TOXICOLOGY AND CARCINOGENESIS
STUDIES OF
8-HYDROXYQUINOLINE
(CAS NO. 148-24-3)
IN F344/N RATS AND B6C3F1 MICE
(FEED STUDIES)
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 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 made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.
NTP TECHNICAL REPORT
ON THE
TOXICOLOGY AND CARCINOGENESIS
STUDIES OF
8-HYDROXYQUINOLINE
(CAS NO. 148-24-3)
IN F344/N RATS AND B6C3F1 MICE
(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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April 1985

NTP TR 276
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis 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.

Five categories of interpretative conclusions were adopted in June 1983 for use in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintets will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.

- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.

- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.

- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

The term chemical carcinogenesis generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term carcinogenesis means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words tumor and neoplasm are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes 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. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J. E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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 Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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(8-QUINOLINOL; OXINE; HYDROXYBENZOPYRIDINE)
CAS NO. 148-24-3
C₉H₇NO  Mol. Wt. 145.15
Melting Pt. 76° C  Boiling Pt. 267° C

ABSTRACT

Carcinogenesis studies of 8-hydroxyquinoline (99% pure), a metal chelator and antimicrobial agent, were conducted by administering the test chemical in feed to groups of 50 male and 50 female F344/N rats and B6C3F₁ mice at concentrations of 0, 1,500, or 3,000 ppm for 103 weeks. These concentrations were selected because the chemical at higher concentrations resulted in reduced feed consumption, decreases in mean body weights, and deaths in the 15-day and 13-week studies. The average daily doses were estimated to be 73 and 143 mg/kg for male rats, 89 and 166 mg/kg for female rats, 217 and 396 mg/kg for male mice, and 349 and 619 mg/kg for female mice.

Survival of dosed male and female rats and mice in the 2-year studies was comparable to that of the corresponding controls. The high dose rats and mice of each sex exhibited slight decreases in mean body weights and decreased feed consumption.

Compound-related gross or microscopic pathologic effects were not observed in either species in the 15-day or 13-week studies. In the 2-year studies, C-cell adenomas/carcinomas of the thyroid gland showed a positive trend (P = 0.03) for male rats (control, 1/50; low dose, 1/49; high dose, 6/47). The incidence of C-cell neoplasms in the high dose group was not significantly increased compared with the controls, and the occurrence of C-cell hyperplasia was not elevated (4/50; 3/49; 1/47). The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in male rats occurred with a positive trend, and the incidence in the high dose group was greater than that in the controls (0/50; 3/50; 4/50). This marginal effect was not supported by an increase in epithelial hyperplasia (5/50; 5/50; 3/50). These marginal increases in male rats were not regarded as being related to the administration of 8-hydroxyquinoline.

In in vitro tests, 8-hydroxyquinoline did not induce either unscheduled DNA synthesis in rat hepatocytes or transformation of BALB/c-3T3 cells.

An audit of the experimental data for these carcinogenesis studies on 8-hydroxyquinoline was conducted. No data discrepancies were found that significantly influenced the final interpretations.

Under the conditions of these studies, there was no evidence of carcinogenicity* for male and female F344/N rats or for male and female B6C3F₁ mice given 8-hydroxyquinoline in feed at concentrations of 1,500 or 3,000 ppm for 103 weeks.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 8-Hydroxyquinoline is based on the 13-week studies that began in January 1979 and ended in April 1979 and on the 2-year studies that began in December 1979 and ended in December 1981 at EG&G Mason Research Institute.

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The members of the Peer Review Panel who evaluated this Technical Report on March 23, 1984, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 8-HYDROXYQUINOLINE

On March 23, 1984, the Technical Report on 8-hydroxyquinoline received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Hubert Humphrey Building in Washington, DC.

Dr. Van Ryzin, a principal reviewer for the Technical Report on the carcinogenesis studies of 8-hydroxyquinoline, agreed with the conclusions. He proposed that discussion of marginal effects be reduced, noting that all of the statistical test results are available in the Appendixes. Dr. J. Huff, NTP, reminded the Panel that incidence rates for neoplasms having a trend or pairwise statistic of $P < 0.05$ are placed routinely in the Results sections. For comparative purposes, the incidence of the same lesion for the other sex of that species is also recorded. Ordinarily, marginal effects in a single group receive little mention in the discussion unless considered compound related.

As a second principal reviewer, Dr. Kociba said he also agreed with the conclusions. He urged inclusion in future studies of routine measurements of hematology, urinalysis, serum chemistry, organ weights, and other parameters to allow for a more complete assessment of both chronic toxicity and carcinogenicity. Dr. E. McConnell, NTP, indicated that these indices are included in most current studies and in those designed during the past 2 years or so. Dr. Kociba asked that dietary exposure levels expressed as parts per million (ppm) also be expressed as milligrams per kilogram body weight (mg/kg) per day to aid in extrapolation. Dr. J. French, NTP, noted that this information is available in the food consumption appendix (Appendix L, page 161) but that these values often lack accuracy because of the group housing used and food scattering. He said the Program will include exposure levels as milligrams per kilogram in the text routinely. Dr. Kociba stressed the importance of including negative as well as positive data on chemicals because negative data are important in determining which parameters to evaluate in safety assessment and health surveillance programs.

As a third principal reviewer, Dr. Kotelchuck agreed in principle with the conclusions but noted an apparent marginal increase in the rate of alveolar/bronchiolar neoplasms among all exposed groups, although in no individual case was there statistical significance. He said, however, that aggregation of the incidence data from both sexes of rats or mice by Chi-square analysis suggested there was equivocal evidence for association of the lung tumors with exposure to 8-hydroxyquinoline. In discussion about the usefulness or appropriateness of grouping lesions across sexes and/or species for analysis, Dr. J. Haseman, NIEHS, said that although statistical procedures for pooling experimental test results across sexes and/or species are available, the NTP does not consider this biologically appropriate and does not do such analyses routinely. Further, a previous Peer Review Panel recommended this not be done. Dr. Kociba observed that combining incidence data from both species may also cancel or diminish overall incidences as well as enhance them. Dr. Davis agreed and said that in view of endocrinologic differences, there was no good biologic justification for combining results from both sexes. Dr. French stated that more clarification of the lung tumor data including the potential positive trends would be added to the Discussion section.

Dr. Davis asked that more prominence be given to nontumor effects or lack of effects reported by others, including hepatic and neurologic toxicity, especially in view of 8-hydroxyquinoline's being used in preparations such as vaginal suppositories. Dr. Swenberg reiterated a previous Panel recommendation that non-NTP data should not be included in the abstract.

