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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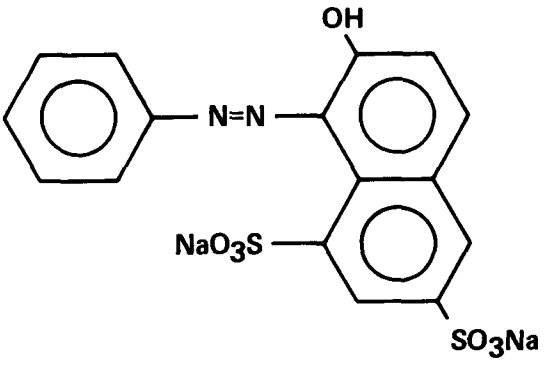
CARCINOGENESIS STUDIES OF C.I. ACID ORANGE 10



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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(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

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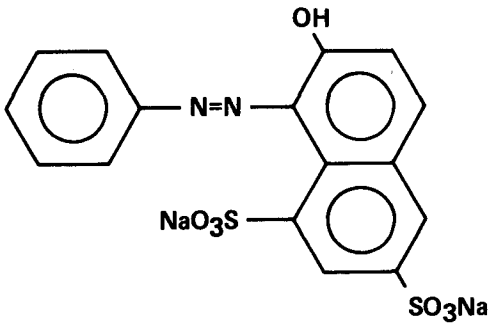


C.I. ACID ORANGE 10

(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

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

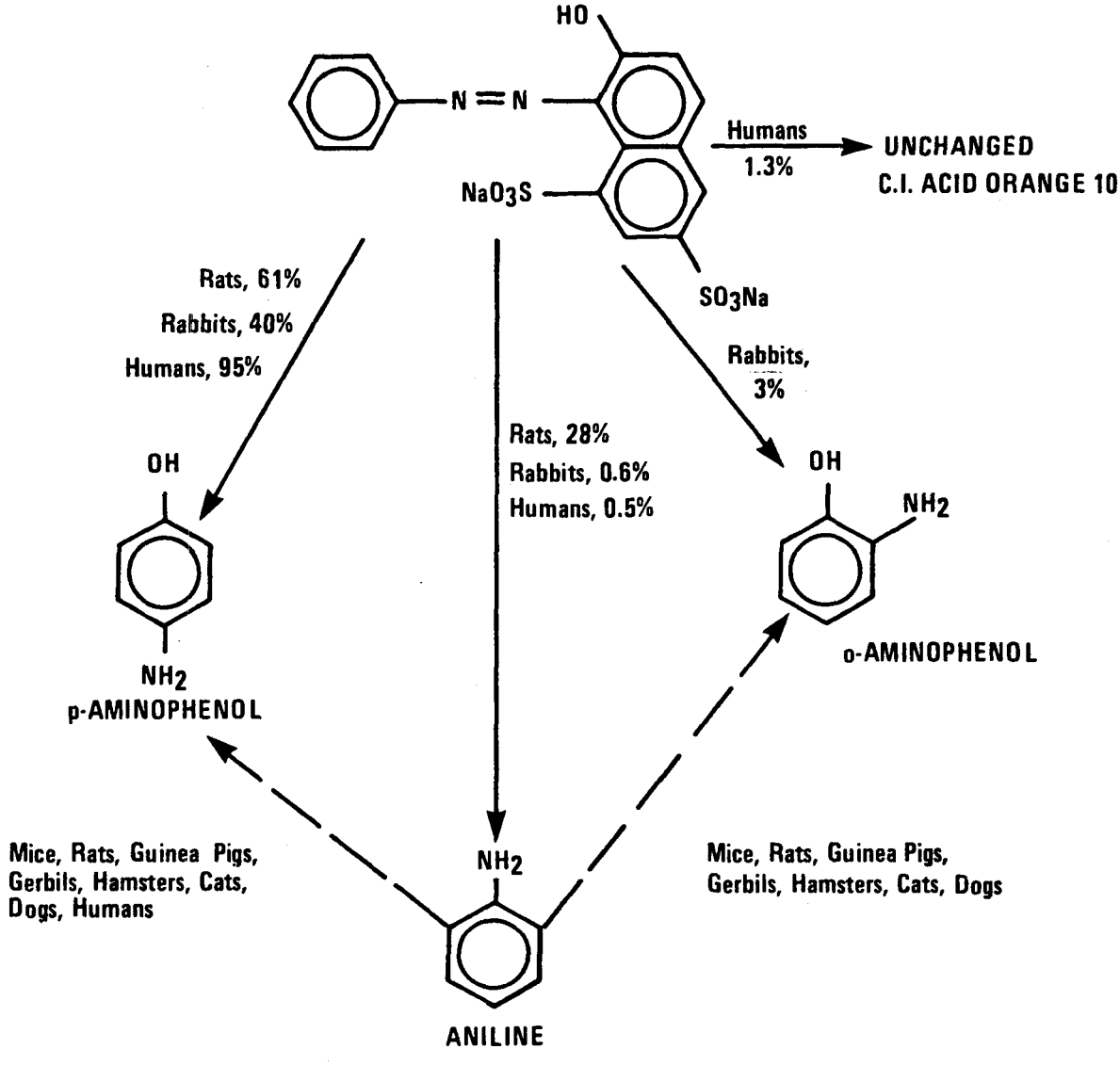


Figure 1. C.I. Acid Orange 10 Metabolism in Rats, Rabbits, and Humans

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.

