 3 (7%) |
| #KIDNEY | (90) | (50) | (50) |
| PERIARTERITIS | | 2 (4%) | 1 (2%) |
| #U.BLADDER/SEROSA | (82) | (48) | (46) |
| PERIARTERITIS | 1 (1%) | | |
| DIGESTIVE SYSTEM | | | |
| *TONGUE | (90) | (50) | (50) |
| HEMORRHAGE | | 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 |
|---|---|---|---|
| #SALIVARY GLAND | (89) | (49) | (47) |
| ATROPHY, FOCAL | 2 (2%) | 1 (2%) | |
| #LIVER | (90) | (50) | (50) |
| INFLAMMATION, CHRONIC FOCAL | 2 (2%) | | |
| INFLAMMATION, CHRONIC NECROTIZIN | | | 1 (2%) |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (1%) | | |
| CIRRHOSIS, NOS | 1 (1%) | | |
| DEGENERATION, NOS | 1 (1%) | | |
| NECROSIS, FOCAL | | 1 (2%) | 1 (2%) |
| METAMORPHOSIS FATTY | | | 1 (2%) |
| BASOPHILIC CYTO CHANGE | 63 (70%) | 38 (76%) | 37 (74%) |
| FOCAL CELLULAR CHANGE | 2 (2%) | 6 (12%) | 3 (6%) |
| ANGIECTASIS | | 1 (2%) | 1 (2%) |
| #HEPATIC CAPSULE | (90) | (50) | (50) |
| NECROSIS, FOCAL | | 1 (2%) | |
| #PORTA HEPATIS | (90) | (50) | (50) |
| FIBROSIS | 1 (1%) | | |
| #LIVER/CENTRILOBULAR | (90) | (50) | (50) |
| CONGESTION, CHRONIC | | 1 (2%) | |
| CONGESTION, CHRONIC PASSIVE | | | 1 (2%) |
| DEGENERATION, NOS | 1 (1%) | | |
| NECROSIS, FOCAL | 1 (1%) | | 2 (4%) |
| #BILE DUCT | (90) | (50) | (50) |
| HYPERPLASIA, NOS | 7 (8%) | 7 (14%) | 4 (8%) |
| HYPERPLASIA, FOCAL | 15 (17%) | 3 (6%) | 6 (12%) |
| #PANCREATIC ACINUS | (88) | (47) | (46) |
| ATROPHY, NOS | 2 (2%) | 3 (6%) | 7 (15%) |
| ATROPHY, FOCAL | 12 (14%) | 5 (11%) | 4 (9%) |
| ATROPHY, DIFFUSE | | 1 (2%) | |
| #STOMACH | (87) | (50) | (49) |
| MINERALIZATION | | | 1 (2%) |
| INFLAMMATION, ACUTE FOCAL | 1 (1%) | | |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| HYPERPLASIA, BASAL CELL | 1 (1%) | | |
| #GASTRIC MUCOSA | (87) | (50) | (49) |
| MINERALIZATION | 1 (1%) | | |

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

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| NECROSIS, FOCAL | 2 (2%) | 1 (2%) | |
| #CARDIAC STOMACH | (87) | (50) | (49) |
| ECTOPIA | 1 (1%) | | |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| HYPERPLASIA, BASAL CELL | 1 (1%) | | |
| #JEJUNUM | (87) | (48) | (47) |
| DILATATION, NOS | | | 1 (2%) |
| FIBROSIS | | | 1 (2%) |
| #COLON | (87) | (47) | (49) |
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| NEMATODIASIS | 8 (9%) | 2 (4%) | 6 (12%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (90) | (50) | (50) |
| CYST, NOS | 1 (1%) | | |
| PYELONEPHRITIS, ACUTE | | 1 (2%) | 1 (2%) |
| NEPHROPATHY | 80 (89%) | 46 (92%) | 41 (82%) |
| DEGENERATION, HYALINE | 1 (1%) | | |
| PIGMENTATION, NOS | 4 (4%) | | |
| #KIDNEY/CORTEX | (90) | (50) | (50) |
| NEPHROSIS, NOS | | 1 (2%) | |
| PIGMENTATION, NOS | 2 (2%) | 1 (2%) | |
| #KIDNEY/TUBULE | (90) | (50) | (50) |
| PIGMENTATION, NOS | 1 (1%) | 2 (4%) | |
| REGENERATION, NOS | 1 (1%) | | |
| #URINARY BLADDER | (82) | (48) | (46) |
| ULCER, ACUTE | | | 1 (2%) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| *PROSTATIC URETHRA | (90) | (50) | (50) |
| METAPLASIA, SQUAMOUS | 1 (1%) | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (84) | (47) | (46) |
| HYPERPLASIA, FOCAL | 1 (1%) | | |

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

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HYPERPLASIA, CHROMOPHOBE-CELL | 9 (11%) | 3 (6%) | 2 (4%) |
| #PITUITARY ACIDOPHIL | (84) | (47) | (46) |
| HYPERPLASIA, FOCAL | 1 (1%) | 1 (2%) | 1 (2%) |
| #ADRENAL | (89) | (49) | (50) |
| NECROSIS, FOCAL | | | 1 (2%) |
| LIPOIDOSIS | | 1 (2%) | |
| #ADRENAL CORTEX | (89) | (49) | (50) |
| LIPOIDOSIS | 3 (3%) | 3 (6%) | 1 (2%) |
| CYTOPLASMIC VACUOLIZATION | 1 (1%) | | |
| HYPERTROPHY, FOCAL | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 2 (4%) |
| HYPERPLASIA, FOCAL | 5 (6%) | 2 (4%) | 6 (12%) |
| ANGIECTASIS | | 1 (2%) | |
| #ADRENAL MEDULLA | (89) | (49) | (50) |
| HYPERPLASIA, NOS | | 4 (8%) | 2 (4%) |
| HYPERPLASIA, FOCAL | 4 (4%) | 1 (2%) | 2 (4%) |
| ANGIECTASIS | 1 (1%) | | |
| #THYROID | (89) | (50) | (49) |
| MINERALIZATION | 1 (1%) | | |
| HYPERPLASIA, C-CELL | 17 (19%) | 11 (22%) | 14 (29%) |
| #PARATHYROID | (70) | (48) | (37) |
| HYPERPLASIA, NOS | | 1 (2%) | 1 (3%) |
| #PANCREATIC ISLETS | (88) | (47) | (46) |
| HYPERPLASIA, NOS | 2 (2%) | | 1 (2%) |
| HYPERPLASIA, FOCAL | 3 (3%) | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (90) | (50) | (50) |
| DILATATION, NOS | 1 (1%) | | |
| DILATATION/DUCTS | | 1 (2%) | 1 (2%) |
| CYST, NOS | | 1 (2%) | |
| HYPERPLASIA, NOS | | 1 (2%) | |
| HYPERPLASIA, CYSTIC | 1 (1%) | 2 (4%) | 1 (2%) |
| *MAMMARY ACINUS | (90) | (50) | (50) |
| HYPERPLASIA, NOS | 5 (6%) | 3 (6%) | 3 (6%) |

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

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| *PREPUTIAL GLAND | (90) | (50) | (50) |
| CYST, NOS | 1 (1%) | | |
| #PROSTATE | (84) | (45) | (45) |
| INFLAMMATION, SUPPURATIVE | 1 (1%) | | |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| INFLAMMATION, ACUTE/CHRONIC | 2 (2%) | 1 (2%) | 1 (2%) |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (1%) | | |
| #PROSTATIC GLAND | (84) | (45) | (45) |
| DILATATION, NOS | 1 (1%) | | |
| HYPERPLASIA, EPITHELIAL | 1 (1%) | | |
| *SEMINAL VESICLE | (90) | (50) | (50) |
| CYST, NOS | 1 (1%) | | |
| #TESTIS | (90) | (50) | (50) |
| STEATITIS | 4 (4%) | 4 (8%) | 1 (2%) |
| ATROPHY, NOS | 1 (1%) | | |
| HYPOSPERMATOGENESIS | 1 (1%) | | |
| #TESTIS/TUBULE | (90) | (50) | (50) |
| DEGENERATION, NOS | | | 2 (4%) |
| ATROPHY, DIFFUSE | | | 1 (2%) |
| *EPIDIDYMIS | (90) | (50) | (50) |
| MINERALIZATION | | | 1 (2%) |
| INFLAMMATION, ACUTE SUPPURATIVE | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| #BRAIN | (90) | (50) | (50) |
| MINERALIZATION | | | 1 (2%) |
| HEMORRHAGE | 1 (1%) | | 4 (8%) |
| NECROSIS, FOCAL | 1 (1%) | | 1 (2%) |
| MALACIA | | 1 (2%) | |
| ATROPHY, PRESSURE | | 1 (2%) | |
| #HIPPOCAMPUS | (90) | (50) | (50) |
| NECROSIS, FOCAL | 1 (1%) | | |
| #CEREBELLUM | (90) | (50) | (50) |
| NECROSIS, HEMORRHAGIC | 1 (1%) | | |

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

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #MEDULLA OBLONGATA | (90) | (50) | (50) |
| NECROSIS, HEMORRHAGIC | 1 (1%) | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (90) | (50) | (50) |
| SYNECHIA, POSTERIOR | 1 (1%) | | |
| *EYE/RETINA | (90) | (50) | (50) |
| DETACHMENT | 1 (1%) | | |
| ATROPHY, NOS | | 1 (2%) | |
| *EYE/CRYSTALLINE LENS | (90) | (50) | (50) |
| DEGENERATION, NOS | 1 (1%) | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| *PERITONEUM | (90) | (50) | (50) |
| EFFUSION, NOS | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | 1 (1%) | | |
| PIGMENTATION, NOS | | 1 (2%) | |
| *PERITONEAL CAVITY | (90) | (50) | (50) |
| ABSCESS, CHRONIC | | 1 (2%) | |
| *INGUINAL REGION | (90) | (50) | (50) |
| NECROSIS, FAT | | 1 (2%) | |
| *PLEURA | (90) | (50) | (50) |
| INFLAMMATION ACTIVE CHRONIC | | | 1 (2%) |
| *MESENTERY | (90) | (50) | (50) |
| STEATITIS | 4 (4%) | | |
| INFLAMMATION, FOCAL GRANULOMATOU | | | 1 (2%) |
| NECROSIS, FAT | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | |
| OMENTUM | | | |
| INFLAMMATION, GRANULOMATOUS | | 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, FOCAL GRANULOMATOU | | 3 | |
| CRANIOBUCCAL POUCH | | | |
| CYSTIC DUCTS | 1 | 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 C.I. ACID ORANGE 10

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 90 | 50 | 50 |
| ANIMALS MISSING | 2 | | |
| ANIMALS NECROPSIED | 88 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 88 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (88) | (50) | (50) |
| EPIDERMAL INCLUSION CYST | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| *SUBCUT TISSUE | (88) | (50) | (50) |
| ABSCESS, CHRONIC | 1 (1%) | | |
| NECROSIS, FAT | | 2 (4%) | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #PERITRACHEAL TISSUE | (86) | (50) | (50) |
| INFLAMMATION, CHRONIC | 1 (1%) | | |
| #LUNG | (88) | (50) | (49) |
| EDEMA, NOS | 2 (2%) | | 1 (2%) |
| HEMORRHAGE | 1 (1%) | | |
| INFLAMMATION, ACUTE FOCAL | | | 1 (2%) |
| PNEUMONIA INTERSTITIAL CHRONIC | 1 (1%) | | |
| GRANULOMA, NOS | | 2 (4%) | 3 (6%) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | | 1 (2%) | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (86) | (50) | (50) |
| DEPLETION | 1 (1%) | | |
| HYPERPLASIA, HEMATOPOIETIC | | 1 (2%) | |
| HYPERPLASIA, RETICULUM CELL | 2 (2%) | 1 (2%) | 5 (10%) |
| HYPOPLASIA, HEMATOPOIETIC | 6 (7%) | 1 (2%) | |
| #SPLEEN | (88) | (50) | (50) |
| CONGESTION, NOS | 1 (1%) | | 2 (4%) |

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

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| CONGESTION, ACUTE | | | 2 (4%) |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (1%) | | |
| FIBROSIS, FOCAL | 1 (1%) | | |
| INFARCT, FOCAL | 1 (1%) | | |
| LYMPHOID DEPLETION | 2 (2%) | | |
| HEMATOPOIESIS | 1 (1%) | | |
| #LYMPH NODE | (86)* | (49) | (50) |
| LYMPHOID DEPLETION | 1 (1%) | | |
| #MANDIBULAR L. NODE | (86) | (49) | (50) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 1 (1%) | | |
| PLASMACYTOSIS | 1 (1%) | | |
| HYPERPLASIA, PLASMA CELL | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| #MESENTERIC L. NODE | (86) | (49) | (50) |
| LYMPHOID DEPLETION | 1 (1%) | | |
| PLASMACYTOSIS | 1 (1%) | | |
| #LUNG | (88) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | 1 (1%) | | |
| #THYMUS | (70) | (41) | (36) |
| HYPERPLASIA, EPITHELIAL | | | 1 (3%) |
| CIRCULATORY SYSTEM | | | |
| #PANCREATIC L.NODE | (86) | (49) | (50) |
| LYMPHANGIECTASIS | 1 (1%) | | |
| #HEART | (88) | (50) | (49) |
| FIBROSIS, FOCAL | 1 (1%) | | |
| #HEART/ATRIUM | (88) | (50) | (49) |
| THROMBOSIS, NOS | 1 (1%) | | |
| #MYOCARDIUM | (88) | (50) | (49) |
| INFLAMMATION, INTERSTITIAL | | 1 (2%) | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | 1 (1%) | 2 (4%) | |
| FIBROSIS, DIFFUSE | 1 (1%) | | |
| DEGENERATION, NOS | 11 (13%) | 23 (46%) | 11 (22%) |
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (87) | (50) | (50) |
| ATROPHY, 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 |
|---|---|---|---|
| #LIVER | (88) | (50) | (50) |
| INFLAMMATION, ACUTE/CHRONIC | 2 (2%) | 1 (2%) | |
| INFLAMMATION, CHRONIC | 3 (3%) | | |
| INFLAMMATION, CHRONIC FOCAL | 19 (22%) | 14 (28%) | 15 (30%) |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (1%) | | 1 (2%) |
| NECROSIS, FOCAL | 1 (1%) | 1 (2%) | |
| NECROSIS, CENTRAL | 1 (1%) | | |
| BASOPHILIC CYTO CHANGE | 62 (70%) | 42 (84%) | 44 (88%) |
| FOCAL CELLULAR CHANGE | 3 (3%) | | 2 (4%) |
| ANGIECTASIS | | 2 (4%) | 1 (2%) |
| #PORTAL TRACT | (88) | (50) | (50) |
| INFLAMMATION, CHRONIC | 1 (1%) | | |
| #LIVER/CENTRILOBULAR | (88) | (50) | (50) |
| NECROSIS, FOCAL | 1 (1%) | | |
| PIGMENTATION, NOS | 1 (1%) | | |
| #BILE DUCT | (88) | (50) | (50) |
| HYPERPLASIA, NOS | 6 (7%) | | |
| HYPERPLASIA, FOCAL | 5 (6%) | 1 (2%) | |
| #PANCREATIC ACINUS | (83) | (50) | (48) |
| DEGENERATION, NOS | 1 (1%) | | |
| ATROPHY, NOS | 5 (6%) | 1 (2%) | 2 (4%) |
| ATROPHY, FOCAL | 1 (1%) | 3 (6%) | 3 (6%) |
| ATROPHY, DIFFUSE | 1 (1%) | | |
| #ESOPHAGUS | (87) | (50) | (49) |
| DILATATION, NOS | | | 1 (2%) |
| HYPERKERATOSIS | | | 1 (2%) |
| #PERIESOPHAGEAL TISSU | (87) | (50) | (49) |
| INFLAMMATION, CHRONIC | 1 (1%) | | |
| #STOMACH | (86) | (50) | (49) |
| FIBROSIS, DIFFUSE | 1 (1%) | | |
| #GASTRIC MUCOSA | (86) | (50) | (49) |
| NECROSIS, FOCAL | 1 (1%) | | |
| #CARDIAC STOMACH | (86) | (50) | (49) |
| EDEMA, NOS | 1 (1%) | | |
| INFLAMMATION, FOCAL | 1 (1%) | | |