Dr. Van Ryzin moved that the Technical Report on the toxicology and carcinogenesis studies of 8-hydroxyquinoline be accepted with the modifications discussed. Dr. Slaga seconded the motion, and the Technical Report was approved unanimously by the Peer Review Panel.
I. INTRODUCTION

Chemical Identification
Uses, Production, and Exposure
Absorption and Excretion
Toxicity
Mutagenicity and Short-Term Tests
Carcinogenicity
Reason for Testing
I. INTRODUCTION

![Chemical Structure of 8-Hydroxyquinoline]

8-HYDROXYQUINOLINE
(8-QUINOLINOL; OXINE; HYDROXYBENZOPYRIDINE)
CAS NO. 148-24-3
C₈H₇NO Mol. Wt. 145.15
Melting Pt. 76° C Boiling Pt. 267° C

Chemical Identification

8-Hydroxyquinoline is a white to off-white crystal or crystalline powder that is insoluble in water or ether and freely soluble in ethanol, acetone, chloroform, benzene, and aqueous mineral acids. It readily forms stable metal chelates, which are soluble or precipitable in organic solvents, depending on the pH of the solution (Hollingshead, 1954). Both technical and reagent-grade 8-hydroxyquinoline are available in the United States (IARC, 1977).

Uses, Production, and Exposure

8-Hydroxyquinoline has a wide variety of uses. Primarily because of their metal chelating properties, 8-hydroxyquinoline and its salts, halogenated derivatives, and metal complexes have been used as analytical reagents (Hollingshead, 1954) and as antimicrobial agents in medicine, fungicides, and insecticides (Harvey, 1975). It is also used as a preservative in cosmetics and tobacco, a chemical intermediate in dye synthesis (IARC, 1977), and a precipitating reagent for uranium and other radioactive metals in nuclear power plant liquid waste effluent. It is used in nuclear medicine with indium-111 (Davis et al., 1978).


There is limited information available on human exposure to 8-hydroxyquinoline. Approximately 660 pounds of this chemical was estimated to be used per year in a wide variety of over-the-counter drugs (NCI/SRI Data Base on Category E Drug Exposure, 1978). This compound is listed as an active ingredient in microbicidal skin ointments, rectal suppositories, and vaginal gels, creams, and douche powders (Federal Register, 1983). Workers who manufacture or handle 8-hydroxyquinoline and its derivatives are presumed to make up the population at greatest risk.

8-Hydroxyquinoline has been placed tentatively in Category III (i.e., information available is inadequate to show that a substance is safe or effective) by the FDA/OTC Advisory Review Panel on Contraceptives and Other Vaginal Drug Products, the FDA committee that reviews non-prescription drugs (Federal Register, 1983). The copper derivative of 8-hydroxyquinoline used as a fungicide in agricultural and industrial applications was listed in the 1980 TSCA inventory (RTECS, 1980).

Absorption and Excretion

Both glucuronide and sulfate conjugates were formed in male Albino Donryu rats when either the parent compound or halogenated derivatives (5-chloro-8-hydroxyquinoline, 5,7-dichloro-8-hydroxyquinoline, or 5-chloro-8-hydroxy-7-iodoquinoline) were administered (3 mg/rat)
intravenously (Sawada et al., 1978). Glucuronides of 8-hydroxyquinoline were excreted in both bile (9% total dose) and urine (60% total dose), whereas the sulfates were excreted only in the urine (23% total dose).

In humans (six volunteers), 750 mg of orally administered 5-chloro-8-hydroxyquinoline was absorbed, and up to one-fourth of this dose was excreted in the urine over 72 hours in the form of the glucuronide (Berggren and Hansson, 1968). Maximum plasma concentrations were reached approximately 4 hours after single oral administrations of 250, 750, or 1,500 mg of 5-chloro-7-iodo-8-hydroxyquinoline to six volunteers each (Jack and Riess, 1973). The plasma half-life was estimated to vary between 11 and 14 hours after a single oral administration. Steady-state plasma concentrations were reached after 5 days of a 7-day course of administration with three daily doses of 250 or 500 mg of iodochlorohydroxyquinoline. No evidence of chemical accumulation in the tissues was found; there was no mention of toxicity.

Toxicity

An LD₅₀ value of 1,200 mg/kg was reported for oral administration of 8-hydroxyquinoline to rats (strain/sex unspecified; AAPCO, 1966); a value of 48 mg/kg was reported for intraperitoneal administration to mice (strain/sex unspecified; Bernstein et al., 1963).

Starting at week 52, feed consumption was stated to have decreased in male and female F344 rats fed diets containing 1,000 ppm 8-hydroxyquinoline (Fukushima et al., 1981). Administration of 8-hydroxyquinoline (8,000 ppm in the diet) for 52 weeks to 6-week-old male F344 rats resulted in weight gain reduction (approximately 22%) (Yamamoto et al., 1971). Depressed final body weights also occurred in rats (strain unknown) fed 100-250 mg/kg 8-hydroxyquinoline for 30-40 days (Galea and Popa, 1972).

Hemosiderosis in the liver and spleen occurred in male F344 rats fed a diet containing 8,000 ppm 8-hydroxyquinoline for 16 weeks (Yamamoto et al., 1971). Liver toxicity, decreased hepatic vitamin C content, and kidney toxicity were observed in rats fed diets containing 100-250 mg/kg 8-hydroxyquinoline for 30-40 days (Galea and Popa, 1972).

Neurotoxic effects of halogenated 8-hydroxyquinoline (5-chloro-7-iodo-8-hydroxyquinoline, 5,7-dichloro-8-hydroxyquinoline, and 5,7-dichloro-2-methyl-8-hydroxyquinoline) were reported in several species. Dose-related increases in mortality and paralysis occurred in 7-day-old chick embryos administered 20 or 30 mg 8-hydroxyquinoline per egg (Preda et al., 1974). 8-Hydroxyquinoline caused depletion of the axonal sheath in sciatic but not lumbar nerves in rats (strain undefined) when administered intravenously (18 mg/kg daily) for 25 days (Murayama et al., 1974). In this study, 5-chloro-7-iodo-8-hydroxyquinoline (18 mg/kg per day for 25 days) caused some degeneration in lumbar and sciatic neurons when given orally and severe neuronal degeneration when given intravenously.

In humans, 5-chloro-7-iodo-8-hydroxyquinoline (an antidiarrheal drug) was associated with an incidence of subacute myelooptic neuropathy (SMON) in Japan between 1956 and 1970 (Oakley, 1973). Recommended oral doses ranged from 250 mg up to 2 g per day (depending on the drug and the degree of halogenation). Neurotoxic symptoms were reported to have increased with increasing doses above 750 mg per day and the length of time on medication. The incidence of SMON in Japan decreased when the drug was removed from the market in 1970.