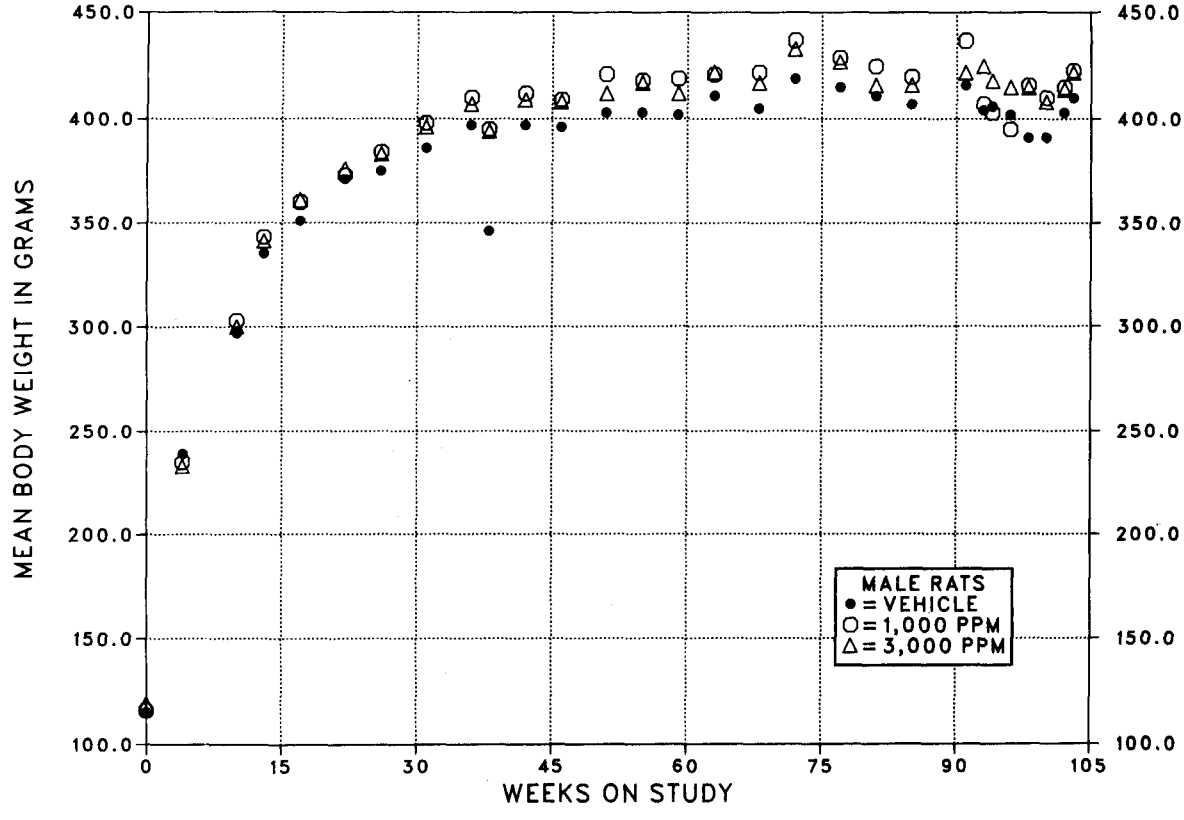
Survival

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



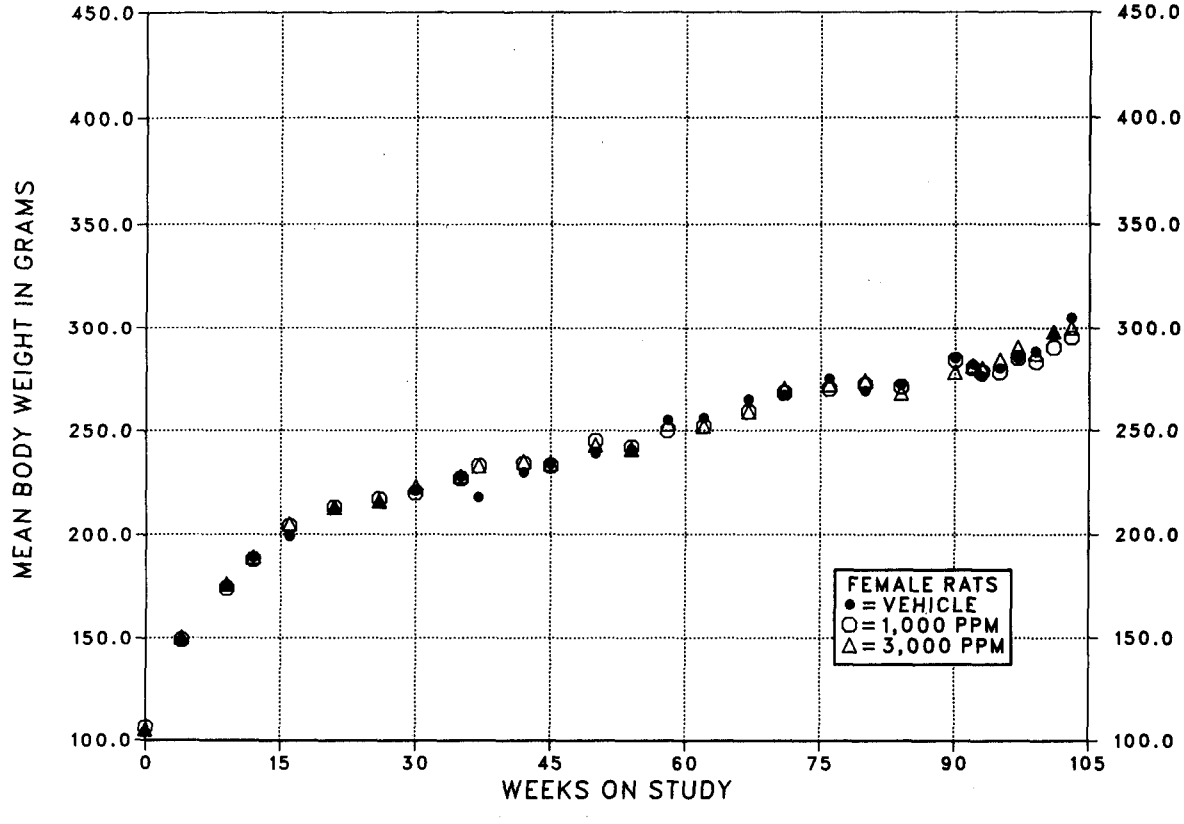


Figure 2. Growth Curves for Rats Fed Diets Containing C.I. Acid Orange 10