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

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| INFLAMMATION, VESICULAR | 1 (1%) | | |
| ULCER, ACUTE | | 1 (2%) | |
| ULCER, CHRONIC | 1 (1%) | | |
| HYPERPLASIA, EPITHELIAL | 1 (1%) | | |
| #GASTRIC FUNDUS | (86) | (50) | (49) |
| NECROSIS, FOCAL | | 1 (2%) | |
| #COLON | (72) | (44) | (31) |
| NEMATODIASIS | 6 (8%) | | 1 (3%) |
| *RECTUM | (88) | (50) | (50) |
| NEMATODIASIS | 1 (1%) | | |
| *RECTAL MUCOUS MEMBRA | (88) | (50) | (50) |
| ATROPHY, NOS | 1 (1%) | | |
| **URINARY SYSTEM** | | | |
| #KIDNEY | (88) | (50) | (50) |
| NEPHROPATHY | 12 (14%) | 5 (10%) | 2 (4%) |
| INFARCT, NOS | 1 (1%) | | |
| PIGMENTATION, NOS | 3 (3%) | | |
| #KIDNEY/CORTEX | (88) | (50) | (50) |
| CYST, NOS | | 1 (2%) | |
| PIGMENTATION, NOS | 1 (1%) | | |
| #KIDNEY/TUBULE | (88) | (50) | (50) |
| PIGMENTATION, NOS | 2 (2%) | | 1 (2%) |
| REGENERATION, NOS | 1 (1%) | | |
| #KIDNEY/PELVIS | (88) | (50) | (50) |
| MINERALIZATION | 2 (2%) | | 2 (4%) |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (83) | (44) | (46) |
| CYST, NOS | | 1 (2%) | |
| HEMORRHAGE, CHRONIC | | | 1 (2%) |
| HYPERPLASIA, CHROMOPHOBE-CELL | 12 (14%) | 8 (18%) | 7 (15%) |
| ANGIECTASIS | 2 (2%) | | |
| #PITUITARY ACIDOPHIL | (83) | (44) | (46) |
| HYPERPLASIA, NOS | 1 (1%) | | |

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

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #ADRENAL | (86) | (50) | (50) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | |
| ABSCESS, CHRONIC | 1 (1%) | | |
| NECROSIS, NOS | | 1 (2%) | |
| ATROPHY, NOS | 1 (1%) | | |
| ANGIECTASIS | 1 (1%) | | 1 (2%) |
| #ADRENAL CORTEX | (86) | (50) | (50) |
| NECROSIS, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | | | 1 (2%) |
| LIPOIDOSIS | 15 (17%) | 7 (14%) | 5 (10%) |
| FOCAL CELLULAR CHANGE | 1 (1%) | | |
| HYPERPLASIA, NOS | 5 (6%) | 1 (2%) | 2 (4%) |
| HYPERPLASIA, FOCAL | 7 (8%) | 13 (26%) | 7 (14%) |
| ANGIECTASIS | 1 (1%) | | |
| #ZONA FASCICULATA | (86) | (50) | (50) |
| LIPOIDOSIS | 1 (1%) | | |
| #ADRENAL MEDULLA | (86) | (50) | (50) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, FOCAL | 1 (1%) | 2 (4%) | 2 (4%) |
| #THYROID | (86) | (50) | (49) |
| THYROGLOSSAL DUCT CYST | | 1 (2%) | |
| CYSTIC FOLLICLES | | 2 (4%) | 1 (2%) |
| HYPERPLASIA, C-CELL | 16 (19%) | 7 (14%) | 6 (12%) |
| HYPERPLASIA, FOLLICULAR-CELL | 1 (1%) | | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (88) | (50) | (50) |
| DILATATION, NOS | 2 (2%) | | |
| DILATATION/DUCTS | 3 (3%) | | |
| CYST, NOS | 2 (2%) | | |
| CYSTIC DUCTS | 2 (2%) | | |
| HYPERPLASIA, NOS | 1 (1%) | 2 (4%) | 1 (2%) |
| HYPERPLASIA, EPITHELIAL | 1 (1%) | | |
| HYPERPLASIA, CYSTIC | 19 (22%) | 2 (4%) | 2 (4%) |
| *MAMMARY ACINUS | (88) | (50) | (50) |
| DILATATION, NOS | 1 (1%) | 1 (2%) | |
| CYST, NOS | 3 (3%) | 3 (6%) | 4 (8%) |

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

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| MULTIPLE CYSTS | 1 (1%) | | 1 (2%) |
| HYPERPLASIA, NOS | 4 (5%) | | |
| HYPERPLASIA, CYSTIC | 2 (2%) | 9 (18%) | 3 (6%) |
| *CLITORAL GLAND | (88) | (50) | (50) |
| CYST, NOS | 1 (1%) | | |
| *VAGINA | (88) | (50) | (50) |
| POLYP | 1 (1%) | | |
| #UTERUS | (87) | (50) | (49) |
| DILATATION, NOS | | | 2 (4%) |
| HEMORRHAGE | | | 1 (2%) |
| #UTERINE SEROSA | (87) | (50) | (49) |
| ANGIECTASIS | | 1 (2%) | |
| #UTERUS/ENDOMETRIUM | (87) | (50) | (49) |
| INFLAMMATION, ACUTE FOCAL | | | 1 (2%) |
| HYPERPLASIA, NOS | 1 (1%) | 1 (2%) | |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| #ENDOMETRIAL GLAND | (87) | (50) | (49) |
| DILATATION, NOS | | 1 (2%) | |
| CYST, NOS | 4 (5%) | 2 (4%) | 2 (4%) |
| #OVARY | (86) | (50) | (48) |
| FOLLICULAR CYST, NOS | 3 (3%) | 3 (6%) | 2 (4%) |
| CORPUS LUTEUM CYST | | | 5 (10%) |
| GRANULOMA, NOS | | 1 (2%) | |
| #OVARY/RETE OVARII | (86) | (50) | (48) |
| HYPERPLASIA, NOS | 1 (1%) | | 1 (2%) |
| #MESOVARIUM | (86) | (50) | (48) |
| NECROSIS, FAT | 1 (1%) | | |
| **NERVOUS SYSTEM** | | | |
| #BRAIN | (88) | (50) | (50) |
| HYDROCEPHALUS, NOS | 8 (9%) | 2 (4%) | 2 (4%) |
| HEMORRHAGE | 1 (1%) | | |
| NECROSIS, FOCAL | 1 (1%) | | |
| ATROPHY, PRESSURE | 2 (2%) | 2 (4%) | |

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

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #HYPOTHALAMUS | (88) | (50) | (50) |
| ATROPHY, PRESSURE | 6 (7%) | 3 (6%) | 5 (10%) |
| #CEREBELLUM | (88) | (50) | (50) |
| MINERALIZATION | 1 (1%) | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (88) | (50) | (50) |
| SYNECHIA, ANTERIOR | 1 (1%) | | |
| SYNECHIA, POSTERIOR | | 1 (2%) | |
| *EYE/RETINA | (88) | (50) | (50) |
| ATROPHY, NOS | 1 (1%) | 1 (2%) | |
| ATROPHY, DIFFUSE | 1 (1%) | | |
| *EYE/CRYSTALLINE LENS | (88) | (50) | (50) |
| DEGENERATION, NOS | 2 (2%) | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | |
| *FEMUR | (88) | (50) | (50) |
| ENOSTOSIS | | | 1 (2%) |
| BODY CAVITIES | | | |
| *ABDOMINAL CAVITY | (88) | (50) | (50) |
| NECROSIS, FAT | | 1 (2%) | |
| *MEDIASTINAL PLEURA | (88) | (50) | (50) |
| STEATITIS | | | 1 (2%) |
| *EPICARDIUM | (88) | (50) | (50) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| *MESENTERY | (88) | (50) | (50) |
| HEMORRHAGE, CHRONIC | | 1 (2%) | |
| INFLAMMATION, GRANULOMATOUS | | | 2 (4%) |
| NECROSIS, FAT | 3 (3%) | | 1 (2%) |
| ALL OTHER SYSTEMS | | | |
| *MULTIPLE ORGANS | (88) | (50) | (50) |
| HEMORRHAGE | 1 (1%) | | |

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

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| BROAD LIGAMENT | | | |
| STEATITIS | 1 | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| ANIMAL MISSING/NO NECROPSY | 2 | | |

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

# APPENDIX D

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED DIETS CONTAINING C.I. ACID ORANGE 10

## TABLE D1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIETS CONTAINING C.I. ACID ORANGE 10

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 49 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 49 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (50) | (49) | (50) |
| EDEMA, NOS | 1 (2%) | | |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| INFLAMMATION, ACUTE FOCAL | | | 1 (2%) |
| INFLAMMATION ACUTE PUSTULAR | 1 (2%) | | |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| INFLAMMATION, CHRONIC FOCAL | | 2 (4%) | |
| INFECTION, FUNGAL | | | 1 (2%) |
| HYPERKERATOSIS | 2 (4%) | | |
| METAPLASIA, OSSEOUS | 1 (2%) | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #TRACHEA | (46) | (44) | (48) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| METAPLASIA, NOS | | | 1 (2%) |
| #TRACHEAL GLAND | (46) | (44) | (48) |
| DILATATION, NOS | | | 1 (2%) |
| #LUNG/BRONCHUS | (49) | (49) | (50) |
| BRONCHIECTASIS | 2 (4%) | 7 (14%) | 1 (2%) |
| #LUNG/BRONCHIOLE | (49) | (49) | (50) |
| BRONCHIOLECTASIS | 10 (20%) | 2 (4%) | 9 (18%) |
| HYPERPLASIA, EPITHELIAL | 1 (2%) | | |
| #LUNG | (49) | (49) | (50) |
| CONGESTION, NOS | 1 (2%) | | 1 (2%) |
| EDEMA, NOS | | 1 (2%) | |
| EDEMA, INTERSTITIAL | 2 (4%) | | |
| HEMORRHAGE | 2 (4%) | 2 (4%) | 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 |
|---|---|---|---|
| INFLAMMATION, INTERSTITIAL | 17 (35%) | 26 (53%) | 29 (58%) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| PNEUMONIA INTERSTITIAL CHRONIC | 1 (2%) | | |
| HYPERPLASIA, CYSTIC | 1 (2%) | | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 11 (22%) | 22 (45%) | 2 (4%) |
| HISTIOCYTOSIS | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (50) | (49) | (50) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| #BONE MARROW | (43) | (44) | (46) |
| ATROPHY, NOS | | 1 (2%) | |
| DEPLETION | | 1 (2%) | |
| HYPERPLASIA, HEMATOPOIETIC | 5 (12%) | 2 (5%) | |
| HYPERPLASIA, ERYTHROID | | 1 (2%) | |
| #SPLEEN | (48) | (46) | (50) |
| CONGESTION, NOS | 1 (2%) | | |
| HEMOSIDEROSIS | | 2 (4%) | |
| LYMPHOID DEPLETION | | 1 (2%) | |
| ANGIECTASIS | 1 (2%) | 1 (2%) | |
| HYPERPLASIA, RETICULUM CELL | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 2 (4%) | | 3 (6%) |
| MASTOCYTOSIS | | 1 (2%) | |
| HEMATOPOIESIS | 9 (19%) | 3 (7%) | 1 (2%) |
| #SPLENIC FOLLICLES | (48) | (46) | (50) |
| INFLAMMATION, ACUTE NECROTIZING | 1 (2%) | | |
| FIBROSIS, MULTIFOCAL | | 1 (2%) | |
| #LYMPH NODE | (37) | (34) | (42) |
| INFLAMMATION, SUPPURATIVE | | 1 (3%) | |
| NECROSIS, FOCAL | | 1 (3%) | |
| LYMPHOID DEPLETION | 1 (3%) | | 1 (2%) |
| HYPERPLASIA, RETICULUM CELL | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 1 (3%) | | 2 (5%) |
| HEMATOPOIESIS | 1 (3%) | | |
| #MANDIBULAR L. NODE | (37) | (34) | (42) |
| HEMOSIDEROSIS | 1 (3%) | | 1 (2%) |
| LYMPHOID DEPLETION | | 1 (3%) | |
| HYPERPLASIA, RETICULUM CELL | 1 (3%) | 1 (3%) | 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 |
|---|---|---|---|
| HYPERPLASIA, LYMPHOID | | 1 (3%) | |
| #LYMPH NODE OF THORAX | (37) | (34) | (42) |
| INFLAMMATION, FOCAL GRANULOMATOU | | 1 (3%) | |
| #BRONCHIAL LYMPH NODE | (37) | (34) | (42) |
| INFLAMMATION, CHRONIC | 1 (3%) | | |
| LYMPHOID DEPLETION | | 1 (3%) | |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| #LUMBAR LYMPH NODE | (37) | (34) | (42) |
| HYPERPLASIA, PLASMA CELL | 1 (3%) | | |
| #MESENTERIC L. NODE | (37) | (34) | (42) |
| CONGESTION, NOS | 3 (8%) | | 2 (5%) |
| HEMORRHAGE | 1 (3%) | | |
| INFLAMMATION, CHRONIC DIFFUSE | 1 (3%) | | |
| INFLAMMATION, GRANULOMATOUS | 1 (3%) | | |
| NECROSIS, FOCAL | | 1 (3%) | |
| HEMOSIDEROSIS | | 1 (3%) | |
| LYMPHOID DEPLETION | 3 (8%) | 1 (3%) | 1 (2%) |
| HYPERPLASIA, NOS | 1 (3%) | | |
| HYPERPLASIA, LYMPHOID | | 1 (3%) | |
| HEMATOPOIESIS | 2 (5%) | | |
| #INGUINAL LYMPH NODE | (37) | (34) | (42) |
| HYPERPLASIA, LYMPHOID | 1 (3%) | | |
| #LUNG/BRONCHIOLE | (49) | (49) | (50) |
| HYPERPLASIA, LYMPHOID | 5 (10%) | 1 (2%) | 2 (4%) |
| #LUNG | (49) | (49) | (50) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | | |
| #SALIVARY GLAND | (50) | (47) | (50) |
| HYPERPLASIA, LYMPHOID | 9 (18%) | 10 (21%) | 7 (14%) |
| #LIVER | (50) | (49) | (50) |
| HEMATOPOIESIS | 3 (6%) | | |
| *GALLBLADDER | (50) | (49) | (50) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| #PANCREAS | (50) | (44) | (50) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | 4 (9%) | 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 |
|---|---|---|---|
| #DUODENUM | (38) | (39) | (46) |
| HYPERPLASIA, LYMPHOID | | 1 (3%) | |
| #JEJUNUM | (38) | (39) | (46) |
| HYPERPLASIA, LYMPHOID | | 1 (3%) | |
| #ILEUM | (38) | (39) | (46) |
| HYPERPLASIA, LYMPHOID | 1 (3%) | | |
| #KIDNEY | (50) | (49) | (50) |
| HYPERPLASIA, LYMPHOID | 13 (26%) | 12 (24%) | 9 (18%) |
| #URINARY BLADDER | (47) | (46) | (48) |
| HYPERPLASIA, LYMPHOID | 11 (23%) | 3 (7%) | 10 (21%) |
| #U.BLADDER/SUBMUCOSA | (47) | (46) | (48) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | | |
| #PROSTATE | (49) | (43) | (47) |
| LEUKOSTASIS | | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | | 2 (5%) | |
| *SEMINAL VESICLE | (50) | (49) | (50) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | 2 (4%) | 1 (2%) |
| #TESTIS | (50) | (48) | (49) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| *VAS DEFERENS | (50) | (49) | (50) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #THYMUS | (27) | (30) | (31) |
| ECTOPIA | 1 (4%) | | |
| CYST, NOS | 1 (4%) | 2 (7%) | |
| NECROSIS, FOCAL | | 1 (3%) | |
| CIRCULATORY SYSTEM | | | |
| #BRAIN/MENINGES | (50) | (47) | (48) |
| PERIVASCULITIS | 1 (2%) | | |
| #BRAIN | (50) | (47) | (48) |
| PERIVASCULITIS | | | 2 (4%) |