Mutagenicity and Short-Term Tests

8-Hydroxyquinoline was mutagenic in Salmonella typhimurium strain TA100 only in the presence of rat liver S9 and was negative or weakly mutagenic in strain TA98 (Bowden et al., 1976; Sugimura et al., 1976; Talcott et al., 1976; Epler et al., 1977; Nagao et al., 1977; Rasanen et al., 1977; Hollstein et al., 1978; Simon and Peirce, 1980; Gocke et al., 1981). Although 8-hydroxyquinoline gave equivocal results for the induction of aneuploidy in the fungus Neurospora crassa (Griffiths, 1979), it did induce chromosomal aberrations in the root tips of the broad bean Vicia faba (Kihlman, 1957). Gocke et al. (1981) reported that 8-hydroxyquinoline failed to induce sex-linked recessive lethal mutations in Drosophila or...
micronuclei in mice; however, the data were inconclusive. Although 8-hydroxyquinoline was reported to induce DNA damage in Chinese hamster V79 cells in vitro (Hiss and Preston, 1977) and chromatin aberrations in human leukocytes in vitro (Epler et al., 1977), analysis of the data indicated that neither finding was significantly (P < 0.05) different from that observed in the controls. In summary, 8-hydroxyquinoline was mutagenic in strain TA100 of Salmonella only in the presence of S9, caused chromosomal aberrations in the plant V. faba, and gave equivocal or inconclusive results in a variety of other short-term tests.

Carcinogenicity

No compound-related histopathologic effects were observed in male and female F344 rats administered 1,000 ppm 8-hydroxyquinoline in the diet for 104 weeks (Fukushima et al., 1981). Similarly, no compound-related histopathologic effects were observed in male or female F344 rats (age not specified) given 8-hydroxyquinoline (0, 0.1, 3, 10, or 30 mg per rat per day) by gavage, five times per week for 52 weeks (Hadidian et al., 1968).

Carcinoma, papilloma, and hyperplasia of the urinary bladder occurred in some of the surviving mice (sex and strain not stated) receiving implanted pellets of 8-hydroxyquinoline and cholesterol at that site (Allen et al., 1957; Boyland and Watson, 1956). Boyland and Watson (1956) reported results of experiments using this route of administration: 4/13 dosed mice had bladder carcinomas and 2/13 had bladder papillomas compared with 0/25 controls. Similar results were observed by Allen et al. (1957): 3/16 surviving dosed mice had bladder carcinomas, 2/16 had bladder papillomas, and 1/24 controls had a carcinoma. The source and purity of the 8-hydroxyquinoline were not stated in either study. Bryan et al. (1964) reported the results of experiments using 8-hydroxyquinoline and paraffin wax pellets implanted into bladders of mice (8- to 13-week-old female Swiss mice): 1/35 surviving dosed mice had bladder carcinoma and 1/35 had bladder papilloma; 1/47 surviving controls had bladder carcinoma, and 1/47 had bladder papilloma. Chemical source and purity were not stated.

Glandular or papillary hyperplasia of the endometrium was seen in 7/30 and carcinoma of the uterus in 4/30 Bethesda black rats (3 months old) receiving a 20% suspension of 8-hydroxyquinoline in 20% gelatin by intravaginal administration of 0.2 ml two times per week for 2 years (Hueper, 1965). In this study, no effects were seen in 80 C57 black mice (2 months old) receiving the same dose for 2 years, but survival was reduced because of infection. Carcinoma of the vagina and cervix were reported after vaginal instillation of 0.1 ml of 8-hydroxyquinoline in polyethylene glycol in 20 female mice (age and strain not given) two times per week for 18 months, but low survival (control, 7/20; dosed, 2/20) precluded judging the results. In a later study, no compound-related cervical or uterine lesions occurred in 20 BALB/c mice receiving 0.1-ml intravaginal administrations of 8-hydroxyquinoline (1%) in gum tragacanth two times per week for up to 50 weeks (Boyland et al., 1966). Inhibition of ovulation and "regenerative nodes" in the uterus reportedly occurred in five CC-57 mice receiving 20% 8-hydroxyquinoline in saline suspension by intravaginal instillation two times per week for 116 weeks; the size of the test groups was not stated (Volson, 1976).

Spermicidal preparations containing 0.02% 8-hydroxyquinoline benzoate, 2% boric acid, and 0.02% phenylmercuric acetate in an emulsion of stearic acid, cetyl alcohol, glycerin, and perfume were tested in female Wistar rats by daily intravaginal swabbing or oral ingestion for 16-18 months (Hoch-Ligeti, 1957). The rats were fed either a low-protein or regular diet (Purina dog chow). Compared with the controls fed a regular diet (1/16 had a mammary tumor), the low-protein-diet controls had a significant increase in the incidence of tumors (liver, 2/39; mammary, 13/39; other, 2/39). The study of rats that received the regular diet and were administered the spermicidal cream by intravaginal swabbing was considered inadequate because only five rats survived to the end of the study. In the oral study, stomach neoplasms were observed at increased incidence in rats that received the low-protein diet and the cream as compared with the low-protein controls (3/29 vs 0/39). In the intravaginal study, uterine neoplasms were observed at increased incidence in rats that received the
low-protein diet and the cream as compared with the low-protein controls (4/10 vs 1/39). Lack of information on the source and purity of the vaginal cream and on experimental detail about the dose delivered by the two routes of administration makes interpretation of that study difficult. These results are further complicated because a mixture of seven chemicals was contained in the spermicidal preparation.

The International Agency for Research Against Cancer Working Group concluded that available data did not allow an evaluation of the carcinogenicity of 8-hydroxyquinoline (IARC, 1977).

Quinoline, the parent compound of 8-hydroxyquinoline, was found to be carcinogenic for male Sprague-Dawley rats, causing hepatocellular carcinomas and hepatic hemangioendotheliomas (Hirao et al., 1976). At dietary concentrations of 0, 500, 1,000, and 2,500 ppm (administered for up to 40 weeks, 20 animals per group), incidences of rats surviving 16-40 weeks with hepatic hemangioendothelioma were 0/6, 6/11, 12/16, and 18/19; the incidences of rats with nodular hyperplasia of the liver were 0/6, 6/11, 4/16, and 0/19, and those with hepatocellular carcinoma were 0/6, 3/11, 3/16, and 0/19. Since quinoline requires metabolic activation for conversion to a mutagen in the Ames Salmonella assay (Bowden et al., 1976; Sugimura et al., 1976; Talcott et al., 1976; Epler et al., 1977; Nagao et al., 1977; Rasanen et al., 1977; Hollstein et al., 1978; Simon et al., 1980; Gocke et al., 1981), metabolic activation in vivo may be required for carcinogenicity. 4-Nitroquinoline-1-oxide also was found to be carcinogenic (Nakahara et al., 1957).