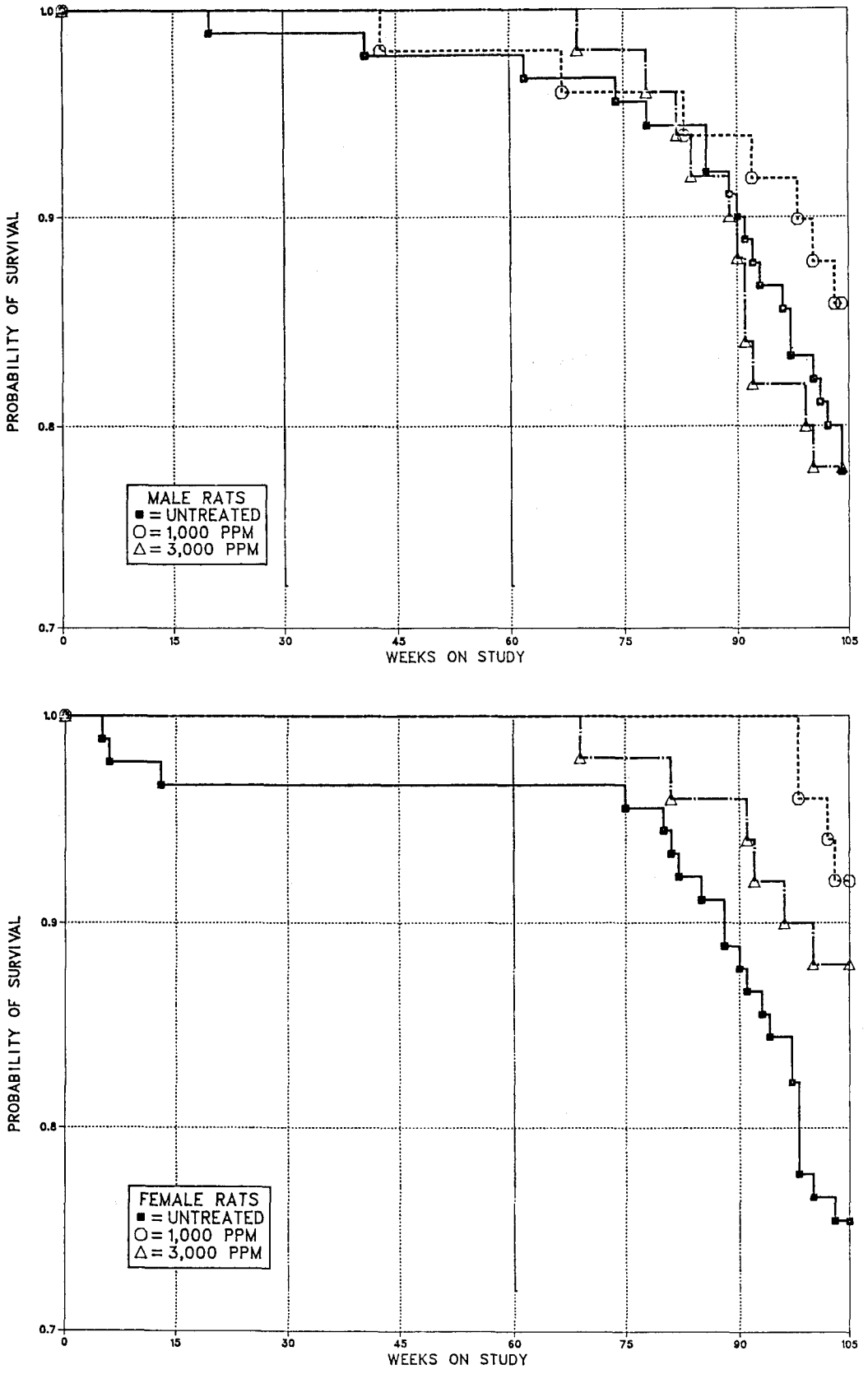


Figure 3. Kaplan-Meier Survival Curves for Rats Fed Diets Containing C.I. Acid Orange 10

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.