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

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| *SUBCUT TISSUE | (50) | (49) | (50) |
| PERIVASCULITIS | | | 1 (2%) |
| #LYMPH NODE | (37) | (34) | (42) |
| LYMPHANGIECTASIS | | | 1 (2%) |
| #LUNG | (49) | (49) | (50) |
| PERIARTERITIS | | 1 (2%) | |
| PERIVASCULITIS | | 2 (4%) | 1 (2%) |
| #HEART | (48) | (49) | (50) |
| MINERALIZATION | | 1 (2%) | |
| THROMBUS, CANALIZED | | | 1 (2%) |
| PERIVASCULITIS | | 1 (2%) | |
| ENDOCARDIOSIS | | | 1 (2%) |
| #MYOCARDIUM | (48) | (49) | (50) |
| MINERALIZATION | 1 (2%) | | |
| INFLAMMATION, ACUTE FOCAL | 1 (2%) | | |
| INFLAMMATION, ACUTE/CHRONIC | | 1 (2%) | 1 (2%) |
| FIBROSIS, MULTIFOCAL | 1 (2%) | | |
| DEGENERATION, NOS | 1 (2%) | 1 (2%) | |
| NECROSIS, FOCAL | | 1 (2%) | |
| #CARDIAC VALVE | (48) | (49) | (50) |
| MINERALIZATION | 8 (17%) | 6 (12%) | 4 (8%) |
| THROMBOSIS, NOS | 1 (2%) | | |
| DEGENERATION, MUCOID | 4 (8%) | | |
| *AORTA | (50) | (49) | (50) |
| PERIARTERITIS | | | 1 (2%) |
| *PROSTATIC ARTERY | (50) | (49) | (50) |
| INFLAMMATION, FOCAL GRANULOMATOU | | | 1 (2%) |
| #KIDNEY | (50) | (49) | (50) |
| PERIVASCULITIS | 2 (4%) | | 1 (2%) |
| #PROSTATE | (49) | (43) | (47) |
| PERIARTERITIS | | | 1 (2%) |
| PERIVASCULITIS | 1 (2%) | | |
| *SEMINAL VESICLE | (50) | (49) | (50) |
| PERIVASCULITIS | | | 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 |
|---|---|---|---|
| #INTERSTITIAL TISSUE | (50) | (48) | (49) |
| PERIVASCULITIS | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #PAROTID GLAND | (50) | (47) | (50) |
| INFLAMMATION, GRANULOMATOUS | 1 (2%) | | |
| #LIVER | (50) | (49) | (50) |
| INFLAMMATION, ACUTE/CHRONIC | 6 (12%) | 4 (8%) | 5 (10%) |
| DEGENERATION, NOS | | 1 (2%) | |
| NECROSIS, FOCAL | 1 (2%) | 2 (4%) | 1 (2%) |
| NECROSIS, COAGULATIVE | 1 (2%) | | |
| PIGMENTATION, NOS | | | 1 (2%) |
| FOCAL CELLULAR CHANGE | 3 (6%) | 1 (2%) | 2 (4%) |
| #LIVER/CENTRILOBULAR | (50) | (49) | (50) |
| NECROSIS, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | 1 (2%) | | |
| ANGIECTASIS | | | 1 (2%) |
| *GALLBLADDER | (50) | (49) | (50) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | 1 (2%) | 1 (2%) |
| #PANCREAS | (50) | (44) | (50) |
| INFLAMMATION, INTERSTITIAL | 1 (2%) | | |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| LIPOIDOSIS | | | 1 (2%) |
| #PANCREATIC ACINUS | (50) | (44) | (50) |
| ATROPHY, NOS | | | 1 (2%) |
| ATROPHY, FOCAL | 1 (2%) | | 4 (8%) |
| ATROPHY, DIFFUSE | | 1 (2%) | |
| #STOMACH | (50) | (45) | (49) |
| CYST, NOS | 1 (2%) | | |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| INFLAMMATION, ACUTE FOCAL | | 2 (4%) | 1 (2%) |
| INFLAMMATION, ACUTE DIFFUSE | | 1 (2%) | |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | 1 (2%) | | |
| HYPERPLASIA, EPITHELIAL | | | 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 |
|---|---|---|---|
| HYPERPLASIA, PAPILLARY | | | 1 (2%) |
| #GASTRIC MUCOSA | (50) | (45) | (49) |
| DILATATION, NOS | | 1 (2%) | |
| POLYPOID HYPERPLASIA | | | 1 (2%) |
| #LARGE INTESTINE | (46) | (45) | (49) |
| NEMATODIASIS | 1 (2%) | | |
| #COLON | (46) | (45) | (49) |
| NEMATODIASIS | 3 (7%) | 1 (2%) | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (49) | (50) |
| MINERALIZATION | | 1 (2%) | |
| CYST, NOS | | 1 (2%) | |
| GLOMERULONEPHRITIS, NOS | 2 (4%) | 1 (2%) | |
| INFLAMMATION, INTERSTITIAL | 4 (8%) | 1 (2%) | |
| INFLAMMATION ACTIVE CHRONIC | | | 1 (2%) |
| PYELONGPHRITIS, ACUTE/CHRONIC | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | 1 (2%) | 1 (2%) | |
| INFLAMMATION, PYOGRANULOMATOUS | 1 (2%) | | |
| NEPHROPATHY | 15 (30%) | 7 (14%) | 15 (30%) |
| #KIDNEY/CORTEX | (50) | (49) | (50) |
| DEGENERATION, NOS | | 1 (2%) | |
| #KIDNEY/TUBULE | (50) | (49) | (50) |
| MINERALIZATION | | | 1 (2%) |
| REGENERATION, NOS | 2 (4%) | 2 (4%) | |
| #URINARY BLADDER | (47) | (46) | (48) |
| INFLAMMATION, MULTIFOCAL | 1 (2%) | | |
| NECROSIS, DIFFUSE | | 1 (2%) | |
| *URETHRA | (50) | (49) | (50) |
| OBSTRUCTION, NOS | | 2 (4%) | |
| INFLAMMATION, ACUTE NECROTIZING | 1 (2%) | | |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| NECROSIS, DIFFUSE | | 1 (2%) | |
| *PROSTATIC URETHRA | (50) | (49) | (50) |
| OBSTRUCTION, 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 |
|---|---|---|---|
| HEMORRHAGE | 1 (2%) | | |
| INFLAMMATION, ACUTE NECROTIZING | 1 (2%) | | |
| *PERIURETHRAL TISSUE | (50) | (49) | (50) |
| INFLAMMATION, ACUTE NECROTIZING | | 1 (2%) | |
| INFLAMMATION, PYOGRANULOMATOUS | | 1 (2%) | |
| **ENDOCRINE SYSTEM** | | | |
| #ADRENAL | (49) | (46) | (48) |
| CYST, NOS | 1 (2%) | | |
| INFLAMMATION, GRANULOMATOUS | 1 (2%) | | |
| ANGIECTASIS | 2 (4%) | | |
| #ADRENAL CORTEX | (49) | (46) | (48) |
| CYST, NOS | | | 1 (2%) |
| HYPERTROPHY, FOCAL | | 3 (7%) | 3 (6%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, FOCAL | 2 (4%) | 4 (9%) | 1 (2%) |
| #ADRENAL MEDULLA | (49) | (46) | (48) |
| FIBROSIS | 1 (2%) | | |
| HYPERPLASIA, FOCAL | 1 (2%) | | 1 (2%) |
| #THYROID | (48) | (40) | (48) |
| FOLLICULAR CYST, NOS | 1 (2%) | | |
| HYPERPLASIA, C-CELL | | 1 (3%) | |
| HYPERPLASIA, FOLLICULAR-CELL | 1 (2%) | | |
| **REPRODUCTIVE SYSTEM** | | | |
| *PENIS | (50) | (49) | (50) |
| NECROSIS, FOCAL | | 1 (2%) | |
| *PREPUCE | (50) | (49) | (50) |
| INFLAMMATION, DIFFUSE | | 1 (2%) | |
| INFLAMMATION, ACUTE FOCAL | 1 (2%) | | |
| INFLAMMATION, ACUTE NECROTIZING | 1 (2%) | | |
| NECROSIS, FOCAL | | 1 (2%) | |
| *PREPUTIAL GLAND | (50) | (49) | (50) |
| INFLAMMATION, ACUTE FOCAL | 1 (2%) | | |
| INFLAMMATION, ACUTE DIFFUSE | | | 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 |
|---|---|---|---|
| #PROSTATE | (49) | (43) | (47) |
| INFLAMMATION, FOCAL | | | 1 (2%) |
| INFLAMMATION, ACUTE DIFFUSE | 1 (2%) | | |
| INFLAMMATION, ACUTE/CHRONIC | | 1 (2%) | 2 (4%) |
| #TESTIS | (50) | (48) | (49) |
| RETENTION OF CONTENT | 1 (2%) | | |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| DEGENERATION, NOS | 2 (4%) | 4 (8%) | 7 (14%) |
| CALCIFICATION, DYSTROPHIC | 1 (2%) | | |
| ATROPHY, NOS | | 2 (4%) | 1 (2%) |
| *EPIDIDYMIS | (50) | (49) | (50) |
| INFLAMMATION, MULTIFOCAL | | | 1 (2%) |
| INFLAMMATION, INTERSTITIAL | 1 (2%) | | |
| INFLAMMATION, ACUTE/CHRONIC | 3 (6%) | 1 (2%) | |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| GRANULOMA, SPERMATIC | | 1 (2%) | |
| CYTOLOGIC DEGENERATION | | 5 (10%) | 3 (6%) |
| HYPERPLASIA, EPITHELIAL | 1 (2%) | | 4 (8%) |
| DYSPLASIA, EPITHELIAL | | | 1 (2%) |
| *VAS DEFERENS | (50) | (49) | (50) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 1 (2%) | | |
| NERVOUS SYSTEM | | | |
| #BRAIN | (50) | (47) | (48) |
| MINERALIZATION | | | 2 (4%) |
| HEMORRHAGE | 1 (2%) | | |
| CALCIFICATION, DYSTROPHIC | 19 (38%) | 19 (40%) | 28 (58%) |
| HEMOSIDEROSIS | 1 (2%) | | |
| #CEREBRAL CORTEX | (50) | (47) | (48) |
| CALCIFICATION, DYSTROPHIC | 4 (8%) | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *MUSCLE OF NECK | (50) | (49) | (50) |
| DEGENERATION, 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 |
|---|---|---|---|
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| *MULTIPLE ORGANS | (50) | (49) | (50) |
| BACTERIAL SEPTICEMIA | | 1 (2%) | |
| SITE UNKNOWN | | | |
| INFLAMMATION, CHRONIC | 1 | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| 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 C.I. ACID ORANGE 10

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (50) | (50) | (49) |
| INFLAMMATION, ACUTE FOCAL | | 1 (2%) | |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (2%) | | |
| METAPLASIA, OSSEOUS | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #TRACHEAL GLAND | (48) | (46) | (47) |
| DILATATION, NOS | 1 (2%) | | |
| #LUNG/BRONCHUS | (50) | (50) | (49) |
| BRONCHIECTASIS | | 1 (2%) | 5 (10%) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| #BRONCHIAL MUCOUS GLA | (50) | (50) | (49) |
| HYPERPLASIA, CYSTIC | | 1 (2%) | 1 (2%) |
| #LUNG | (50) | (50) | (49) |
| RETENTION OF CONTENT | | | 1 (2%) |
| HEMORRHAGE | 1 (2%) | 1 (2%) | |
| INFLAMMATION, INTERSTITIAL | 36 (72%) | 30 (60%) | 32 (65%) |
| INFLAMMATION, ACUTE/CHRONIC | | 1 (2%) | |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (2%) | | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 35 (70%) | 30 (60%) | 32 (65%) |
| #LUNG/ALVEOLI | (50) | (50) | (49) |
| INFLAMMATION, ACUTE FOCAL | 1 (2%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (50) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | 5 (10%) | | 9 (18%) |