Reason for Testing

8-Hydroxyquinoline was tested by the NTP Carcinogenesis Program because of its various uses and its proposed use as a dental antibacterial agent and because its parent compound quinoline and 4-nitroquinoline-1-oxide are carcinogenic to rodents. Previous long-term studies available when this study was initiated were considered to be inadequate. The dietary route was chosen to obtain a systemic exposure and not necessarily for its relevance to human exposure.
II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 8-HYDROXYQUINOLINE
PREPARATION AND ANALYSIS OF FORMULATED DIETS
FIFTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES

Study Design
Source and Specifications of Test Animals
Animal Maintenance
Clinical Examinations and Pathology
Statistical Methods
II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 8-HYDROXYQUINOLINE

8-Hydroxyquinoline was obtained in one batch (Lot no. 7223-J) from Ashland Chemical Company (Englewood, NJ). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G).

The test chemical was identified as 8-hydroxyquinoline by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Overall data indicated a purity of approximately 99%. This conclusion was based on elemental analyses that agreed with theoretical values; a value of 0.58% water by Karl Fischer titration; a value of 101.6% for titration of the amine function with perchloric acid; thin-layer chromatography, which detected one minor impurity by each of two systems; and gas chromatography, which detected impurities totaling 0.15% of the major peak area in one system and 0.07% in a second system.

A chemical stability test performed at Midwest Research Institute indicated that 8-hydroxyquinoline was stable at temperatures as high as 60°C for 2 weeks (Appendix G). 8-Hydroxyquinoline was stored in the dark at 0°C ± 5°C. Results of periodic reanalyses of 8-hydroxyquinoline by infrared spectroscopy and gas chromatography indicated no notable chemical changes throughout the studies.

PREPARATION AND ANALYSIS OF FORMULATED DIETS

The appropriate amount of 8-hydroxyquinoline was weighed and then mixed with an aliquot of feed in a mortar with a pestle. This premix was then layered between the remaining feed in a Patterson-Kelly(R) V-blender and mixed for 15 minutes.

Results of the initial stability study at the analytical chemistry laboratory indicated that formulated diets were stable for 2 weeks at 5°C but not at 25°C or 45°C (Appendix H). Formulated diets were stored at 5°C.

Analysis of dosed feed mixtures to confirm homogeneity of the feed blends was conducted at both the testing and analytical chemistry laboratories (Appendix H). In addition, periodic analyses for 8-hydroxyquinoline in the feed mixtures were performed by the testing and analytical chemistry laboratories to confirm that the feed mixtures were administered to the animals at the correct concentrations. A recovery study indicated that 8-hydroxyquinoline was completely recovered from freshly prepared feed blends when methanol was used; but when feed blends had been stored for a period of time, recovery of the chemical was significantly reduced. Since 0.5% hydrochloric acid in methanol gave much greater recovery of test chemical from "aged" feed samples, it subsequently was used in the routine dose analysis procedure (Appendix I). The initial low recovery of 8-hydroxyquinoline in the stability study was attributed to poor extractability rather than chemical instability.

Results of analyses of formulated diets at the testing laboratory indicated that all but one of the analyzed diets prepared during the 2-year studies were properly formulated (Appendix J, Table J2). A summary of the analytical results is presented in Table 1 and Appendix J, Tables J2 and J3.

| TABLE 1. ANALYSES OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Target Concentration            | 1,500 ppm       | 5,000 ppm       |
| Experimental mean (ppm)         | 1,486           | 2,982           |
| Standard deviation (ppm)        | 89              | 132             |
| Coefficient of variation (percent) | 6.0            | 4.4             |
| Range (ppm)                     | 1,300-1,580     | 2,760-3,230     |
| Number of samples               | 13              | 13              |

FIFTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F1 mice were obtained from Charles River Breeding
II. MATERIALS AND METHODS

Laboratories and held for 20 days before the studies began.

Groups of five males and five females of each species were fed diets containing 0, 3,000, 6,000, 12,000, 25,000, or 50,000 ppm 8-hydroxyquinoline for 15 days. Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 2.

Animals were observed two times per day for signs of moribundity or mortality and weighed on days 0, 14, and 16. Necropsies were performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative effects of repeated administration of 8-hydroxyquinoline and to determine the concentrations to be used in the 2-year studies.

Four- to 5-week-old F344/N rats and 5- to 6-week-old B6C3F1 mice of each sex were obtained from Charles River Breeding Laboratories, observed for 15 days, and then randomized by weight and assigned to test groups so that the average group weights were approximately equal for all animals of the same sex and species.

Groups of 10 rats of each sex were fed diets containing 0, 800, 1,500, 3,000, 6,000, or 12,000 ppm 8-hydroxyquinoline for 13 weeks. Groups of 10 mice of each sex were fed diets containing 0, 400, 800, 1,500, 3,000, or 6,000 ppm 8-hydroxyquinoline.

Rats and mice were housed five per cage in polycarbonate cages. Formulated diets, control diets, and water via an automatic watering system were available ad libitum. Further experimental details are summarized in Table 2.

Animals were checked two times per day for mortality and signs of moribundity; moribund animals were killed. Feed consumption was measured weekly by cage. Animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. Necropsies were performed on all animals, except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 2.

TWO-YEAR STUDIES

Study Design

Diets containing 1,500 or 3,000 ppm 8-hydroxyquinoline were fed to groups of 50 rats or 50 mice of each sex for 103 weeks. Controls consisted of 50 untreated rats and 50 untreated mice of either sex.

Source and Specifications of Test Animals

The male and female F344/N rats and B6C3F1 (C57BL/6N X C3H/HeN MTV-) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for testing were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. The rats were shipped to the testing laboratory at 5 weeks of age and the mice at 4-6 weeks of age. The animals were quarantined at the testing facility (rats: 16 days; mice: 14 days). Thereafter, a complete pathologic examination was performed on a selected number of animals to assess their health. The rats were placed on study at 7 weeks of age and the mice at 6-8 weeks. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix K).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F1 test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoretograms that demonstrate phenotype expressions of known genetic loci.