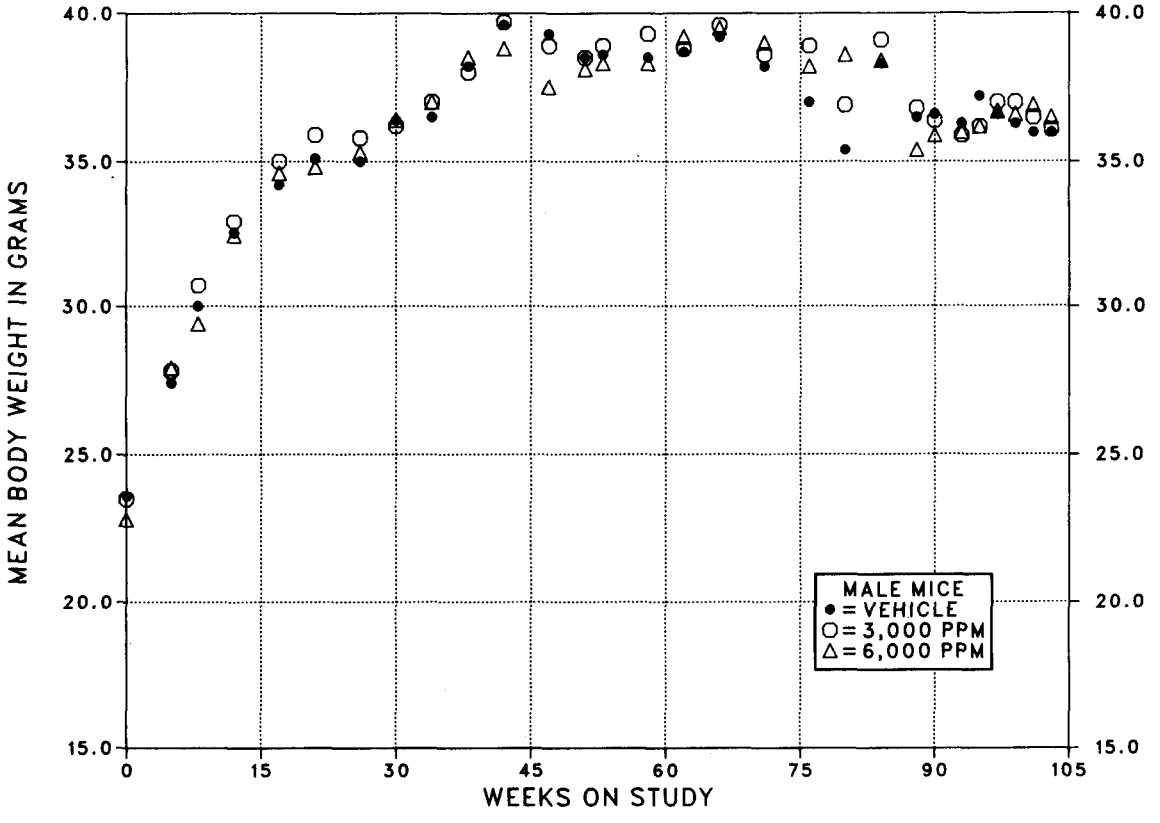
Survival

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



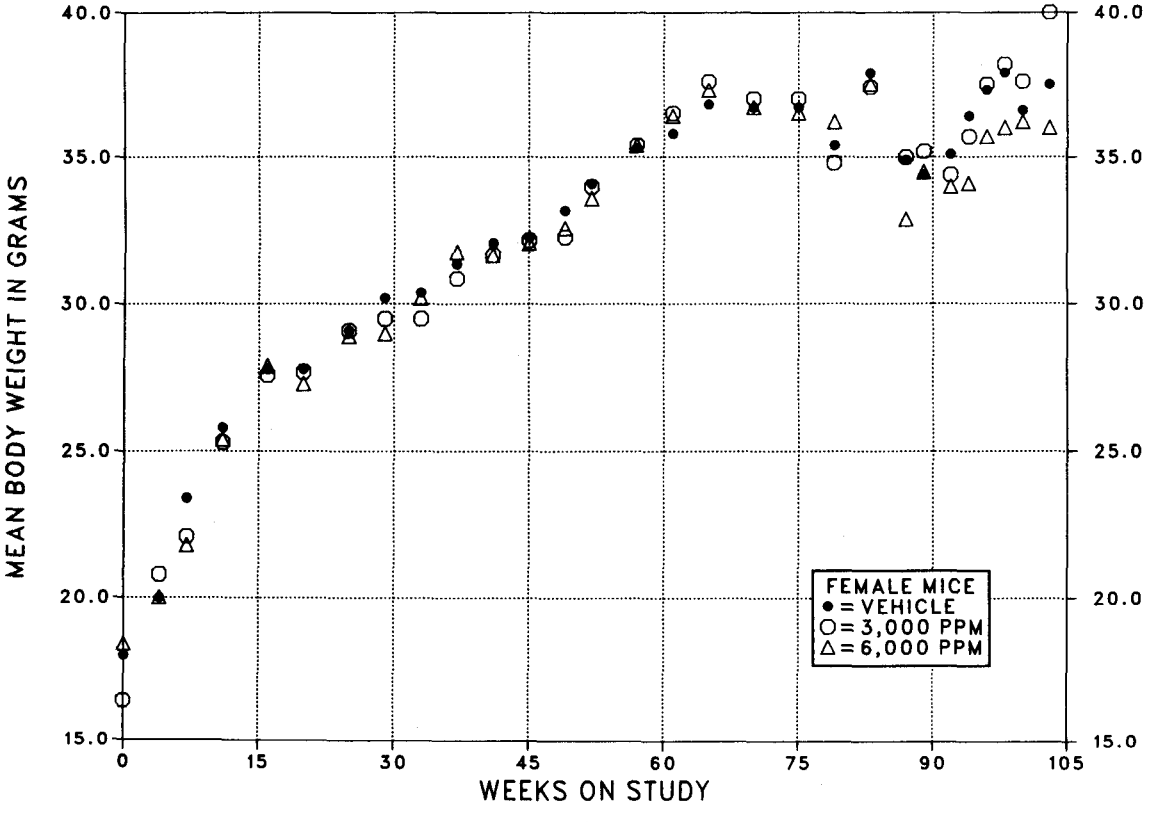


Figure 4. Growth Curves for Mice Fed Diets Containing C.I. Acid Orange 10

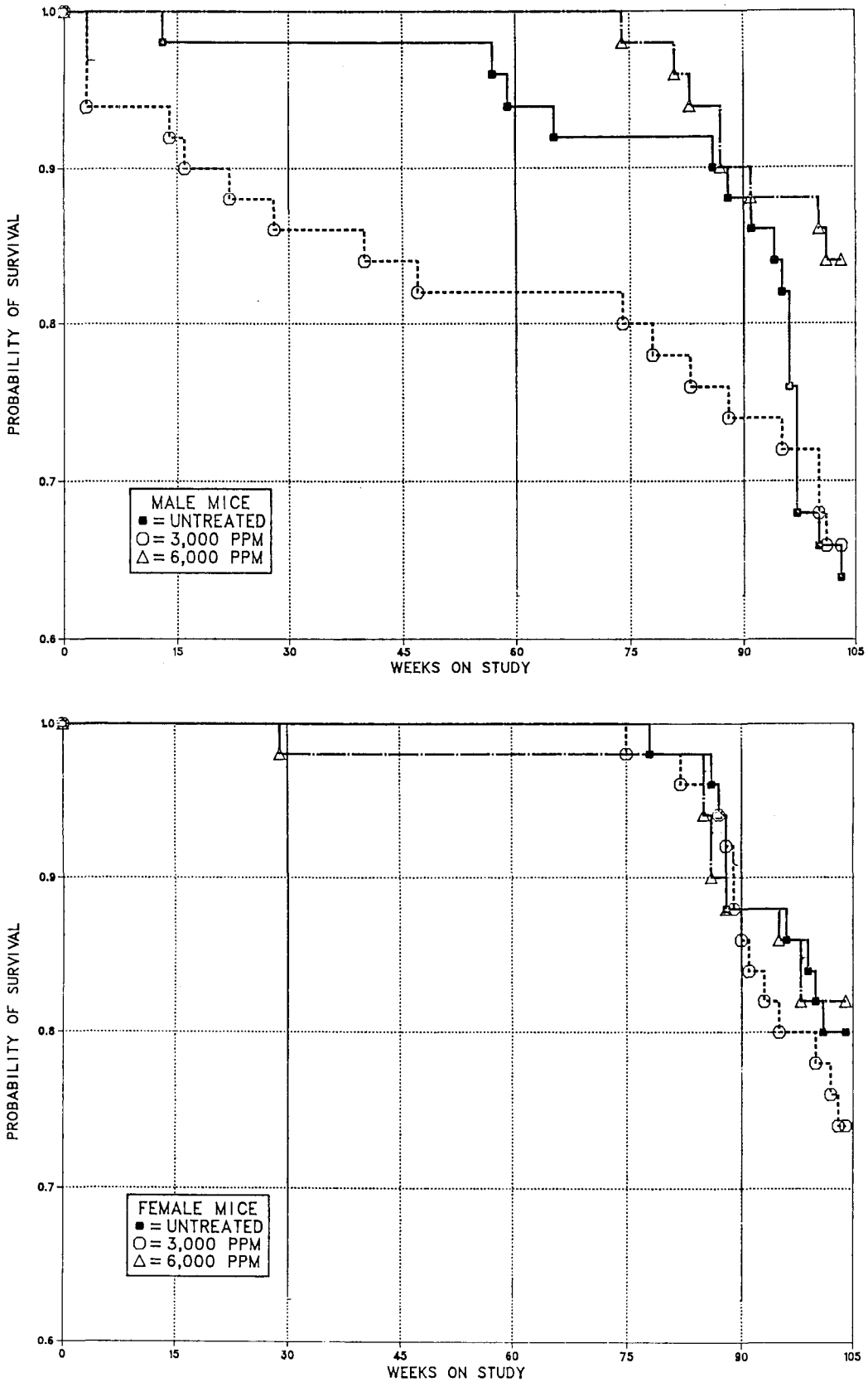


Figure 5. Kaplan-Meier Survival Curves for Mice Fed Diets Containing C.I. Acid Orange 10

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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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 FIBROMA	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN LYMPHOCYTIC LEUKEMIA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X
LYMPH NODES *TRANSITIONAL-CELL CARCINOMA, META*	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART NEURILEMOMA, MALIGNANT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER NEOPLASTIC NODULE	+	+	+	+	+	+	+	+	+	+	+ X	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KIDNEY/PELVIS TRANSITIONAL-CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY CHROMOPHOBE ADENOMA CHROMOPHOBE CARCINOMA	+	+ X	+ X	+	-	+ X	+	+	+	+ X	+	+ X	+	+	+ X	+	+	+	+	+	+ X	+ X	+	+	+ X
ADRENAL CORTICAL ADENOMA CORTICAL CARCINOMA PHEOCHROMOCYTOMA PHEOCHROMOCYTOMA, MALIGNANT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA C-CELL CARCINOMA	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	-	-	+	+	+	+
PANCREATIC ISLETS ISLET-CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOMA, NOS ADENOCARCINOMA, NOS FIBROADENOMA	N	+	+ X	+	+	+	N	N	+	+	+ X	+	+	N	+	N	N	+	+	+	+	+	+	+	+ X
PREPUTIAL/CLITORAL GLAND SQUAMOUS CELL CARCINOMA	N	N 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 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 ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+ X	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN EPENDYMOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS SARCOMA, NOS MALIGNANT LYMPHOMA, NOS 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 FIBROSARCOMA	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ADENOCARCINOMA, NOS, METASTATIC ALVEOLAR/BRONCHIOLAR ADENOMA FIBROSARCOMA, METASTATIC	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	X	+	+	X	+	+	+	+	+
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+
SPLEEN HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES MALIGNANT LYMPHOMA, NOS	+	+	+	-	+	-	+	+	+	+	X	+	+	+	+	+	+	-	-	-	+	+	+	+	+
THYMUS	-	+	+	-	-	-	+	+	+	+	-	-	-	+	-	-	-	+	-	-	+	+	-	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	-
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA MALIGNANT LYMPHOMA, NOS	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	X	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+
SMALL INTESTINE	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY TUBULAR-CELL ADENOCARCINOMA MALIGNANT LYMPHOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS CHROMOPHOBE ADENOMA	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+
PARATHYROID	-	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	-	+	+	-	-	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOMA, NOS ADENOCARCINOMA, NOS	+	+	+	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
UTERUS LEIOMYOMA HEMANGIOMA	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY HEMANGIOMA	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
SPECIAL SENSE ORGANS																									
LACRIMAL GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N X	N	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 LYMPHOCYTIC LEUKEMIA	N	N	N	N X	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N 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 (δ)% (Karl Fischer)