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

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #BONE MARROW | (46) | (45) | (49) |
| INFARCT, FOCAL | | | 1 (2%) |
| HEMOSIDEROSIS | 1 (2%) | | |
| ANGIECTASIS | 1 (2%) | | |
| MYELOFIBROSIS | | 2 (4%) | 1 (2%) |
| HYPERPLASIA, HEMATOPOIETIC | | 1 (2%) | |
| HYPERPLASIA, NEUTROPHILIC | | | 1 (2%) |
| HYPERPLASIA, RETICULUM CELL | 1 (2%) | | |
| HYPOPLASIA, HEMATOPOIETIC | 1 (2%) | 1 (2%) | |
| HYPOPLASIA, ERYTHROID | | 1 (2%) | |
| #SPLEEN | (50) | (50) | (49) |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (2%) | | |
| NECROSIS, FOCAL | | 2 (4%) | |
| HEMOSIDEROSIS | | | 1 (2%) |
| LYMPHOID DEPLETION | 1 (2%) | | |
| HYPERPLASIA, LYMPHOID | 3 (6%) | 1 (2%) | 4 (8%) |
| HEMATOPOIESIS | 6 (12%) | 2 (4%) | 1 (2%) |
| #SPLENIC FOLLICLES | (50) | (50) | (49) |
| DEGENERATION, NOS | 2 (4%) | | |
| #LYMPH NODE | (35) | (38) | (41) |
| HYPERPLASIA, LYMPHOID | 2 (6%) | 2 (5%) | |
| #MANDIBULAR L. NODE | (35) | (38) | (41) |
| DEGENERATION, NOS | 1 (3%) | | |
| HEMOSIDEROSIS | | | 2 (5%) |
| HYPERPLASIA, LYMPHOID | 1 (3%) | | |
| #LYMPH NODE OF THORAX | (35) | (38) | (41) |
| HEMORRHAGE | | | 1 (2%) |
| LYMPHOID DEPLETION | | 1 (3%) | |
| #MEDIASTINAL L.NODE | (35) | (38) | (41) |
| INFLAMMATION, GRANULOMATOUS | 1 (3%) | | |
| #MESENTERIC L. NODE | (35) | (38) | (41) |
| DEGENERATION, NOS | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 1 (3%) | | |
| HEMATOPOIESIS | | | 1 (2%) |
| #LUNG/BRONCHIOLE | (50) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | 4 (8%) | 5 (10%) | 4 (8%) |

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

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #LUNG | (50) | (50) | (49) |
| LEUKOCYTOSIS, NOS | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | 6 (12%) | 1 (2%) |
| #SALIVARY GLAND | (48) | (44) | (47) |
| HYPERPLASIA, LYMPHOID | 12 (25%) | 11 (25%) | 18 (38%) |
| #LIVER | (50) | (50) | (49) |
| LEUKOCYTOSIS, NOS | | 1 (2%) | |
| HEMATOPOIESIS | 2 (4%) | 1 (2%) | |
| *GALLBLADDER | (50) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | 2 (4%) | | |
| #PANCREAS | (46) | (47) | (46) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | 8 (17%) | 1 (2%) |
| #KIDNEY | (50) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | 25 (50%) | 23 (46%) | 17 (35%) |
| #PERIRENAL TISSUE | (50) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| *URETER | (50) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | | |
| #URINARY BLADDER | (45) | (44) | (46) |
| HYPERPLASIA, LYMPHOID | 18 (40%) | 23 (52%) | 18 (39%) |
| #UTERUS | (48) | (50) | (48) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | | |
| #THYMUS | (35) | (24) | (34) |
| CYST, NOS | | | 1 (3%) |
| HYPERPLASIA, EPITHELIAL | | | 1 (3%) |
| HYPERPLASIA, RETICULUM CELL | | | 1 (3%) |
| #THYMIC CORTEX | (35) | (24) | (34) |
| LYMPHOID DEPLETION | 2 (6%) | 1 (4%) | 2 (6%) |
| CIRCULATORY SYSTEM | | | |
| #BRAIN | (50) | (50) | (49) |
| PERIVASCULITIS | 2 (4%) | 2 (4%) | 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 |
|---|---|---|---|
| #CEREBELLUM | (50) | (50) | (49) |
| PERIVASCULITIS | | 1 (2%) | |
| *SUBCUT TISSUE | (50) | (50) | (49) |
| PERIVASCULITIS | 1 (2%) | | |
| #HEART/ATRIUM | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| #MYOCARDIUM | (50) | (50) | (49) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| #CARDIAC VALVE | (50) | (50) | (49) |
| MINERALIZATION | 10 (20%) | 1 (2%) | 8 (16%) |
| #STOMACH | (50) | (48) | (47) |
| PERIVASCULITIS | 1 (2%) | | |
| #URINARY BLADDER | (45) | (44) | (46) |
| PERIVASCULITIS | | | 1 (2%) |
| #BROAD LIGAMENT | (48) | (50) | (48) |
| PERIVASCULITIS | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (48) | (44) | (47) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | |
| #LIVER | (50) | (50) | (49) |
| INFLAMMATION, ACUTE/CHRONIC | 18 (36%) | 12 (24%) | 24 (49%) |
| ABSCESS, CHRONIC | | | 1 (2%) |
| NECROSIS, FOCAL | 2 (4%) | 3 (6%) | |
| NECROSIS, COAGULATIVE | | | 1 (2%) |
| CYTOPLASMIC VACUOLIZATION | 1 (2%) | | |
| FOCAL CELLULAR CHANGE | | | 3 (6%) |
| *GALLBLADDER | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | 1 (2%) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| #PANCREAS | (46) | (47) | (46) |
| DILATATION/DUCTS | | 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 |
|---|---|---|---|
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | 1 (2%) |
| INFLAMMATION, INTERSTITIAL | 3 (7%) | 1 (2%) | 2 (4%) |
| INFLAMMATION, CHRONIC DIFFUSE | | | 1 (2%) |
| #PANCREATIC ACINUS | (46) | (47) | (46) |
| ATROPHY, NOS | 1 (2%) | | 1 (2%) |
| ATROPHY, FOCAL | 1 (2%) | 5 (11%) | 3 (7%) |
| #PERIESOPHAGEAL TISSU | (49) | (49) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| #STOMACH | (50) | (48) | (47) |
| CYST, NOS | | | 1 (2%) |
| MULTIPLE CYSTS | 1 (2%) | | |
| INFLAMMATION, ACUTE FOCAL | | 3 (6%) | |
| INFLAMMATION, ACUTE DIFFUSE | | | 1 (2%) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| #GASTRIC MUCOSA | (50) | (48) | (47) |
| CYST, NOS | 1 (2%) | | |
| #GASTRIC SUBMUCOSA | (50) | (48) | (47) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| #CARDIAC STOMACH | (50) | (48) | (47) |
| ULCER, ACUTE | 1 (2%) | | |
| #COLON | (48) | (47) | (47) |
| NEMATODIASIS | 5 (10%) | | |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| INFLAMMATION, INTERSTITIAL | 5 (10%) | 11 (22%) | 11 (22%) |
| INFARCT, FOCAL | | 1 (2%) | |
| #PERIRENAL TISSUE | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| #KIDNEY/GLOMERULUS | (50) | (50) | (49) |
| AMYLOIDOSIS | | 1 (2%) | |
| #KIDNEY/TUBULE | (50) | (50) | (49) |
| REGENERATION, NOS | 1 (2%) | 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 |
|---|---|---|---|
| #URINARY BLADDER | (45) | (44) | (46) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (47) | (42) | (41) |
| HYPERPLASIA, FOCAL | 1 (2%) | | |
| HYPERPLASIA, CHROMOPHOBE-CELL | 1 (2%) | 1 (2%) | 1 (2%) |
| #ADRENAL | (46) | (47) | (47) |
| CYTOLOGIC DEGENERATION | | | 1 (2%) |
| #ADRENAL CORTEX | (46) | (47) | (47) |
| CYTOLOGIC DEGENERATION | | | 2 (4%) |
| HYPERTROPHY, FOCAL | 1 (2%) | 1 (2%) | |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| #ZONA GLOMERULOSA | (46) | (47) | (47) |
| ATROPHY, DIFFUSE | | | 1 (2%) |
| #ZONA RETICULARIS | (46) | (47) | (47) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| #ADRENAL MEDULLA | (46) | (47) | (47) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #PERIADRENAL TISSUE | (46) | (47) | (47) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | |
| INFLAMMATION, ACUTE/CHRONIC | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| #THYROID | (49) | (45) | (47) |
| CYST, NOS | | 1 (2%) | |
| INFLAMMATION, ACUTE FOCAL | | | 1 (2%) |
| ABSCESS, NOS | | 1 (2%) | |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| HYPERPLASIA, FOLLICULAR-CELL | 1 (2%) | | |
| #PARATHYROID | (30) | (32) | (25) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (4%) |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 1 (2%) | | 2 (4%) |

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

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #UTERUS | (48) | (50) | (48) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| INFLAMMATION, FOCAL GRANULOMATOU | | | 1 (2%) |
| FIBROSIS, FOCAL | 1 (2%) | | |
| #UTERUS/ENDOMETRIUM | (48) | (50) | (48) |
| DILATATION, NOS | 1 (2%) | 8 (16%) | 4 (8%) |
| CYST, NOS | 1 (2%) | | |
| INFLAMMATION, ACUTE | 3 (6%) | 5 (10%) | 3 (6%) |
| INFLAMMATION, ACUTE FOCAL | | 1 (2%) | |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| HYPERPLASIA, NOS | 2 (4%) | | |
| HYPERPLASIA, CYSTIC | 27 (56%) | 24 (48%) | 21 (44%) |
| #UTERUS/MYOMETRIUM | (48) | (50) | (48) |
| EDEMA, NOS | | | 1 (2%) |
| DEGENERATION, NOS | | 1 (2%) | |
| #OVARY/OVIDUCT | (48) | (50) | (48) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | 1 (2%) |
| #OVARY/PAROVARIAN | (44) | (48) | (42) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 4 (8%) | 6 (14%) |
| #OVARY | (44) | (48) | (42) |
| CYST, NOS | 8 (18%) | 6 (13%) | 9 (21%) |
| MULTIPLE CYSTS | 1 (2%) | | |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | 2 (5%) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| NERVOUS SYSTEM | | | |
| *NEURON | (50) | (50) | (49) |
| NECROSIS, NOS | 1 (2%) | | |
| *AXON AND AXON HILLOC | (50) | (50) | (49) |
| DEGENERATION, NOS | 1 (2%) | | |
| #CEREBRAL VENTRICLE | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 3 (6%) | 1 (2%) |
| #BRAIN | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 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 |
|---|---|---|---|
| ABSCESS, NOS | | | 1 (2%) |
| CALCIFICATION, DYSTROPHIC | 32 (64%) | 23 (46%) | 29 (59%) |
| **SPECIAL SENSE ORGANS** | | | |
| NONE | | | |
| **MUSCULOSKELETAL SYSTEM** | | | |
| *ABDOMINAL MUSCLE | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | 1 (2%) | | |
| **BODY CAVITIES** | | | |
| *ABDOMINAL CAVITY | (50) | (50) | (49) |
| NECROSIS, FAT | | 1 (2%) | |
| *PERITONEUM | (50) | (50) | (49) |
| INFLAMMATION ACTIVE CHRONIC | 1 (2%) | | |
| INFLAMMATION, ACUTE/CHRONIC | 2 (4%) | | 2 (4%) |
| *MESENTERY | (50) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| NECROSIS, FOCAL | | | 1 (2%) |
| **ALL OTHER SYSTEMS** | | | |
| *MULTIPLE ORGANS | (50) | (50) | (49) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| THORAX | | | |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 |
| ADIPOSE TISSUE | | | |
| STEATITIS | 1 | | |
| INFLAMMATION, FOCAL GRANULOMATOU | | | 1 |
| NECROSIS, FAT | 1 | | |
| **SPECIAL MORPHOLOGY SUMMARY** | | | |
| AUTOLYSIS/NO NECROPSY | | | 1 |

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

# APPENDIX E

## HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS RECEIVING NO TREATMENT

**TABLE E1. HISTORICAL INCIDENCE OF LIVER TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT *(a)***

| Chemical | Neoplastic Nodule | Hepatocellular Carcinoma |
|---|---|---|
| **Rates At Battelle Columbus Laboratories** | | |
| C.I. Acid Orange 10*(b)* | 5/90 | 0/90 |
| Chlorobenzene | 4/50 | 0/50 |
| C.I. Disperse Yellow 3 | 1/49 | 1/49 |
| D and C Red 9 | 0/50 | 1/50 |
| C.I. Solvent Yellow 14 | 5/50 | 1/50 |
| Ascorbic Acid | 1/49 | 1/49 |
| Total | 16/338 (5%) | 4/338 (1%) |
| SD*(c)* | 3.9% | 1.0% |
| **ALL NTP Laboratories** | | |
| Total | 78/2306 (3%) | 18/2306 (1%) |
| SD*(c)* | 3.5% | 1.1% |
| Overall Historical Range | | |
| High | 6/49 | 2/49 |
| Low | 0/50 | 0/90 |

*(a)* Data as of March 16, 1983 for studies of at least 104 weeks.

*(b)* This control group was also used in studies of C.I. Acid Red 14 and FD&C Yellow 6.

*(c)* Standard deviation.

**TABLE E2. HISTORICAL INCIDENCE OF LEUKEMIA IN F344/N RATS RECEIVING NO TREATMENT *(a)***

| Chemical | Males | Females |
|---|---|---|
| **Rates at Battelle Columbus Laboratories** | | |
| C.I. Acid Orange 10*(b)* | 22/90 | 16/88 |
| Chlorobenzene | 19/50 | 9/49 |
| C.I. Disperse Yellow 3 | 13/50 | 8/50 |
| D and C Red 9 | 10/50 | 10/50 |
| C.I. Solvent Yellow 14 | 23/50 | 9/50 |
| Ascorbic Acid | 17/50 | 6/50 |
| Total | 104/340 (31%) | 58/337 (17%) |
| SD*(c)* | 9.7% | 2.8% |
| **All NTP Laboratories** | | |
| Total | 648/2320 (28%) | 414/2370 (17%) |
| SD*(c)* | 10.2% | 7.4% |
| Overall Historical Range | | |
| High | 23/50 | 19/50 |
| Low | 5/50 *(d)* | 3/50 *(d)* |

*(a)* Data as of March 16, 1983 for studies of at least 104 weeks.

*(b)* This control group was also used in studies of C.I. Acid Red 14 and FD&C Yellow 6.

*(c)* Standard deviation.

*(d)* Excluding one study with 0/50 leukemia but 7/50 lymphomas (males) and 0/48 leukemia but 5/48 lymphomas (females).