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**TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF 8-HYDROXYQUINOLINE**

<table>
<thead>
<tr>
<th>EXPERIMENTAL DESIGN</th>
<th>Fifteen-Day Studies</th>
<th>Thirteen-Week Studies</th>
<th>Two-Year Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing Laboratory</strong></td>
<td>EG&amp;G Mason Research Institute</td>
<td>EG&amp;G Mason Research Institute</td>
<td>EG&amp;G Mason Research Institute</td>
</tr>
<tr>
<td><strong>Size of Test Groups</strong></td>
<td>5 males and 5 females of each species</td>
<td>10 males and 10 females of each species</td>
<td>50 males and 50 females of each species</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>0, 3,000, 6,000, 12,000, 25,000, or 50,000 ppm 8-hydroxyquinoline in the diet</td>
<td>Rats--0, 800, 1,500, 3,000, 6,000, or 12,000 ppm 8-hydroxyquinoline in the diet; mice--0, 400, 800, 1,500, 3,000, or 6,000 ppm</td>
<td>0, 1,500, or 3,000 ppm 8-hydroxyquinoline in the diet</td>
</tr>
<tr>
<td><strong>Date of First Dose</strong></td>
<td>11/13/78</td>
<td>11/13/78</td>
<td>Rats--12/21/79; mice--12/5/79</td>
</tr>
<tr>
<td><strong>Date of Last Dose</strong></td>
<td>11/27/78</td>
<td>1/24/79</td>
<td>Rats--12/09/81; mice--11/25/81</td>
</tr>
<tr>
<td><strong>Duration of Dosing</strong></td>
<td>15 d</td>
<td>13 wk</td>
<td>103 wk</td>
</tr>
<tr>
<td><strong>Type and Frequency of Observation</strong></td>
<td>Observed 2 × d for signs of moribundity and mortality; weighed initially, on d 14, and on d 16</td>
<td>Observed 2 × d for signs of moribundity and mortality; weight and feed consumption measured 1 × wk</td>
<td>Observed 2 × d for signs of moribundity and mortality; weighed initially, weekly for the first 12 wks, and every 4 wks thereafter; feed consumption: 1 × 4 wk</td>
</tr>
<tr>
<td><strong>Necropsy and Histologic Examination</strong></td>
<td>Necropsies performed on all animals</td>
<td>Necropsies performed on all animals. The following tissues were examined histologically: tissue masses, regional lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary glands, thyroid gland, parathyroids, small intestine, colon, liver, prostate/testis or ovaries/uterus, gallbladder (mice), lungs and bronchi, heart, brain, esophagus, stomach, thyroid gland, parathyroids, colon, esophagus, stomach, duodenum, ileum, jejunum, mesenteric lymph node, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testis or ovaries/uterus, nasal cavity, brain, pituitary gland, eyes, external and middle ear, spinal cord</td>
<td></td>
</tr>
</tbody>
</table>

**ANIMALS AND ANIMAL MAINTENANCE**

<table>
<thead>
<tr>
<th>Strain and Species</th>
<th>F344/N rats; B6C3F1 mice</th>
<th>F344/N rats; B6C3F1 mice</th>
<th>F344/N rats; B6C3F1 mice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal Source</strong></td>
<td>Charles River Breeding Labs (Portage, MI)</td>
<td>Same as 15-d studies</td>
<td>Same as 15-d studies</td>
</tr>
<tr>
<td><strong>Testing Laboratory</strong></td>
<td>EG&amp;G Mason Research Institute</td>
<td>Same as 15-d studies</td>
<td>Same as 15-d studies</td>
</tr>
<tr>
<td><strong>Animal Identification</strong></td>
<td>Ear punch</td>
<td>Ear punch</td>
<td>Ear punch</td>
</tr>
<tr>
<td><strong>Time Held Before Start of Test</strong></td>
<td>20 d</td>
<td>15 d</td>
<td>Rats--16 d; mice--14 d</td>
</tr>
<tr>
<td><strong>Age When Placed on Study</strong></td>
<td>7 wk</td>
<td>Rats--6-7 wk; mice--7-8 wk</td>
<td>Rats--7 wk; mice--6-8 wk</td>
</tr>
<tr>
<td><strong>Age When Killed</strong></td>
<td>9 wk</td>
<td>Rats--20-21 wk; mice--20-21 wk</td>
<td>Rats--111 wk; mice--110-113 wk</td>
</tr>
</tbody>
</table>

8-Hydroxyquinoline, NTP TR 276 22
| Table 2. Experimental Design and Materials and Methods in the Feed Studies of 8-Hydroxyquinoline (Continued) |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Necropsy Dates | Fifteen-Day Studies | Thirteen-Week Studies | Two-Year Studies |
| Rats--11/30-12/4/78; mice--12/4-12/5/78 | Rats--5/2-5/9/79; mice--4/25-5/2/79 | Rats--12/16-12/22/81; mice--12/2-12/9/81 |
| Method of Animal Distribution | Assigned to groups so that all cage weights were approximately equal (± 5 g) | Assigned to groups so that average body weight of each group was approximately equal | Random numbers table used to determine placement |
| Feed | Available ad libitum; ground Wayne Lab-Blox® (Allied Mills, Chicago, IL) | Ground Wayne Lab-Blox® meal; available ad libitum | Same as 15-d studies |
| Water | Automatic watering system (Edstrom Industries, Waterford, WI), freely available | Same as 15-d studies | Same as 15-d studies |
| Cages | Polycarbonate (Lab Products, Garfield, NJ); changed 2 × wk | Same as 15-d studies | Same as 15-d studies |
| Cage Filters | Nonwoven fiber filters (Lab Products or Snow Filtration, Cincinnati, OH) | Same as 15-d studies | Same as 15-d studies |
| Animals per Cage | 5 | 5 | 5 |
| Animal Room Environment | Temp--19.27°C; humidity--3%-39%; fluorescent light 12 h/d; 10 room air changes/h | Temp--15.6°-26.7°C; humidity--8%-68%; fluorescent light 12 h/d; 10 room air changes/h | Temp--17.2°-30.6°C; humidity--5%-78%; fluorescent light 12 h/d; 12 room air changes/h |
| Other Chemicals on Test in Same Room | None | None | None |
| CHEMISTRY | Lot Numbers Used | 7223-J | Same as 15-d studies |
| Supplier | Ashland Chemical Co., (Englewood, NJ) | Same as 15-d studies | Same as 15-d studies |
| CHEMICAL/VEHICLE | Preparation | Premix prepared with a mortar and pestle; final preparation mixed for 15 min in an 8-qt Patterson-Kelly® V-blender without intensifier bar | 8-Hydroxyquinoline and an aliquot of feed were mixed with a mortar and pestle to homogeneity. Premix sandwiched between the remaining meal in an 8-qt Patterson-Kelly® V-blender without an intensifier bar and mixed 15 min | Same as 13-wk studies |
| Maximum Storage Time | 2 wk | 2 wk | 2 wk |
| Storage Conditions | Stored in double plastic bags at 4°C | Same as 15-d studies | Stored in double plastic bags in covered plastic buckets at 0° ± 5°C |
II. MATERIALS AND METHODS

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid B6C3F1 mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because matched concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Details of animal maintenance are summarized in Table 2. Cage rotation was not carried out during these studies.