Lot No. 2735

3.9 ± 0.2 (δ)% (Karl Fischer)

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

Lot No. 1112
80 ± 2 (δ)%

Lot No. 2735
80.3 ± 0.4(δ)%
(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 μg
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 μg
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: C18μ-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 5×10^{-3}M tetrabutyl ammonium hydroxide, 2.2×10^{-3}M K_2HPO_4 and 6.08×10^{-3}N H_3PO_4

(2) methanol with 5×10^{-3}M tetrabutyl ammonium hydroxide, 2.2×10^{-3}M K_2HPO_4 and 6.08×10^{-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, ε) 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(δ)		
254 shoulder	19.6 ± 0.1(δ)		
260 shoulder	15.7 ± 0.1(δ)		
331	10.4 ± 0.1(δ)		
410 shoulder	5.80 ± 0.06(δ)	400 shoulder	10.0
478	17.6 ± 0.3(δ)	476	17.6
Solvent: H_2O		Solvent: pH 7.4 buffer (Jones and Thomas, 1968)	

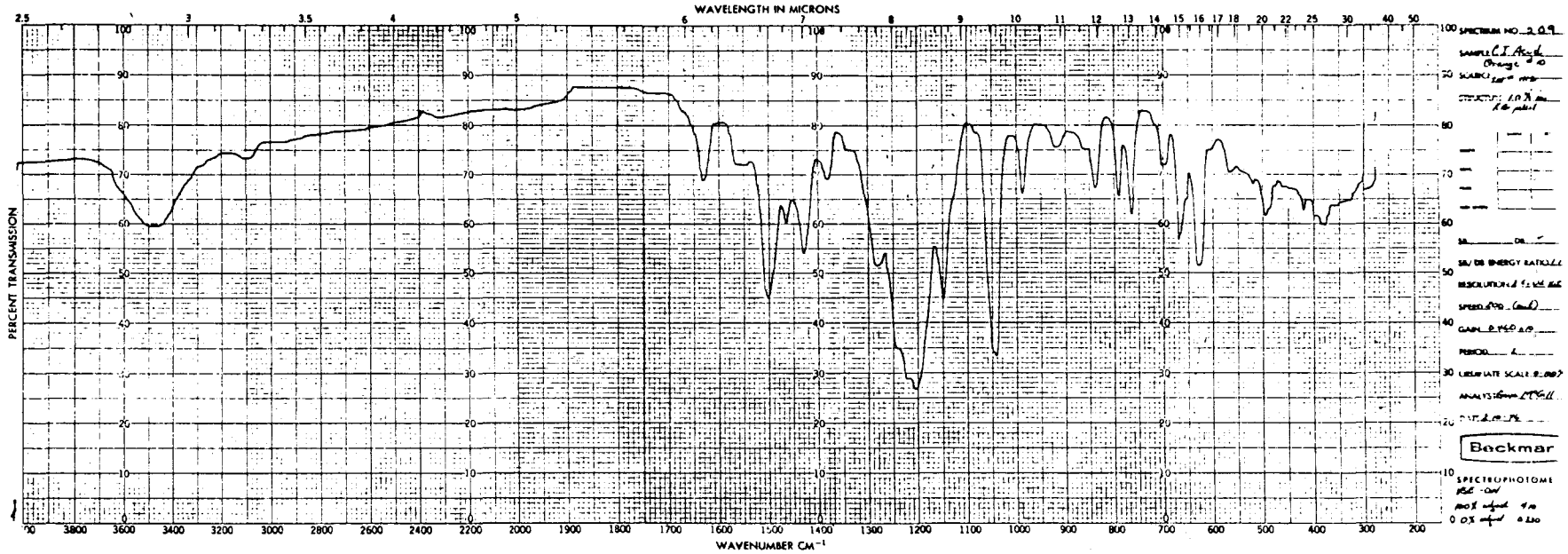


Figure 6. Infrared Absorption Spectrum of C.I. Acid Orange 10 (Lot No. 1112)

(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. δ = 6.97 ppm
b.,c. δ = 7.40-7.80 ppm
d. δ = 8.03 ppm
e. δ = 8.18 ppm
f. δ = 8.31 ppm
g. δ = 8.93 ppm
h. δ = 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(δ)		
247.5	21.0 ± 0.2(δ)		
254 shoulder	19.4 ± 0.1(δ)		
261 shoulder	15.0 ± 0.1(δ)		
331	10.2 ± 0.1(δ)		
415 shoulder	6.03 ± 0.08(δ)	400 shoulder	10.0
480	17.5 ± 0.2(δ)	476	17.6
490 shoulder	17.3 ± 0.2(δ)		
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, δ 6.89 ppm, Jad = 10Hz;
(b,c) m, δ 7.16-7.70 ppm;
(d,e,f) m, δ 7.76-8.26 ppm;
(g,d) δ 8.75 ppm, Jfg = 2Hz