**TABLE E3. HISTORICAL INCIDENCE OF MESOTHELIOMA IN MALE F344/N RATS RECEIVING NO TREATMENT *(a)***

| Chemical | Tunica Vaginalis | Other Locations |
|---|---|---|
| **Rates at Battelle Columbus Laboratories** | | |
| C.I. Acid Orange 10*(b)* | 0/90 | 3/90 |
| Chlorobenzene | 0/50 | 1/50 |
| C.I. Disperse Yellow 3 | 1/50 | 4/50 |
| D and C Red 9 | 1/50 | 1/50 |
| C.I. Solvent Yellow 14 | 0/50 | 1/50 |
| Ascorbic Acid | 1/50 | 0/50 |
| Total | 3/340 (1%) | 10/340 (3%) |
| SD*(c)* | 1.1% | 2.7% |
| **All NTP Laboratories** | | |
| Total | 30/2320 (1%) | 23/2320 (1%) |
| SD*(c)* | 1.7% | 1.7% |
| Overall Historical Range | | |
| High | 4/50 | 4/50 |
| Low | 0/90 | 0/50 |

*(a)* Data as of March 16, 1983 for studies of at least 104 weeks.

*(b)* This control group was also used in studies of C.I. Acid Red 14 and FD&C Yellow 6.

*(c)* Standard deviation.

# APPENDIX F

## ANALYSIS OF PRIMARY TUMORS IN F344/N RATS AND B6C3F$_1$ MICE

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

| | Control | 1,000 ppm | 3,000 ppm |
|---|---|---|---|
| **Integumentary System: Fibroma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 5/90 (6%) | 4/50 (8%) | 2/50 (4%) |
| Adjusted *(b)* | 6.9% | 9.5% | 4.9% |
| Terminal *(c)* | 5/72 (7%) | 4/42 (10%) | 1/39 (3%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.458N | P=0.447 | P=0.515N |
| Incidental Tumor Test | P=0.411N | P=0.447 | P=0.453N |
| Cochran-Armitage Trend Test | P=0.442N | | |
| Fisher Exact Test | | P=0.407 | P=0.515N |
| Weeks to First Observed Tumor | 104 | 104 | 92 |
| **Integumentary System: Fibroma or Fibrosarcoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 6/90 (7%) | 6/50 (12%) | 3/50 (6%) |
| Adjusted *(b)* | 8.0% | 14.0% | 7.2% |
| Terminal *(c)* | 5/72 (7%) | 5/42 (12%) | 1/39 (3%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.537N | P=0.250 | P=0.596N |
| Incidental Tumor Test | P=0.506N | P=0.231 | P=0.527N |
| Cochran-Armitage Trend Test | P=0.518N | | |
| Fisher Exact Test | | P=0.219 | P=0.593N |
| Weeks to First Observed Tumor | 86 | 103 | 92 |
| **Hematopoietic System: Lymphocytic Leukemia** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 22/90 (24%) | 4/50 (8%) | 3/50 (6%) |
| Adjusted *(b)* | 26.7% | 8.6% | 6.4% |
| Terminal *(c)* | 13/72 (18%) | 1/42 (2%) | 0/39 (0%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.006N | P=0.018N | P=0.011N |
| Incidental Tumor Test | P=0.002N | P=0.021N | P=0.002N |
| Cochran-Armitage Trend Test | P=0.003N | | |
| Fisher Exact Test | | P=0.013N | P=0.005N |
| Weeks to First Observed Tumor | 74 | 43 | 84 |
| **Liver: Neoplastic Nodule** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 5/90 (6%) | 3/50 (6%) | 8/50 (16%) *(e)* |
| Adjusted *(b)* | 6.9% | 7.1% | 20.5% |
| Terminal *(c)* | 5/72 (7%) | 3/42 (7%) | 8/39 (21%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.022 | P=0.633 | P=0.036 |
| Incidental Tumor Test | P=0.022 | P=0.633 | P=0.036 |
| Cochran-Armitage Trend Test | P=0.026 | | |
| Fisher Exact Test | | P=0.593 | P=0.044 |
| Weeks to First Observed Tumor | 104 | 104 | 104 |
| **Pituitary: Chromophobe Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 4/84 (5%) | 2/47 (4%) | 0/46 (0%) |
| Adjusted *(b)* | 5.8% | 4.9% | 0.0% |
| Terminal *(c)* | 4/69 (6%) | 2/41 (5%) | 0/35 (0%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.146N | P=0.590N | P=0.182N |
| Incidental Tumor Test | P=0.146N | P=0.590N | P=0.182N |
| Cochran-Armitage Trend Test | P=0.135N | | |
| Fisher Exact Test | | P=0.631N | P=0.170N |
| Weeks to First Observed Tumor | 104 | 104 | — |

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

| | Control | 1,000 ppm | 3,000 ppm |
|---|---|---|---|
| **Pituitary: Chromophobe Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 1/84 (1%) | 4/47 (9%) | 2/46 (4%) |
| Adjusted *(b)* | 1.4% | 9.8% | 5.7% |
| Terminal *(c)* | 1/69 (1%) | 4/41 (10%) | 2/35 (6%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.265 | P=0.062 | P=0.273 |
| Incidental Tumor Test | P=0.265 | P=0.062 | P=0.273 |
| Cochran-Armitage Trend Test | P=0.299 | | |
| Fisher Exact Test | | P=0.055 | P=0.285 |
| Weeks to First Observed Tumor | 104 | 104 | 104 |
| **Pituitary: Chromophobe Adenoma or Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 5/84 (6%) | 6/47 (13%) | 2/46 (4%) |
| Adjusted *(b)* | 7.2% | 14.6% | 5.7% |
| Terminal *(c)* | 5/69 (7%) | 6/41 (15%) | 2/35 (6%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.491N | P=0.180 | P=0.547N |
| Incidental Tumor Test | P=0.491N | P=0.180 | P=0.547N |
| Cochran-Armitage Trend Test | P=0.445N | | |
| Fisher Exact Test | | P=0.154 | P=0.523N |
| Weeks to First Observed Tumor | 104 | 104 | 104 |
| **Adrenal: All Pheochromocytoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 14/89 (16%) | 4/49 (8%) | 9/50 (18%) |
| Adjusted *(b)* | 18.4% | 9.2% | 21.6% |
| Terminal *(c)* | 10/71 (14%) | 3/42 (7%) | 7/39 (18%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.383 | P=0.138N | P=0.434 |
| Incidental Tumor Test | P=0.425 | P=0.154N | P=0.438 |
| Cochran-Armitage Trend Test | P=0.406 | | |
| Fisher Exact Test | | P=0.159N | P=0.451 |
| Weeks to First Observed Tumor | 86 | 92 | 69 |
| **Thyroid: C-Cell Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 2/89 (2%) | 5/50 (10%) | 2/49 (4%) *(f)* |
| Adjusted *(b)* | 2.8% | 11.9% | 5.1% |
| Terminal *(c)* | 2/71 (3%) | 5/42 (12%) | 2/39 (5%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.435 | P=0.063 | P=0.465 |
| Incidental Tumor Test | P=0.435 | P=0.063 | P=0.465 |
| Cochran-Armitage Trend Test | P=0.437 | | |
| Fisher Exact Test | | P=0.057 | P=0.446 |
| Weeks to First Observed Tumor | 104 | 104 | 104 |
| **Pancreatic Islets: Islet Cell Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 3/88 (3%) | 1/47 (2%) | 3/46 (7%) |
| Adjusted *(b)* | 4.2% | 2.4% | 7.9% |
| Terminal *(c)* | 3/71 (4%) | 1/42 (2%) | 3/38 (8%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.287 | P=0.506N | P=0.360 |
| Incidental Tumor Test | P=0.287 | P=0.506N | P=0.360 |
| Cochran-Armitage Trend Test | P=0.281 | | |
| Fisher Exact Test | | P=0.566N | P=0.337 |
| Weeks to First Observed Tumor | 104 | 104 | 104 |

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

| | Control | 1,000 ppm | 3,000 ppm |
|---|---|---|---|
| **Mammary Gland: Fibroadenoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 2/90 (2%) | 3/50 (6%) | 0/50 (0%) |
| Adjusted *(b)* | 2.7% | 7.1% | 0.0% |
| Terminal *(c)* | 1/72 (1%) | 3/42 (7%) | 0/39 (0%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.330N | P=0.269 | P=0.384N |
| Incidental Tumor Test | P=0.366N | P=0.246 | P=0.454N |
| Cochran-Armitage Trend Test | P=0.321N | | |
| Fisher Exact Test | | P=0.243 | P=0.412N |
| Weeks to First Observed Tumor | 97 | 104 | — |
| **Preputial Gland: Sebaceous Adenoma or Adenocarcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 1/90 (1%) | 0/50 (0%) | 3/50 (6%) |
| Adjusted *(b)* | 1.4% | 0.0% | 7.3% |
| Terminal *(c)* | 1/72 (1%) | 0/42 (0%) | 2/39 (5%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.057 | P=0.607N | P=0.124 |
| Incidental Tumor Test | P=0.089 | P=0.607N | P=0.172 |
| Cochran-Armitage Trend Test | P=0.060 | | |
| Fisher Exact Test | | P=0.643N | P=0.130 |
| Weeks to First Observed Tumor | 104 | — | 91 |
| **Testis: Interstitial Cell Tumor** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 86/90 (96%) | 49/50 (98%) | 49/50 (98%) |
| Adjusted *(b)* | 100.0% | 100.0% | 100.0% |
| Terminal *(c)* | 72/72 (100%) | 42/42 (100%) | 39/39 (100%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.293 | P=0.474N | P=0.325 |
| Incidental Tumor Test | P=0.530 | P=0.448 | P=0.582 |
| Cochran-Armitage Trend Test | P=0.329 | | |
| Fisher Exact Test | | P=0.412 | P=0.412 |
| Weeks to First Observed Tumor | 74 | 67 | 78 |
| **Tunica Vaginalis: Mesothelioma, NOS or Malignant** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 0/90 (0%) | 3/50 (6%) | 2/50 (4%) |
| Adjusted *(b)* | 0.0% | 6.4% | 5.1% |
| Terminal *(c)* | 0/72 (0%) | 1/42 (2%) | 2/39 (5%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.156 | P=0.044 | P=0.118 |
| Incidental Tumor Test | P=0.218 | P=0.027 | P=0.118 |
| Cochran-Armitage Trend Test | P=0.157 | | |
| Fisher Exact Test | | P=0.044 | P=0.126 |
| Weeks to First Observed Tumor | — | 67 | 104 |
| **All Sites: Mesothelioma, NOS or Malignant** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 3/90 (3%) | 3/50 (6%) | 2/50 (4%) |
| Adjusted *(b)* | 4.0% | 6.4% | 5.1% |
| Terminal *(c)* | 2/72 (3%) | 1/42 (2%) | 2/39 (5%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.540 | P=0.396 | P=0.595 |
| Incidental Tumor Test | P=0.570 | P=0.327 | P=0.549 |
| Cochran-Armitage Trend Test | P=0.549 | | |
| Fisher Exact Test | | P=0.366 | P=0.588 |
| Weeks to First Observed Tumor | 97 | 67 | 104 |

*(a)* Number of tumor bearing animals/number of animals examined at the site.

*(b)* Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

*(c)* 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 prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

*(e)* One male rat in the 3,000 ppm dose group had both a neoplastic nodule and a carcinoma of the liver.

*(f)* One additional male rat in the 3,000 ppm dose group had a C-cell adenoma of the thyroid gland.

**TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS**

| | Control | 1,000 ppm | 3,000 ppm |
|---|---|---|---|
| **Integumentary System: Fibroma or Fibrosarcoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 2/88 (2%) | 3/50 (6%) | 0/50 (0%) |
| Adjusted *(b)* | 3.0% | 6.5% | 0.0% |
| Terminal *(c)* | 2/66 (3%) | 3/46 (7%) | 0/44 (0%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.266N | P=0.340 | P=0.332N |
| Incidental Tumor Test | P=0.266N | P=0.340 | P=0.332N |
| Cochran-Armitage Trend Test | P=0.314N | | |
| Fisher Exact Test | | P=0.251 | P=0.405N |
| Weeks to First Observed Tumor | 104 | 104 | — |
| **Hematopoietic System: Lymphocytic Leukemia** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 16/88 (18%) | 2/50 (4%) | 0/50 (0%) |
| Adjusted *(b)* | 21.4% | 4.2% | 0.0% |
| Terminal *(c)* | 10/66 (15%) | 1/46 (2%) | 0/44 (0%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P<0.001N | P=0.009N | P=0.001N |
| Incidental Tumor Test | P=0.002N | P=0.026N | P=0.004N |
| Cochran-Armitage Trend Test | P<0.001N | | |
| Fisher Exact Test | | P=0.014N | P<0.001N |
| Weeks to First Observed Tumor | 5 | 102 | — |
| **Hematopoietic System: Leukemia or Lymphoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 18/88 (20%) | 4/50 (8%) | 1/50 (2%) |
| Adjusted *(b)* | 23.2% | 8.5% | 2.2% |
| Terminal *(c)* | 10/66 (15%) | 3/46 (7%) | 0/44 (0%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.001N | P=0.027N | P=0.002N |
| Incidental Tumor Test | P=0.010N | P=0.113N | P=0.016N |
| Cochran-Armitage Trend Test | P=0.002N | | |
| Fisher Exact Test | | P=0.043N | P=0.001N |
| Weeks to First Observed Tumor | 5 | 102 | 100 |
| **Pituitary: Chromophobe Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 25/83 (30%) | 13/44 (30%) | 11/46 (24%) |
| Adjusted *(b)* | 35.0% | 30.4% | 25.8% |
| Terminal *(c)* | 19/64 (30%) | 11/40 (28%) | 9/40 (23%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.173N | P=0.324N | P=0.192N |
| Incidental Tumor Test | P=0.305N | P=0.519N | P=0.328N |
| Cochran-Armitage Trend Test | P=0.268N | | |
| Fisher Exact Test | | P=0.558N | P=0.295N |
| Weeks to First Observed Tumor | 81 | 98 | 92 |
| **Pituitary: Chromophobe Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 5/83 (6%) | 1/44 (2%) | 1/46 (2%) |
| Adjusted *(b)* | 7.8% | 2.5% | 2.5% |
| Terminal *(c)* | 5/64 (8%) | 1/40 (3%) | 1/40 (3%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.194N | P=0.244N | P=0.244N |
| Incidental Tumor Test | P=0.194N | P=0.244N | P=0.244N |
| Cochran-Armitage Trend Test | P=0.231N | | |
| Fisher Exact Test | | P=0.320N | P=0.301N |
| Weeks to First Observed Tumor | 104 | 104 | 104 |