Clinical Examinations and Pathology

All animals were observed two times per day for mortality and signs of moribundity. Clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks of the study and once per month thereafter. Mean body weights were determined for each group. Moribund animals were killed, as were animals that survived to the end of the study. Necropsies were performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 2.

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 histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group.

Nonneoplastic lesions are not specifically examined routinely by the quality assurance pathologist or PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

Statistical Methods

Data Recording: 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, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the
form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not 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 method for testing for a dose-related trend. All reported P values for the survival analysis are two-sided.

Calculation of Incidence Rates: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators included only those animals for which the 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 number of animals on which necropsies were performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect 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. All reported P values for tumor analyses are one-sided.

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 method to obtain a single overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill period, and the terminal kill period. The denominators of these proportions were the number of animals on which necropsies were actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher's exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.
III. RESULTS

RATS

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results
III. RESULTS: RATS

FIFTEEN-DAY STUDIES

Two male rats that received 50,000 ppm 8-hydroxyquinoline died, one on day 12 and the other on day 13 (Table 3). One male rat that received 25,000 ppm died during the necropsy period. None of the female rats died. Male rats that received 25,000 or 50,000 ppm and females that received 50,000 ppm lost weight during the study. Male and female rats that received 50,000 ppm appeared emaciated. Although feed consumption was not measured, rats of each sex that received 12,000 ppm or more appeared to eat less than did the controls.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FIFTEEN-DAY FEED STUDIES OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>Survival</th>
<th>Mean Body Weights (grams)</th>
<th>Final Weight Relative to Controls (percent)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>5/5</td>
<td>162 ± 3</td>
<td>225 ± 6 + 73 ± 3 98.7</td>
</tr>
<tr>
<td>3,000</td>
<td>5/5</td>
<td>151 ± 3</td>
<td>222 ± 4 + 71 ± 3 96.9</td>
</tr>
<tr>
<td>6,000</td>
<td>5/5</td>
<td>152 ± 3</td>
<td>218 ± 4 + 66 ± 3 96.9</td>
</tr>
<tr>
<td>12,000</td>
<td>5/5</td>
<td>152 ± 4</td>
<td>192 ± 5 + 40 ± 2 93.3</td>
</tr>
<tr>
<td>25,000</td>
<td>5/5</td>
<td>151 ± 4</td>
<td>145 ± 4 - 6 ± 3 64.4</td>
</tr>
<tr>
<td>50,000</td>
<td>(c) 3/6</td>
<td>152 ± 5</td>
<td>105 ± 5 - 47 ± 9 46.7</td>
</tr>
</tbody>
</table>

FALE

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>Survival</th>
<th>Mean Body Weights (grams)</th>
<th>Final Weight Relative to Controls (percent)</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td>5/5</td>
<td>124 ± 3</td>
<td>153 ± 3 + 29 ± 1 97.3</td>
</tr>
<tr>
<td>3,000</td>
<td>5/5</td>
<td>123 ± 3</td>
<td>149 ± 3 + 26 ± 5 99.4</td>
</tr>
<tr>
<td>6,000</td>
<td>5/5</td>
<td>123 ± 3</td>
<td>152 ± 2 + 29 ± 2 99.2</td>
</tr>
<tr>
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<tr>
<td>25,000</td>
<td>5/5</td>
<td>124 ± 4</td>
<td>131 ± 4 + 7 ± 1 86.6</td>
</tr>
<tr>
<td>50,000</td>
<td>5/6</td>
<td>123 ± 4</td>
<td>103 ± 5 - 20 ± 2 66.9</td>
</tr>
</tbody>
</table>

(a) Number surviving/number initially in the group.  
(b) Initial body weight ± standard error of the mean for all animals in the group. Subsequent calculations are based on those animals surviving to the end of the study.  
(c) Deaths occurred on days 12 and 13.
III. RESULTS: RATS

THIRTEEN-WEEK STUDIES

None of the rats died (Table 4). Final mean body weights relative to those of the controls were depressed 18.0% for male rats that received 12,000 ppm 8-hydroxyquinoline and 10.5% and 9.5% for female rats that received 6,000 or 12,000 ppm, respectively. Feed consumption by male rats was unaffected by 8-hydroxyquinoline, but feed consumption by female rats that received 3,000, 6,000, or 12,000 ppm was approximately 75% that of the controls.

Necropsies were performed on all animals. No compound-related histopathologic lesions were found in the high dose (12,000 ppm) male rats. Lymphoid hyperplasia in the pancreatic lymph nodes was found in 2/10 females that received 12,000 ppm and in none of the controls. This lesion was not considered to be compound related.

In the absence of either dose-related increases in mortality or compound-related histopathologic lesions, body weight data formed the basis for the selection of concentrations of 1,500 and 3,000 ppm 8-hydroxyquinoline in feed for rats in the 2-year studies.

### TABLE 4. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>Survival (a)</th>
<th>Mean Body Weight (grams)</th>
<th>Final Weight Relative to Controls (percent)</th>
<th>Feed Consumption (c)</th>
<th>Calculated Dose (mg/kg/day)</th>
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<tr>
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<td></td>
<td>Initial (b)</td>
<td>Final</td>
<td>Change</td>
<td>Controls</td>
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</tr>
<tr>
<td>0</td>
<td>10/10</td>
<td>181 ± 4</td>
<td>344 ± 5</td>
<td>+163 ± 5</td>
<td>--</td>
</tr>
<tr>
<td>800</td>
<td>10/10</td>
<td>182 ± 4</td>
<td>333 ± 6</td>
<td>+151 ± 7</td>
<td>96.8</td>
</tr>
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<td>1,500</td>
<td>10/10</td>
<td>183 ± 4</td>
<td>338 ± 8</td>
<td>+157 ± 6</td>
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<td>10/10</td>
<td>182 ± 4</td>
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</tr>
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<td>6,000</td>
<td>10/10</td>
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<td>+146 ± 4</td>
<td>95.1</td>
</tr>
<tr>
<td>12,000</td>
<td>10/10</td>
<td>182 ± 4</td>
<td>328 ± 6</td>
<td>+145 ± 6</td>
<td>82.0</td>
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<td></td>
<td></td>
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<td>10/10</td>
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<td>210 ± 4</td>
<td>+75 ± 2</td>
<td>--</td>
</tr>
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<td>207 ± 3</td>
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<td>135 ± 3</td>
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<td>94.3</td>
</tr>
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<td>136 ± 3</td>
<td>188 ± 3</td>
<td>+62 ± 1</td>
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</tr>
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<td>12,000</td>
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<td>136 ± 3</td>
<td>180 ± 3</td>
<td>+58 ± 3</td>
<td>90.5</td>
</tr>
</tbody>
</table>