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

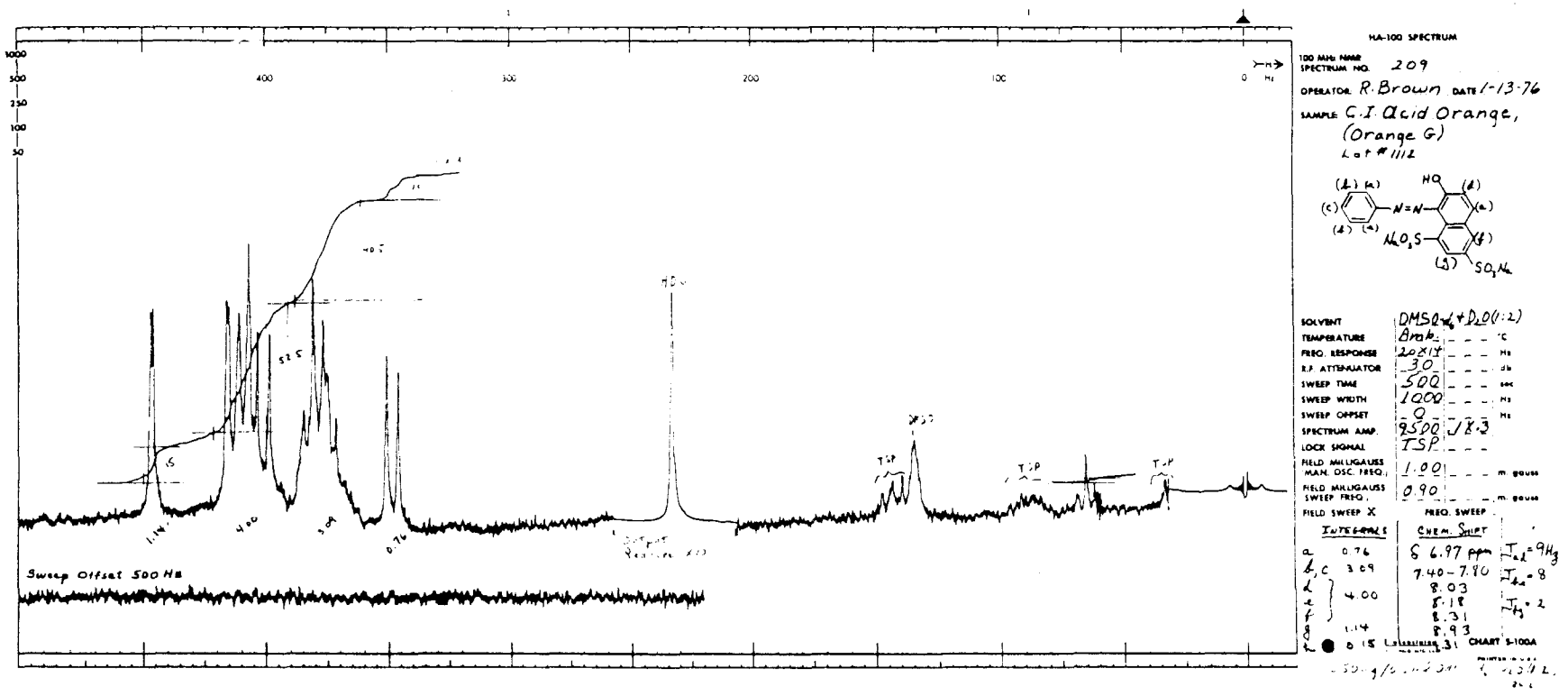
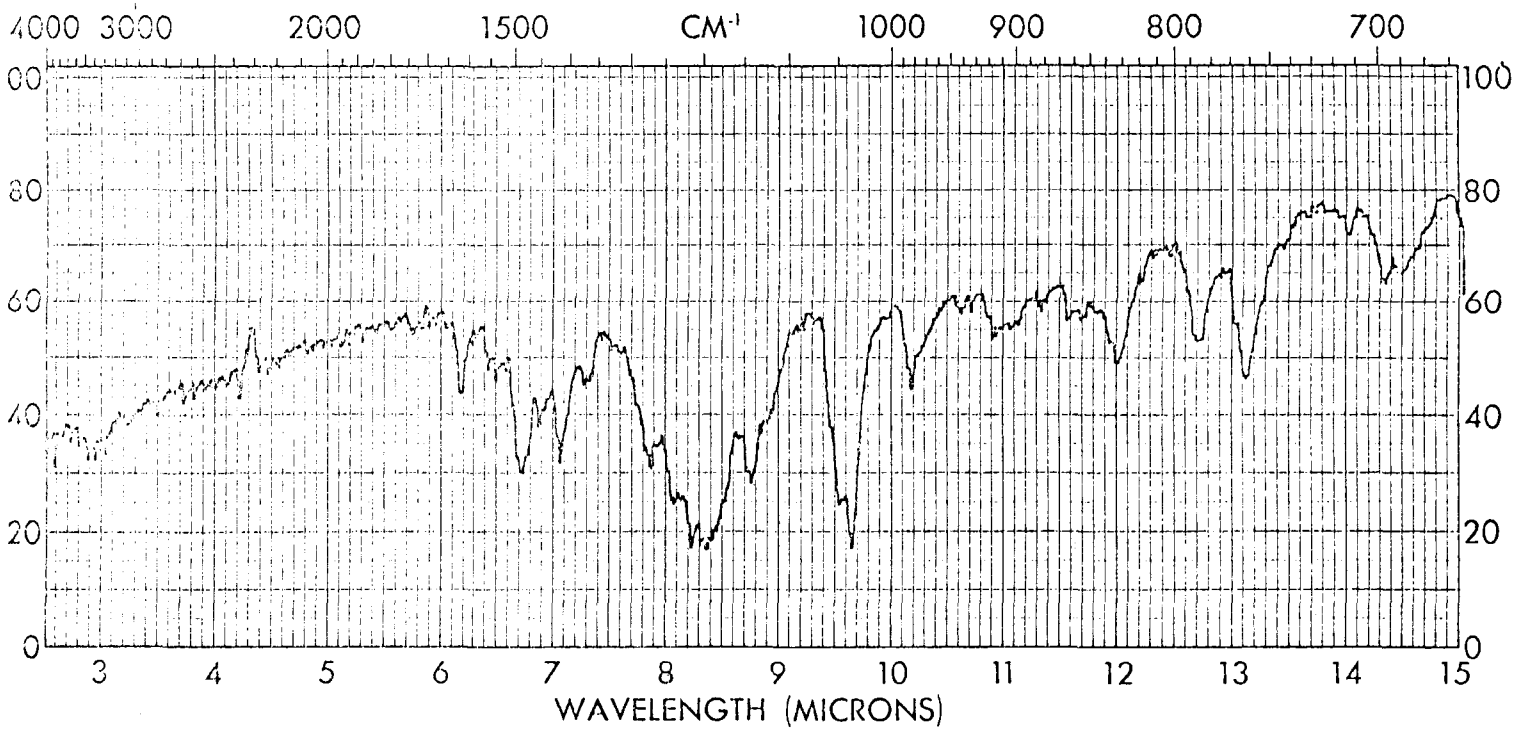