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

| | Control | 1,000 ppm | 3,000 ppm |
|---|---|---|---|
| **Pituitary: Chromophobe Adenoma or Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 30/83 (36%) | 14/44 (32%) | 12/46 (26%) |
| Adjusted *(b)* | 42.2% | 32.8% | 28.2% |
| Terminal *(c)* | 24/64 (38%) | 12/40 (30%) | 10/50 (25%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.083N | P=0.180N | P=0.094N |
| Incidental Tumor Test | P=0.161N | P=0.318N | P=0.173N |
| Cochran-Armitage Trend Test | P=0.150N | | |
| Fisher Exact Test | | P=0.388N | P=0.166N |
| Weeks to First Observed Tumor | 81 | 98 | 92 |
| **Adrenal: Cortical Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 6/86 (7%)*(e)* | 4/50 (8%) | 2/50 (4%) |
| Adjusted *(b)* | 9.2% | 8.5% | 4.5% |
| Terminal *(c)* | 6/65 (9%) | 3/46 (7%) | 2/44 (5%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.254N | P=0.594N | P=0.293N |
| Incidental Tumor Test | P=0.287N | P=0.621N | P=0.293N |
| Cochran-Armitage Trend Test | P=0.323N | | |
| Fisher Exact Test | | P=0.536 | P=0.382N |
| Weeks to First Observed Tumor | 104 | 102 | 104 |
| **Adrenal: All Pheochromocytoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 4/86 (5%) | 4/50 (8%) | 0/50 (0%) |
| Adjusted *(b)* | 6.2% | 8.7% | 0.0% |
| Terminal *(c)* | 4/65 (6%) | 4/46 (9%) | 0/44 (0%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.111N | P=0.446 | P=0.125N |
| Incidental Tumor Test | P=0.111N | P=0.446 | P=0.125N |
| Cochran-Armitage Trend Test | P=0.146N | | |
| Fisher Exact Test | | P=0.328 | P=0.156N |
| Weeks to First Observed Tumor | 104 | 104 | 104 |
| **Mammary Gland: Fibroadenoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 18/88 (20%) | 7/50 (14%) | 6/50 (12%) |
| Adjusted *(b)* | 23.8% | 15.2% | 13.3% |
| Terminal *(c)* | 11/66 (17%) | 7/46 (15%) | 5/44 (11%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.084N | P=0.131N | P=0.101N |
| Incidental Tumor Test | P=0.157N | P=0.409N | P=0.196N |
| Cochran-Armitage Trend Test | P=0.134N | | |
| Fisher Exact Test | | P=0.240N | P=0.153N |
| Weeks to First Observed Tumor | 81 | 104 | 100 |
| **Uterus: Endometrial Stromal Polyp** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 9/87 (10%) | 7/50 (14%) | 6/49 (12%) |
| Adjusted *(b)* | 12.9% | 15.2% | 13.6% |
| Terminal *(c)* | 7/66 (11%) | 7/46 (15%) | 6/44 (14%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.571 | P=0.505 | P=0.597 |
| Incidental Tumor Test | P=0.525 | P=0.398 | P=0.538 |
| Cochran-Armitage Trend Test | P=0.449 | | |
| Fisher Exact Test | | P=0.352 | P=0.470 |
| Weeks to First Observed Tumor | 88 | 104 | 104 |

*(a)* Number of tumor bearing animals/number of animals examined at the site.

*(b)* Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

*(c)* 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 prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

*(e)* One additional control female rat had a cortical carcinoma of the adrenal gland.

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

| | Control | 3,000 ppm | 6,000 ppm |
|---|---|---|---|
| **Skin: Fibroma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 0/50 (0%) | 1/49 (2%) | 3/50 (6%) |
| Adjusted *(b)* | 0.0% | 3.0% | 7.1% |
| Terminal *(c)* | 0/33 (0%) | 1/33 (3%) | 3/42 (7%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.093 | P=0.500 | P=0.167 |
| Incidental Tumor Test | P=0.093 | P=0.500 | P=0.167 |
| Cochran-Armitage Trend Test | P=0.061 | | |
| Fisher Exact Test | | P=0.495 | P=0.121 |
| Weeks to First Observed Tumor | — | 103 | 103 |
| **Subcutaneous Tissue: Fibrosarcoma or Sarcoma, NOS** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 6/50 (12%) | 1/49 (2%) | 2/50 (4%) |
| Adjusted *(b)* | 17.0% | 3.0% | 4.5% |
| Terminal *(c)* | 4/33 (12%) | 1/33 (3%) | 1/42 (2%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.045N | P=0.061N | P=0.083N |
| Incidental Tumor Test | P=0.089N | P=0.103N | P=0.164N |
| Cochran-Armitage Trend Test | P=0.071N | | |
| Fisher Exact Test | | P=0.059N | P=0.135N |
| Weeks to First Observed Tumor | 97 | 103 | 87 |
| **Lung: Alveolar/Bronchiolar Adenoma or Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 1/49 (2%) | 3/49 (6%) | 2/50 (4%) |
| Adjusted *(b)* | 3.1% | 8.5% | 4.8% |
| Terminal *(c)* | 1/32 (3%) | 2/33 (6%) | 2/42 (5%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.493 | P=0.300 | P=0.595 |
| Incidental Tumor Test | P=0.533 | P=0.279 | P=0.595 |
| Cochran-Armitage Trend Test | P=0.407 | | |
| Fisher Exact Test | | P=0.309 | P=0.508 |
| Weeks to First Observed Tumor | 103 | 88 | 103 |
| **Hematopoietic System: All Lymphomas** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 4/50 (8%) | 5/49 (10%) | 5/50 (10%) |
| Adjusted *(b)* | 9.7% | 14.1% | 10.9% |
| Terminal *(c)* | 1/33 (3%) | 3/33 (9%) | 2/42 (5%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.532 | P=0.426 | P=0.578 |
| Incidental Tumor Test | P=0.331 | P=0.267 | P=0.361 |
| Cochran-Armitage Trend Test | P=0.432 | | |
| Fisher Exact Test | | P=0.487 | P=0.500 |
| Weeks to First Observed Tumor | 88 | 88 | 83 |
| **Hematopoietic System: Lymphoma or Leukemia** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 5/50 (10%) | 5/49 (10%) | 5/50 (10%) |
| Adjusted *(b)* | 12.1% | 14.1% | 10.9% |
| Terminal *(c)* | 1/33 (3%) | 3/33 (9%) | 2/42 (5%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.463N | P=0.587 | P=0.544N |
| Incidental Tumor Test | P=0.401 | P=0.345 | P=0.414 |
| Cochran-Armitage Trend Test | P=0.566 | | |
| Fisher Exact Test | | P=0.616 | P=0.630N |
| Weeks to First Observed Tumor | 88 | 88 | 83 |

**TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)**

| | Control | 3,000 ppm | 6,000 ppm |
|---|---|---|---|
| **Liver: Hepatocellular Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 14/50 (28%) | 5/49 (10%) | 12/50 (24%) |
| Adjusted *(b)* | 36.7% | 14.3% | 27.1% |
| Terminal *(c)* | 10/33 (30%) | 4/33 (12%) | 10/42 (24%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.189N | P=0.028N | P=0.208N |
| Incidental Tumor Test | P=0.289N | P=0.046N | P=0.306N |
| Cochran-Armitage Trend Test | P=0.356N | | |
| Fisher Exact Test | | P=0.022N | P=0.410N |
| Weeks to First Observed Tumor | 86 | 78 | 81 |
| **Liver: Hepatocellular Carcinoma or Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 15/50 (30%) | 7/49 (14%) | 12/50 (24%) |
| Adjusted *(b)* | 39.5% | 20.2% | 27.1% |
| Terminal *(c)* | 11/33 (33%) | 6/33 (18%) | 10/42 (24%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.127N | P=0.057N | P=0.147N |
| Incidental Tumor Test | P=0.201N | P=0.088N | P=0.223N |
| Cochran-Armitage Trend Test | P=0.276N | | |
| Fisher Exact Test | | P=0.050N | P=0.327N |
| Weeks to First Observed Tumor | 86 | 78 | 81 |

*(a)* Number of tumor bearing animals/number of animals examined at the site.

*(b)* Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

*(c)* 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 prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

**TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE**

| | Control | 3,000 ppm | 6,000 ppm |
|---|---|---|---|
| **Hematopoietic System: All Lymphomas** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 9/50 (18%) | 13/50 (26%) | 10/49 (20%) |
| Adjusted *(b)* | 20.5% | 30.6% | 23.2% |
| Terminal *(c)* | 6/40 (15%) | 9/38 (24%) | 8/41 (20%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.467 | P=0.211 | P=0.512 |
| Incidental Tumor Test | P=0.356 | P=0.232 | P=0.452 |
| Cochran-Armitage Trend Test | P=0.431 | | |
| Fisher Exact Test | | P=0.235 | P=0.480 |
| Weeks to First Observed Tumor | 88 | 75 | 95 |
| **Hematopoietic System: Lymphoma or Leukemia** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 10/50 (20%) | 14/50 (28%) | 10/49 (20%) |
| Adjusted *(b)* | 22.1% | 32.0% | 23.2% |
| Terminal *(c)* | 6/40 (15%) | 9/38 (24%) | 8/41 (20%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.534N | P=0.223 | P=0.586N |
| Incidental Tumor Test | P=0.441 | P=0.263 | P=0.541 |
| Cochran-Armitage Trend Test | P=0.526 | | |
| Fisher Exact Test | | P=0.241 | P=0.579 |
| Weeks to First Observed Tumor | 87 | 75 | 95 |
| **Circulatory System: Hemangioma or Hemangiosarcoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 4/50 (8%) | 3/50 (6%) | 1/49 (2%) |
| Adjusted *(b)* | 9.4% | 7.3% | 2.4% |
| Terminal *(c)* | 3/40 (8%) | 2/38 (5%) | 1/41 (2%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.133N | P=0.518N | P=0.177N |
| Incidental Tumor Test | P=0.180N | P=0.494N | P=0.296N |
| Cochran-Armitage Trend Test | P=0.138N | | |
| Fisher Exact Test | | P=0.500N | P=0.188N |
| Weeks to First Observed Tumor | 78 | 89 | 104 |
| **Liver: Hepatocellular Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 3/50 (6%) | 1/50 (2%) | 3/49 (6%) |
| Adjusted *(b)* | 7.5% | 2.6% | 7.3% |
| Terminal *(c)* | 3/40 (8%) | 1/38 (3%) | 3/41 (7%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.582N | P=0.324N | P=0.652N |
| Incidental Tumor Test | P=0.582N | P=0.324N | P=0.652N |
| Cochran-Armitage Trend Test | P=0.585 | | |
| Fisher Exact Test | | P=0.309N | P=0.651 |
| Weeks to First Observed Tumor | 103 | 104 | 104 |
| **Liver: Hepatocellular Carcinoma or Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 3/50 (6%) | 3/50 (6%) | 3/49 (6%) |
| Adjusted *(b)* | 7.5% | 7.3% | 7.3% |
| Terminal *(c)* | 3/40 (8%) | 2/38 (5%) | 3/41 (7%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.574N | P=0.642 | P=0.652N |
| Incidental Tumor Test | P=0.582N | P=0.656N | P=0.652N |
| Cochran-Armitage Trend Test | P=0.574 | | |
| Fisher Exact Test | | P=0.661N | P=0.651 |
| Weeks to First Observed Tumor | 103 | 88 | 104 |

**TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)**

| | Control | 3,000 ppm | 6,000 ppm |
|---|---|---|---|
| **Pituitary: Chromophobe Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 3/47 (6%) | 4/42 (10%)*(e)* | 1/41 (2%) |
| Adjusted *(b)* | 7.9% | 12.1% | 2.9% |
| Terminal *(c)* | 3/38 (8%) | 4/33 (12%) | 1/35 (3%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.287N | P=0.423 | P=0.335N |
| Incidental Tumor Test | P=0.287N | P=0.423 | P=0.335N |
| Cochran-Armitage Trend Test | P=0.308N | | |
| Fisher Exact Test | | P=0.436 | P=0.362N |
| Weeks to First Observed Tumor | 103 | 104 | 104 |
| **Mammary Gland: Adenoma, NOS** | | | |
| Tumor Rates | | | |
| Overall *(a)* | 3/50 (6%) | 2/50 (4%)*(f)* | 0/49 (0%) |
| Adjusted *(b)* | 7.1% | 4.9% | 0.0% |
| Terminal *(c)* | 1/40 (3%) | 1/38 (3%) | 0/41 (0%) |
| Statistical Tests *(d)* | | | |
| Life Table Test | P=0.086N | P=0.522N | P=0.124N |
| Incidental Tumor Test | P=0.092N | P=0.510N | P=0.144N |
| Cochran-Armitage Trend Test | P=0.084N | | |
| Fisher Exact Test | | P=0.500N | P=0.125N |
| Weeks to First Observed Tumor | 100 | 93 | — |

*(a)* Number of tumor bearing animals/number of animals examined at the site.
*(b)* Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
*(c)* 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 prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).
*(e)* One additional female mouse in the 3,000 ppm dose group had an adenoma, NOS of the pituitary gland.
*(f)* One additional female mouse in the 3,000 ppm dose group had an adenocarcinoma of the mammary gland.

# APPENDIX G

## ANALYSIS OF C.I. ACID ORANGE 10 (LOT NOS. 1112 AND 2735) MIDWEST RESEARCH INSTITUTE

# APPENDIX G

## A. ELEMENTAL ANALYSIS

### Lot No. 1112

| Element | C | H | N | Na | S | Cl |
|---|---|---|---|---|---|---|
| Theory | 42.48 | 2.23 | 6.19 | 10.17 | 14.18 | — |
| Theory (80% C.I. Acid Orange 10, 4.2% water, and 12.2% sodium chloride) *(a)* | 33.98 | 2.25 | 4.95 | 12.93 | 11.34 | 7.40 |
| Determined: | 34.22 | 2.17 | 4.65 | 12.7 ± 0.118 | 11.1 | 7.37 |
| | 34.33 | 2.19 | 4.69 | | 11.3 | 7.40 |

*(a)* The value of 12.2% sodium chloride was based on the analytical result for ionic chloride of 7.4% and assumed all of the chloride to be present as sodium chloride. C.I. Acid Orange 10 was assumed to be 80%, based on titanous chloride titration of the azo group, and water was determined to be 4.2% by Karl Fischer analysis. The sum of these values (including calculated oxygen values) equals 96.4% which implies that these components account for most but not all of the actual composition of this lot.

### Lot No. 2735

| Element | C | H | N | Na | S | Cl | $CO_3$ |
|---|---|---|---|---|---|---|---|
| Theory (100% compound): | 42.48 | 2.23 | 6.19 | 10.17 | 14.18 | — | — |
| Theory (80.3% C.I. Acid Orange 10, 3.9% water, 13.5% sodium chloride and 2.7% sodium carbonate) *(a)*: | 34.4 | 1.79 | 4.97 | 14.7 | 11.4 | 8.2 | 1.50 |
| Determined: | 35.75 | 2.40 | 4.89 | 11.93 | 10.85 ± 0.40 | 8.22 ± 0.06 | 1.50 |
| | 35.61 | 2.44 | 4.78 | 11.89 | | | |

*(a)* The value of 13.5% sodium chloride was based on the analytical result for ionic chloride of 8.2% and assumed all of the chloride to be present as sodium chloride. C.I. Acid Orange 10 was assumed to be 80.3% based on titanous chloride titration of the azo group, and water was determined to be 3.9% by Karl Fischer analysis. The value of sodium carbonate was based on the analytical result for carbonate of 1.5% and assumed all of the carbonate to be present as sodium carbonate. The sum of these 4 components is 100.4%.