(a) Number surviving/number per group
(b) Initial body weight ± standard error of the mean for all animals in the group
(c) Grams per kilogram body weight per day during week 12
### III. RESULTS: RATS

#### TWO-YEAR STUDIES

**Body Weights and Clinical Signs**
Throughout most of the study, mean body weights of high dose rats of each sex were slightly lower than those of the controls (Table 5 and Figure 1). The average daily feed consumption per rat by low dose and high dose rats was 9% and 88% that of the controls for males and 89% and 78% for females (Appendix L, Tables L1 and L2). Approximate chemical consumption for low dose and high dose rats (rats were group housed) was 73 and 143 mg/kg for males and 89 and 166 mg/kg for females.

### TABLE 5. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Weeks on Study</th>
<th>Control (grams)</th>
<th>No. of Survivors</th>
<th>Av. Wt. (grams)</th>
<th>No. of Survivors</th>
<th>Av. Wt. (grams)</th>
<th>No. of Survivors</th>
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<tbody>
<tr>
<td></td>
<td>Av. WL</td>
<td>% Weight</td>
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<td></td>
<td>(grams)</td>
<td>Percentage of controls</td>
<td>(grams)</td>
<td>Percentage of controls</td>
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<tr>
<td>81</td>
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<td>84</td>
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<td>91.5</td>
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<td>87</td>
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<td>91.2</td>
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<tr>
<td>90</td>
<td>361</td>
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<td>360</td>
<td>90.9</td>
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<tr>
<td>93</td>
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<td>50</td>
<td>371</td>
<td>90.6</td>
<td>49</td>
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<tr>
<td>96</td>
<td>383</td>
<td>50</td>
<td>382</td>
<td>90.3</td>
<td>49</td>
<td>414</td>
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<tr>
<td>99</td>
<td>394</td>
<td>50</td>
<td>393</td>
<td>90.0</td>
<td>49</td>
<td>426</td>
</tr>
<tr>
<td>102</td>
<td>405</td>
<td>50</td>
<td>404</td>
<td>89.7</td>
<td>48</td>
<td>439</td>
</tr>
</tbody>
</table>

8-Hydroxyquinoline, NTP TR 276
FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED 8-HYDROXYQUINOLINE IN FEED FOR TWO YEARS
III. RESULTS: RATS

Survival

Estimates of the probabilities of the survival of male and female rats fed a control diet and diets containing 8-hydroxyquinoline as described earlier are shown in the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of either sex (Table 6).

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidences of animals with neoplastic or nonneoplastic lesions. Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Appendix E, Tables E1 and E2, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).

<table>
<thead>
<tr>
<th>TABLE 6. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>MALE (a)</td>
</tr>
<tr>
<td>Animals initially in study</td>
</tr>
<tr>
<td>Nonaccidental deaths before termination (b)</td>
</tr>
<tr>
<td>Killed at termination</td>
</tr>
<tr>
<td>Died during termination period</td>
</tr>
<tr>
<td>Survival P values (c)</td>
</tr>
<tr>
<td>FEMALE (a)</td>
</tr>
<tr>
<td>Animals initially in study</td>
</tr>
<tr>
<td>Nonaccidental deaths before termination (b)</td>
</tr>
<tr>
<td>Killed at termination</td>
</tr>
<tr>
<td>Died during termination period</td>
</tr>
<tr>
<td>Survival P values (c)</td>
</tr>
</tbody>
</table>

(a) Terminal kill period: males, week 104; females, weeks 104-105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the results of the life table exact pairwise comparisons with the controls are in the dosed columns.
FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 8-HYDROXYQUINOLINE IN FEED FOR TWO YEARS
III. RESULTS: RATS

_Lung:_ Incidences of epithelial hyperplasia were not significantly different in dosed and control groups of male rats (Table 7). Alveolar/bronchiolar adenomas or carcinomas (combined) in male rats occurred with a statistically significant positive trend, and the incidence in the high dose group was significantly greater than that in the controls. The incidences of alveolar/bronchiolar adenomas in female rats were as follows: control, 1/50; low dose, 2/50; high dose, 2/50. No carcinomas were observed in female rats.

_Thyroid Gland:_ The incidence of C-cell hyperplasia was greater in the controls than in the male or female dosed groups (Table 8). Incidences of C-cell carcinomas and C-cell adenomas or carcinomas (combined) in male rats and C-cell adenomas in female rats were significantly increased by trend tests. The incidences in the dosed groups were not significantly different from those in the controls by either survival-adjusted test.

_Other Tumor Effects:_ Marginal decreases were observed in the incidences of neoplastic nodules in the livers of dosed male rats (control, 6/49; low dose, 1/50; high dose, 3/48) and of mononuclear cell leukemias in male rats (control, 17/50; low dose, 8/50; high dose 9/50) (Appendix E, Table E1). These differences were not considered compound related.

---

**TABLE 7. ANALYSIS OF LUNG LESIONS IN MALE RATS IN THE TWO-YEAR STUDIES OF 8-HYDROXYQUINOLINE (a)**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1,500 ppm (b)</th>
<th>3,000 ppm (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelial Hyperplasia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>5/50 (10%)</td>
<td>5/50 (10%)</td>
<td>3/50 (6%)</td>
</tr>
<tr>
<td><strong>Alveolar/Bronchiolar Adenoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>0/29 (0%)</td>
<td>2/34 (6%)</td>
<td>2/34 (6%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>0.0%</td>
<td>5.9%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>P = 0.097</td>
<td>P = 0.274</td>
<td>P = 0.143</td>
</tr>
<tr>
<td>Life Table Tests</td>
<td>P = 0.094</td>
<td>P = 0.274</td>
<td>P = 0.131</td>
</tr>
<tr>
<td><strong>Alveolar/Bronchiolar Carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>0/50 (0%)</td>
<td>1/50 (2%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td><strong>Alveolar/Bronchiolar Adenoma or Carcinoma (c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>0/50 (0%)</td>
<td>3/50 (6%)</td>
<td>4/50 (8%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>0.0%</td>
<td>7.3%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>0/29 (0%)</td>
<td>2/34 (6%)</td>
<td>2/33 (6%)</td>
</tr>
<tr>
<td>Life Table Tests</td>
<td>P = 0.081</td>
<td>P = 0.143</td>
<td>P = 0.090</td>
</tr>
<tr>
<td>Incidental Tumor Tests</td>
<td>P = 0.018</td>
<td>P = 0.142</td>
<td>P = 0.037</td>
</tr>
</tbody>
</table>