Figure 7. Nuclear Magnetic Resonance Spectrum of C.I. Acid Orange 10 (Lot No. 1112)



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)

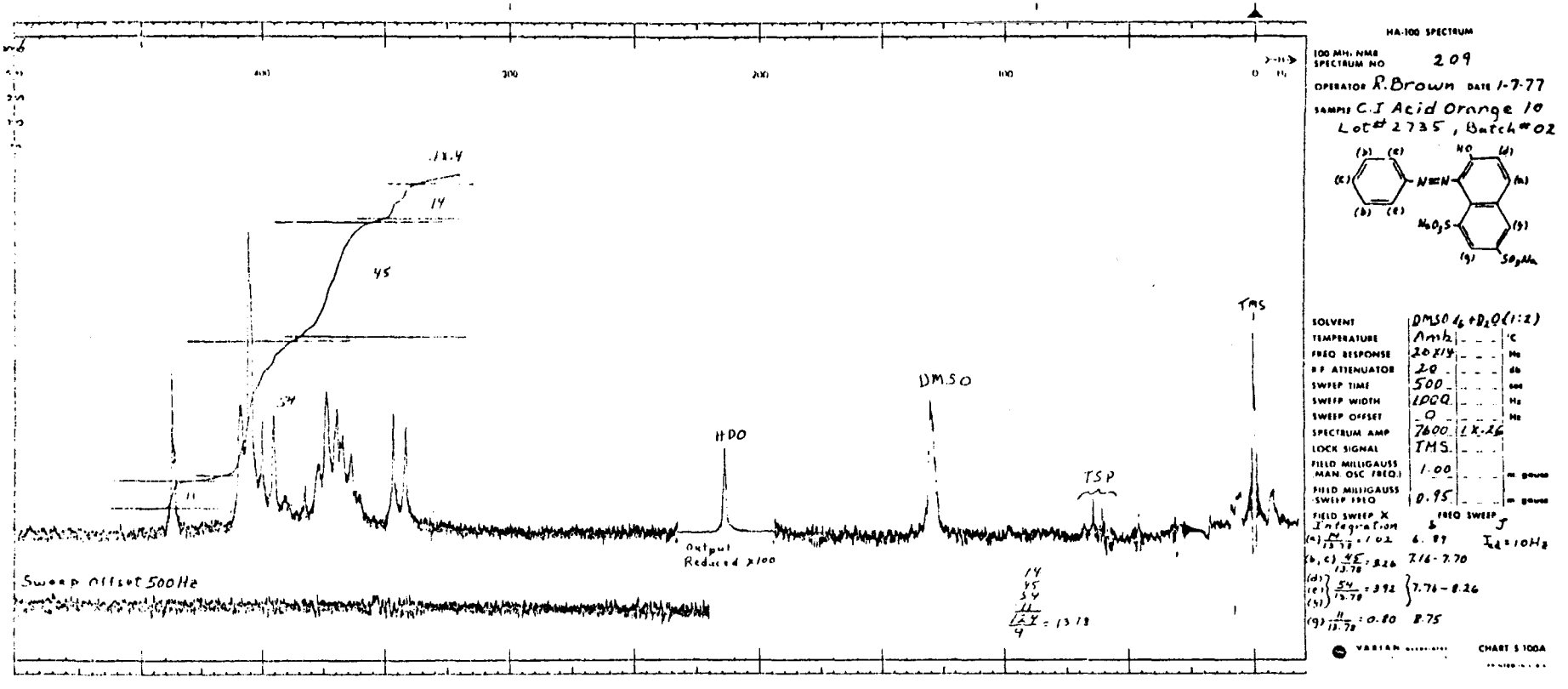


Figure 9. Nuclear Magnetic Resonance Spectrum of C.I. Acid Orange 10 (Lot No. 2735)

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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