## B. WATER ANALYSIS

### Lot No. 1112

4.22 ± 0.08 ($\delta$)% (Karl Fischer)

### Lot No. 2735

3.9 ± 0.2 ($\delta$)% (Karl Fischer)

## C. TITRATION OF AZO GROUPS WITH TITANOUS CHLORIDE (Horowitz, 1975)

**Lot No. 1112**
80 ± 2 ($\delta$)%

**Lot No. 2735**
80.3 ± 0.4($\delta$)%
(Modification of method—samples weighed directly into titration vessel)

## D. MELTING POINT

| Determined | Literature Values |
|---|---|
| **Lot No. 1112** | |
| 295°-325° C, dec. (visual, capillary) | No literature value found. |
| No endotherms or exotherms observed between 35° and 400° C (Du Pont 900 DTA). | |
| **Lot No. 2735** | |
| 300°-375° C, dec. (visual, capillary) | No literature value found. |
| No endotherms or exotherms observed between 35° and 400° C (DuPont 900 DTA). | |

## E. THIN LAYER CHROMATOGRAPHY

**Lot No. 1112**
Plates: Silica gel 60F-254
Amount Spotted: 100 $\mu$g
Ref. Standard: Methyl red
Visualization: Visible light
Ultraviolet light, 254 and 366 nm
Solvent System: *n*-butanol:methylethyl ketone: ammonium hydroxide:water (50:30:10:10)

| Sample 1 (Top) Rf | Sample 2 (Middle) Rf | Sample 3 (Bottom) Rf |
|---|---|---|
| 0.45 (minor) | 0.45 (minor) | 0.47 (minor) |
| 0.16 (major) | 0.14 (major) | 0.16 (major) |
| 0.12 (trace) | 0.10 (trace) | 0.13 (trace) |
| 0.02 (trace) | 0.02 (trace) | 0.02 (trace) |
| Origin (trace) | Origin (trace) | Origin (trace) |

Visually, all three samples gave spots with similar Rf values, and their appearances were similar in color (or fluorescence) and intensity for all visualization methods. Spots at Rf of 0.16 and 0.45 were the only visible-absorbing components.

**Lot No. 2735**

Plates: Silica gel G-25; UV254
Amount Spotted: 100 $\mu$g
Visualization: Visible light and ultraviolet light, 254 and 366 nm.

Solvent System 1: *n*-butanol:methylethyl ketone:conc. ammonium hydroxide:water (50:30:10:10)

| Sample 1 (Top) Rf | Sample 2 (Middle) Rf | Sample 3 (Bottom) Rf |
|---|---|---|
| 0.37 (trace) | 0.34 (trace) | 0.34 (trace) |
| 0.05 (major) | 0.04 (major) | 0.04 (major) |
| Origin (slight trace) | Origin (slight trace) | Origin (slight trace) |

Visually, all three samples gave spots with similar Rf values, and their appearances were similar in color (or fluorescence) and intensity for all visualization methods.

Solvent System 2: ethanol:*n*-butanol:conc. ammonium hydroxide: water (60:20:10:10).

| Sample 1 (Top) Rf | Sample 2 (Middle) Rf | Sample 3 (Bottom) Rf |
|---|---|---|
| 0.70 (trace) | 0.69 (trace) | 0.69 (trace) |
| 0.46 (major) | 0.46 (major) | 0.47 (major) |
| 0.43 (slight trace) | 0.42 (slight trace) | 0.43 (slight trace) |

Visually, all three samples gave spots with similar Rf values, and their appearances were similar in color (or fluorescence) and intensity for all visualization methods.

## F. HIGH-PRESSURE LIQUID CHROMATOGRAPHY

Instrument: Waters ALC 202 with Model 660 solvent programmer
Column: C18$\mu$-Bondapak, 300 × 4 mm I.D.
Detector: Ultraviolet, 254 nm

**Lot No. 1112**

Solvent Program: 45% A:55% B
(1) 0.005M tetrabutyl ammonium hydroxide and 1% Acetic acid in water
(2) 0.005M tetrabutyl ammonium hydroxide and 1% Acetic acid in methanol

Flow Rate: 1.5 ml/min
Results: Major peak and one minor peak

| Peak | Retention Time (min) | Retention Time (Relative to Acid Orange 10) | Area (Relative to Acid Orange 10) |
|---|---|---|---|
| major | 8.5 | 1.0 | 100.00 |
| minor | 26.6 | 3.1 | 4.3 |

**Lot No. 2735**

Solvent: 40% B

(1) water with $5 \times 10^{-3}$M tetrabutyl ammonium hydroxide, $2.2 \times 10^{-3}$M $K_2HPO_4$ and $6.08 \times 10^{-3}$N $H_3PO_4$

(2) methanol with $5 \times 10^{-3}$M tetrabutyl ammonium hydroxide, $2.2 \times 10^{-3}$M $K_2HPO_4$ and $6.08 \times 10^{-3}$N $H_3PO_4$

Flow Rate: 1 ml/min
Concentration: 1 mg/ml water, filtered
Results: Major peak and two impurities

| Peak | Retention Time (min) | Retention Time (Relative to C.I. Acid Orange 10) | Area* (Relative to C.I. Acid Orange 10) |
|---|---|---|---|
| 1 | 2.6 | 0.60 | 0.4 |
| 2 | 4.2 | 1.00 | 100 |
| 3 | 9.4 | 2.2 | shoulder, 0.1 |
| 4 | 13.2 | 3.1 | 0.4 |
| 5 | 18.2 | 4.3 | |
| 6 | 20.1 | 4.8 | 0.2 |
| 7 | 25.0 | 6.0 | 2.6 |

*The values reported are the areas of the impurity peaks, expressed as percentages of the area of the major peak. Since the identity of the impurity is unknown, the percentages cannot take into account differences in the absolute absorbance (molar absorptivity, $\varepsilon$) of the dye and the impurity. Detector response is dependent upon the absorbance of a substance at the detection wavelength used. Therefore, area percentages reported do not necessarily reflect the actual weight percentage of the impurity in the sample.

## G. SPECTRAL DATA

**Lot No. 1112**

(1) Infrared

Instrument: Beckman IR-12
Cell: 0.5% potassium bromide pellet

Identical to literature spectrum (Sadtler Standard Spectra)

Results: See Figure 6

(2) Ultraviolet/visible

| λmax (nm) | $\varepsilon \times 10^{-3}$ | λmax (nm) | $\varepsilon \times 10^{-3}$ |
|---|---|---|---|
| 247.5 | 21.5 ± 0.1($\delta$) | | |
| 254 shoulder | 19.6 ± 0.1($\delta$) | | |
| 260 shoulder | 15.7 ± 0.1($\delta$) | | |
| 331 | 10.4 ± 0.1($\delta$) | | |
| 410 shoulder | 5.80 ± 0.06($\delta$) | 400 shoulder | 10.0 |
| 478 | 17.6 ± 0.3($\delta$) | 476 | 17.6 |
| Solvent: $H_2O$ | | Solvent: pH 7.4 buffer (Jones and Thomas, 1968) | |

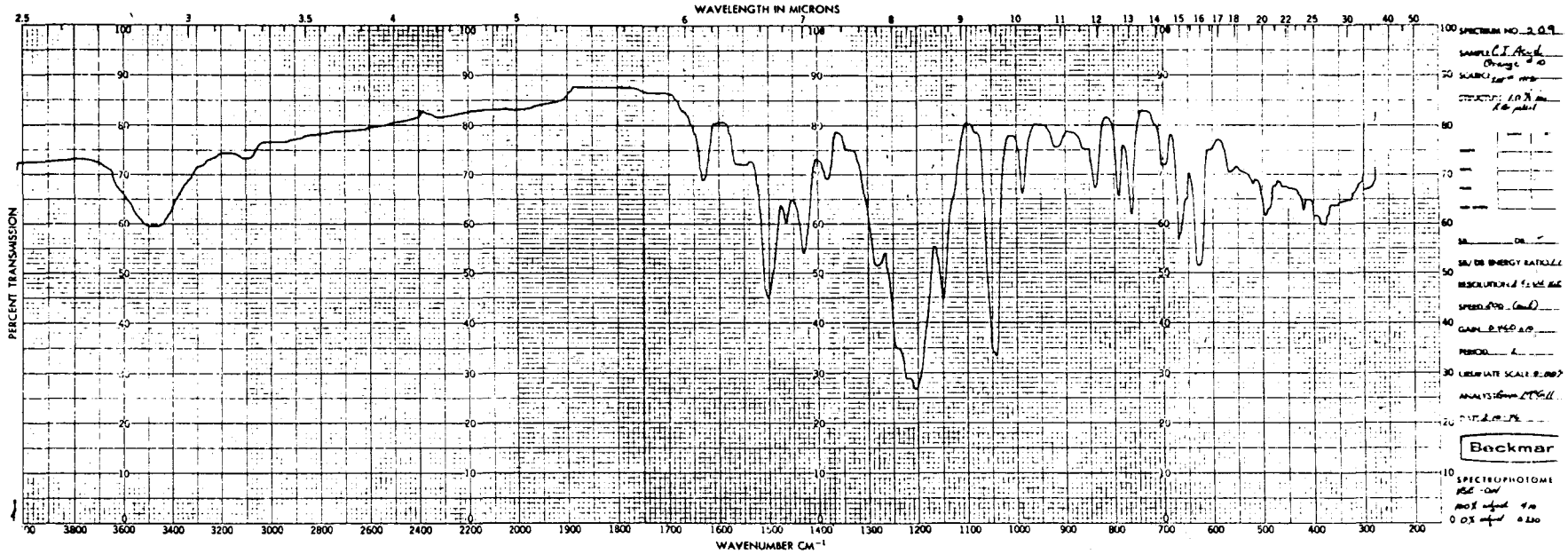



**Figure 6. Infrared Absorption Spectrum of C.I. Acid Orange 10 (Lot No. 1112)**

(3) Nuclear magnetic resonance

Instrument: Varian HA-100
Solvent: DMSO-d6:$D_2O$ (1:2) with internal TSP

No literature spectrum found. Conforms to structure.

Assignments:
(Refer to Figure 7)

a. $\delta$ = 6.97 ppm
b.,c. $\delta$ = 7.40-7.80 ppm
d. $\delta$ = 8.03 ppm
e. $\delta$ = 8.18 ppm
f. $\delta$ = 8.31 ppm
g. $\delta$ = 8.93 ppm
h. $\delta$ = 1.31 ppm (impurity)
Jad = 9 Hz
Jbe = 8 Hz
Jfg = 2 Hz

Integration ratios:
a = 0.76
b,c = 3.09
d,e,f = 4.00
g = 1.14
h = 0.14 (impurity)

**Lot No. 2735**

(1) Infrared

Instrument: Perkin Elmer Model 137 Infracord

Consistent with literature spectrum (Sadtler Standard Spectra)

Cell: 1.5% KBr pellet

Results: See Figure 8.

(2) Ultraviolet/visible

Instrument: Cary 118

Literature Values

| λmax (nm) | $\epsilon \times 10^{-3}$ | λmax (nm) | $\epsilon \times 10^{-3}$ |
|---|---|---|---|
| 214 shoulder | 21.7 ± 0.1($\delta$) | | |
| 247.5 | 21.0 ± 0.2($\delta$) | | |
| 254 shoulder | 19.4 ± 0.1($\delta$) | | |
| 261 shoulder | 15.0 ± 0.1($\delta$) | | |
| 331 | 10.2 ± 0.1($\delta$) | | |
| 415 shoulder | 6.03 ± 0.08($\delta$) | 400 shoulder | 10.0 |
| 480 | 17.5 ± 0.2($\delta$) | 476 | 17.6 |
| 490 shoulder | 17.3 ± 0.2($\delta$) | | |
| Solvent: $H_2O$ | | Solvent: pH 7.4 buffer (Jones and Thomas, 1968) | |

(3) Nuclear magnetic resonance

Solvent: $D_2O$: Dimethylsulfoxide-d6 (2:1) with internal sodium 3-trimethylsilylpropionate-2,2,3,3-d4

Literature Values
No literature spectrum. Conforms to structure and to spectrum of C.I. Acid Orange 10, Lot No.: 1112, Batch No. 01.

Assignments: (See Figure 9)
(a) d, $\delta$ 6.89 ppm, Jad = 10Hz;
(b,c) m, $\delta$ 7.16-7.70 ppm;
(d,e,f) m, $\delta$ 7.76-8.26 ppm;
(g,d) $\delta$ 8.75 ppm, Jfg = 2Hz

Integration ratios:
(a) 1.02
(b,c) 3.26
(d,e,f) 3.92
(g) 0.80

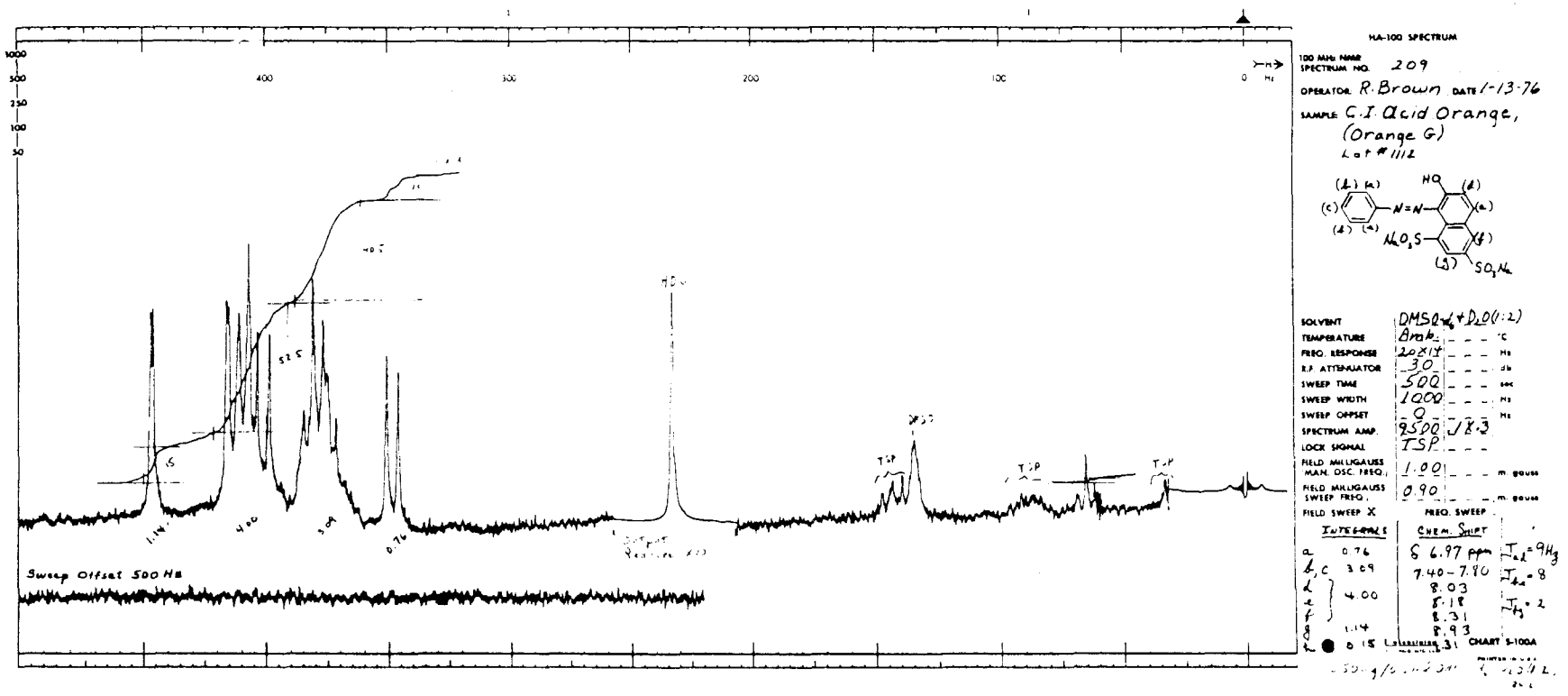
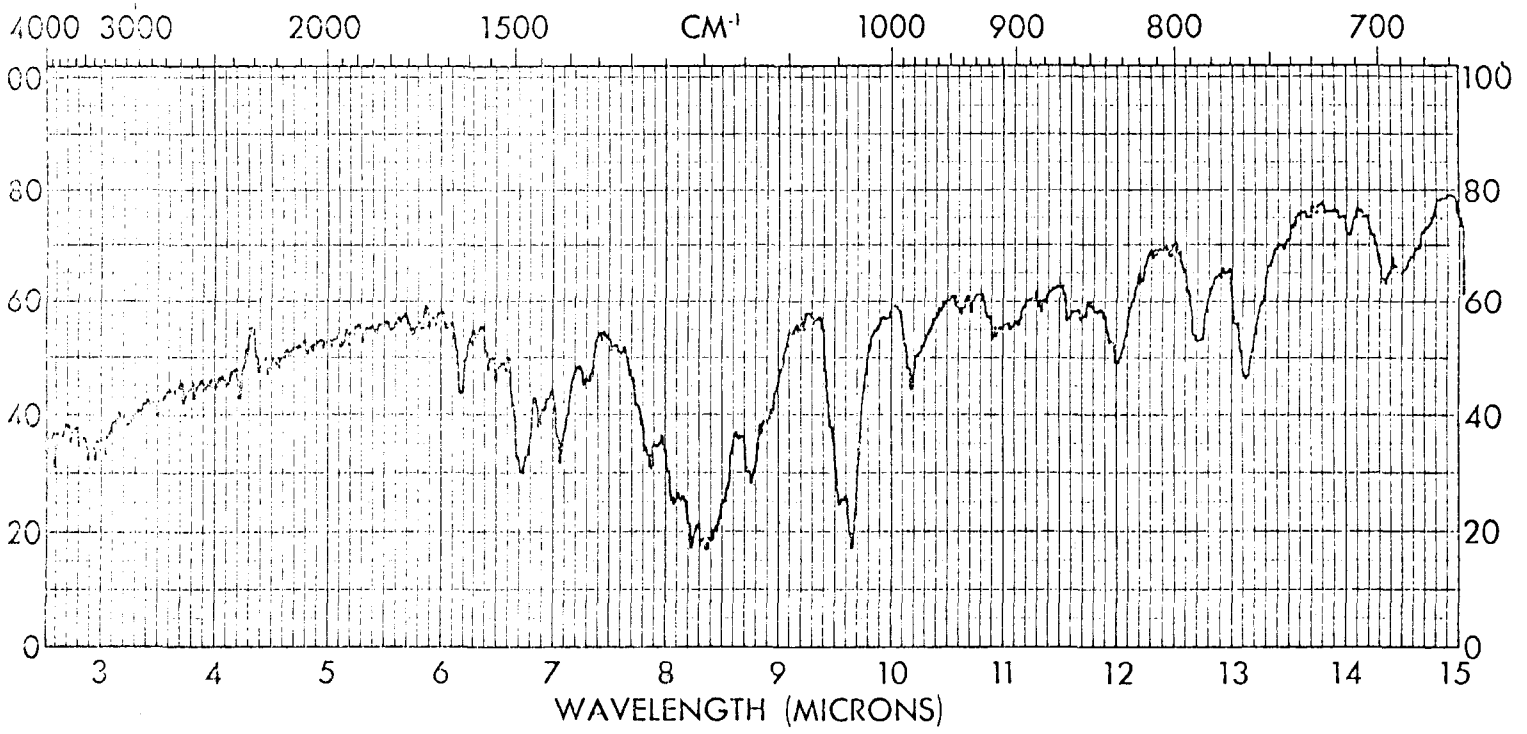



**Figure 7. Nuclear Magnetic Resonance Spectrum of C.I. Acid Orange 10 (Lot No. 1112)**




| | | | |
|---|---|---|---|
| SPECTRUM NO. 209 | ORIGIN | LEGEND | REMARKS |
| SAMPLE | | 1. | 1.5% in KBr |
| C.I. Acid Orange 10 | PURITY | 2. | pellet |
| Lot # 2735 | PHASE | DATE 2-8-71 | |
| Batch No. 02 | THICKNESS | OPERATOR McGill | |

SPECTRUM NO. SAMPLE

THE PERKIN-ELMER CORPORATION, NORWALK, CONN.

**Figure 8. Infrared Absorption Spectrum of C.I. Acid Orange 10 (Lot No. 2735)**

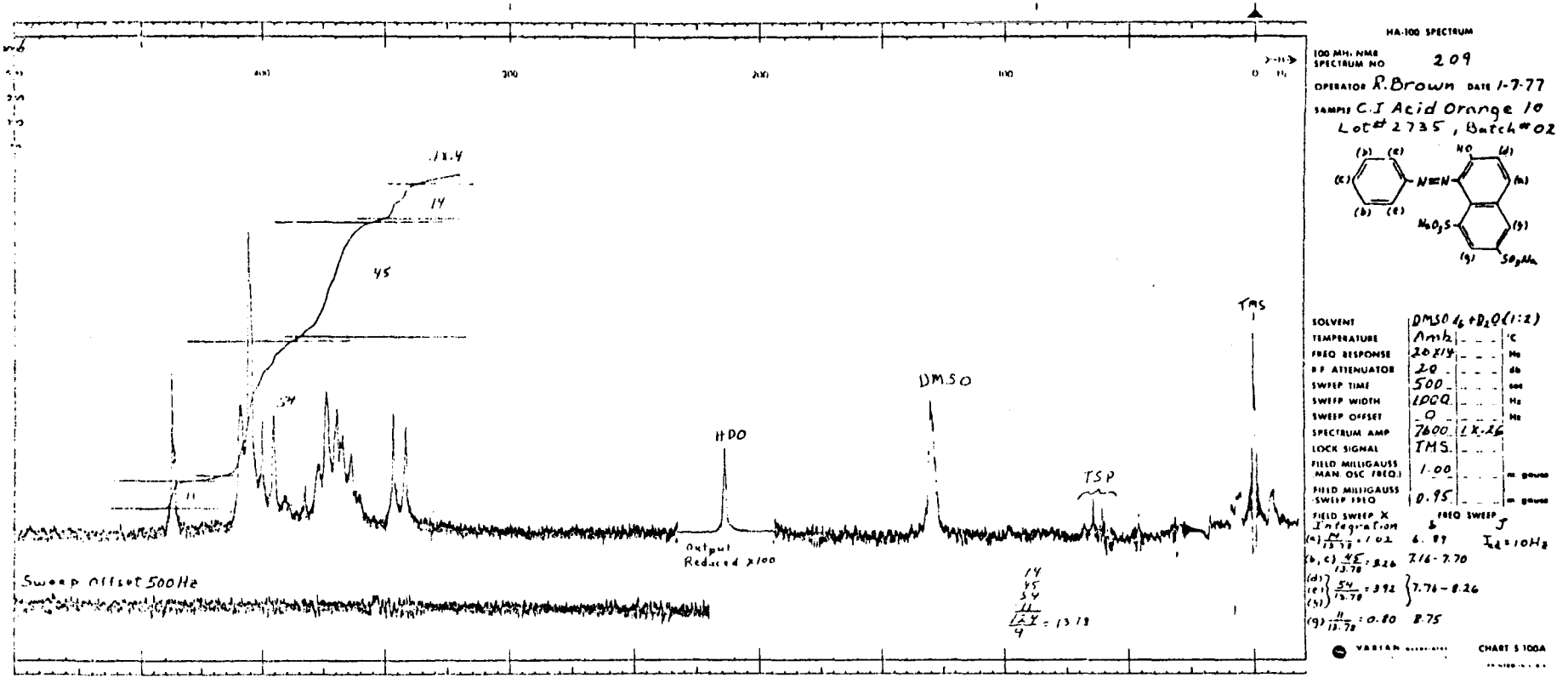



**Figure 9. Nuclear Magnetic Resonance Spectrum of C.I. Acid Orange 10 (Lot No. 2735)**

# APPENDIX H

## ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF C.I. ACID ORANGE 10

## APPENDIX H

A 100-mg sample of the dye-feed mixture was mixed with 40 ml of distilled water and vortexed for 30 seconds. The suspension was centrifuged for 10 minutes at 10,000 rpm in a Sorvall RC-2B at 4°C. An appropriate volume of the supernatant was removed and diluted with distilled water to achieve a final concentration in the linear portion of the standard curve. Internal standards were prepared using control powdered feed and assayed in the same manner. All samples and standards were run in triplicate. The absorbance was determined at 482 nm in a Gilford 2400-S spectrophotometer. The spectrophotometer was blanked with a 100-mg feed sample treated in the same manner as the samples. The standard curve developed with feed-dye standards (triplicate) automatically incorporates a correction for recovery. The concentration of dye in a feed sample could be read directly from the curve without any further adjustment for recovery.

Results of analyses are presented in Table H1.

**TABLE H1. ANALYSIS OF C.I. ACID ORANGE 10 IN FORMULATED DIETS**

| | Concentration(a) of C.I. Acid Orange 10 in Diet for Target Concentration of | | |
|---|---|---|---|
| **Date Mixed** | **1,000 ppm** | **3,000 ppm** | **6,000 ppm** |
| 03/25/77 | 955 | 3,020 | 6,050 |
| | 1,080 | | |
| 03/24/77 | | 3,030 | |
| | | 3,140 | |
| 06/02/77 | 1,020 | 3,050 | 6,000 |
| | 1,030 | 3,030 | |
| | | 2,990 | |
| 08/17/77 | 1,070 | 3,120 | 5,940 |
| | 1,050 | 3,180 | |
| | | 3,040 | |
| 10/19/77 | 1,000 | 3,000 | 5,850 |
| | 1,020 | 2,980 | |
| | | 3,010 | |
| 01/28/78 | 950 | 3,500 | 6,040 |
| | 1,000 | 3,350 | |
| | | 3,420 | |
| 04/03/78 | 1,030 | 3,120 | 6,160 |
| | 1,010 | 3,190 | |
| | | 3,090 | |
| 06/13/78 | 1,040 | 2,910 | 5,990 |
| | 1,010 | 2,980 | |
| | | 2,970 | |
| 07/05/78 | 1,020 | 3,000 | 6,020 |
| | 990 | 2,890 | |
| | | 2,920 | |
| 09/07/78 | 940 | 3,020 | 5,880 |
| | 1,070 | 3,000 | |
| | | 2,970 | |
| 11/09/78 | 1,000 | 3,270 | 6,210 |
| | 1,080 | 3,200 | |
| | 1,140(b) | 3,220 | |
| 01/10/79 | | 3,270 | 6,340 |
| Mean | 1,020 | 3,090 | 6,040 |
| Standard Deviation | 48 | 150 | 145 |
| Coefficient of Variation (%) | 4.0 | 4.9 | 2.4 |
| Range (ppm) | 940-1,080 | 2,920-3,500 | 5,850-6,340 |
| Number of Samples | 20 | 31 | 11 |

(a) The data presented are the average of duplicate analyses. Doses were mixed (and analyzed) separately for male rats, female rats, and mice.

(b) Referee analysis at Midwest Research Institute.

# APPENDIX I

## DATA AUDIT SUMMARY

# APPENDIX I

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year toxicology and carcinogenesis studies of C.I. Acid Orange 10 in rats and mice were audited for accuracy, consistency, and completeness. The laboratory experiments were conducted for the NTP by Batelle Columbus Laboratories, Columbus, Ohio, under a subcontract with Tracor Jitco, Inc., the prime contractor for the National Cancer Institute. Animal exposures to C.I. Acid Orange 10 began in December 1976 (rats) and January 1977 (mice) and ended in December 1978 (rats) and January 1979 (mice). The studies were completed before October 1981, when the NTP implemented its requirement that studies be conducted in compliance with the Good Laboratory Practice (GLP) regulations of the Food and Drug Administration. The retrospective audit was conducted for the NIEHS at the NTP Archives in August 1984 by Argus Research Laboratories, Dr. J.E. Goeke, Principal Investigator. The other individuals who conducted the audit are listed in the full audit report which is on file at the NIEHS. The audit included a review of:

1) All records concerning animal receipt, quarantine, randomization and disposition prior to study start.
2) All chemistry records.
3) Body weight (by cage) and clinical observation data for a random 10% sample of the study animals.
4) Food consumption (by cage) for approximately 10% of the animals.
5) In-life records concerning environmental conditions, palpable masses, and mortality.
6) All post-mortem records for individual animals concerning identification, disposition and condition codes, and correlation between gross observations and microscopic diagnoses.
7) Wet tissues from a random 10% sample of the study animals to verify animal identification and to examine for untrimmed lesions.
8) Blocks and slides of tissues from all control and high-dose animals to examine for inventory and correspondence.
9) Tabulated pathology diagnoses for a random 10% of study animals to verify computer data entry.

Procedures and information regarding animal receipt, quarantine, randomization, and room environmental conditions were presented in the Materials and Methods Report submitted by the study laboratory, but further documentation of these items was not among the archival records. Other documentation for the in-life, chemistry, and histopathology portions of the studies were present and recorded in an adequate manner. Examination of bags of residual wet tissues revealed some instances of missing bags or bags that could not be identified due to the absence of outer labels and the effacement of inner labels by leaking formalin. Feet were not saved, precluding the retrospective verification of animal identity by inspection of residual wet tissues.

The only data corrections arising from the audit involved certain group mean body weights and the length of time animals were not dosed just prior to terminal sacrifice. These errors were corrected and the corrections were incorporated into the body weight tables and curves of the final Technical Report.

The audit findings were reviewed by NTP staff. The documents and materials at the NTP Archives support the data and results presented in the Technical Report.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