(a) The statistical analyses used are described in Chapter II (Statistical Methods) and Appendix E (Footnotes).
(b) The equivalent dose in milligrams per kilogram per day is given in Chapter III (Body Weights and Clinical Signs) and in Appendix L.
(c) Historical incidence: testing laboratory--13/696 (1.9%); NTP laboratories--57/2,387 (2.4%)
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-Cell Hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>4/50 (8%)</td>
<td>3/49 (6%)</td>
<td>1/47 (2%)</td>
</tr>
<tr>
<td><strong>C-Cell Adenoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>1/50 (2%)</td>
<td>1/49 (2%)</td>
<td>2/47 (4%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>0.0%</td>
<td>0.0%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>0/29 (0%)</td>
<td>0/34 (0%)</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>Life Table Tests</td>
<td>P=0.018</td>
<td>(a)</td>
<td>P=0.080</td>
</tr>
<tr>
<td>Incidental Tumor Tests</td>
<td>P=0.016</td>
<td>(a)</td>
<td>P=0.068</td>
</tr>
<tr>
<td><strong>C-Cell Carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>0/50 (0%)</td>
<td>0/49 (0%)</td>
<td>4/47 (9%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>0.0%</td>
<td>0.0%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>0/29 (0%)</td>
<td>0/34 (0%)</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>Life Table Tests</td>
<td>P=0.018</td>
<td>(a)</td>
<td>P=0.080</td>
</tr>
<tr>
<td>Incidental Tumor Tests</td>
<td>P=0.016</td>
<td>(a)</td>
<td>P=0.068</td>
</tr>
<tr>
<td>C-Cell Adenoma or Carcinoma (b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>1/50 (2%)</td>
<td>1/49 (2%)</td>
<td>6/47 (13%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>2.5%</td>
<td>2.9%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>0/29 (0%)</td>
<td>1/34 (3%)</td>
<td>5/33 (15%)</td>
</tr>
<tr>
<td>Life Table Tests</td>
<td>P=0.030</td>
<td>P=0.735N</td>
<td>P=0.080</td>
</tr>
<tr>
<td>Incidental Tumor Tests</td>
<td>P=0.025</td>
<td>P=0.717</td>
<td>P=0.062</td>
</tr>
<tr>
<td><strong>FEMALE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-Cell Hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>9/48 (19%)</td>
<td>6/50 (12%)</td>
<td>1/49 (2%)</td>
</tr>
<tr>
<td>C-Cell Adenoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>1/48 (2%)</td>
<td>2/50 (4%)</td>
<td>5/49 (10%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>2.2%</td>
<td>4.8%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>0/37 (0%)</td>
<td>1/40 (3%)</td>
<td>4/36 (11%)</td>
</tr>
<tr>
<td>Life Table Tests</td>
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<td>P=0.097</td>
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<tr>
<td>Incidental Tumor Tests</td>
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<td>P=0.350</td>
<td>P=0.076</td>
</tr>
<tr>
<td>C-Cell Carcinoma</td>
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<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>2/48 (4%)</td>
<td>0/50 (0%)</td>
<td>1/49 (2%)</td>
</tr>
<tr>
<td>C-Cell Adenoma or Carcinoma (b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>3/48 (6%)</td>
<td>2/50 (4%)</td>
<td>6/49 (12%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>7.5%</td>
<td>4.8%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>2/37 (5%)</td>
<td>1/40 (3%)</td>
<td>5/36 (14%)</td>
</tr>
<tr>
<td>Life Table Tests</td>
<td>P=0.154</td>
<td>P=0.485N</td>
<td>P=0.227</td>
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<tr>
<td>Incidental Tumor Tests</td>
<td>P=0.128</td>
<td>P=0.602N</td>
<td>P=0.197</td>
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</table>

(a) No P value is presented because no tumors were observed in the 1,500-ppm and control groups.
(b) Historical incidence: testing laboratory--54/664 (8.1%); NTP laboratories--203/2,282 (8.9%).
III. RESULTS: MICE

FIFTEEN-DAY STUDIES

All mice that received 25,000 or 50,000 ppm 8-hydroxyquinoline in feed died before the end of the study (Table 9). Four of five male mice that received 12,000 ppm lost weight. Although feed consumption was not measured, mice that received 12,000 ppm or more ate noticeably less than did the controls. Five of five female mice that received 50,000 ppm and 4/5 female mice that received 25,000 ppm were emaciated according to necropsy reports.

TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIFTEEN-DAY FEED STUDIES OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>Survival</th>
<th>Mean Body Weights (grams)</th>
<th>Final Weight Relative to Controls (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial (b)</td>
<td>Final</td>
</tr>
<tr>
<td>MALE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5/6</td>
<td>26.6 ± 0.5</td>
<td>29.0 ± 0.8</td>
</tr>
<tr>
<td>3,000</td>
<td>5/5</td>
<td>26.6 ± 0.4</td>
<td>26.8 ± 2.1</td>
</tr>
<tr>
<td>5,000</td>
<td>5/5</td>
<td>26.4 ± 0.8</td>
<td>25.8 ± 0.7</td>
</tr>
<tr>
<td>12,000</td>
<td>5/5</td>
<td>26.7 ± 0.7</td>
<td>25.7 ± 0.8</td>
</tr>
<tr>
<td>25,000</td>
<td>(d) 0/5</td>
<td>26.5 ± 0.4</td>
<td>(e)</td>
</tr>
<tr>
<td>50,000</td>
<td>(e) 0/5</td>
<td>26.5 ± 0.4</td>
<td>(e)</td>
</tr>
<tr>
<td>FEMALE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5/6</td>
<td>19.8 ± 0.7</td>
<td>21.6 ± 0.8</td>
</tr>
<tr>
<td>3,000</td>
<td>5/5</td>
<td>20.2 ± 0.5</td>
<td>21.4 ± 0.7</td>
</tr>
<tr>
<td>5,000</td>
<td>5/6</td>
<td>20.2 ± 0.5</td>
<td>20.9 ± 0.6</td>
</tr>
<tr>
<td>12,000</td>
<td>5/6</td>
<td>20.1 ± 0.4</td>
<td>20.8 ± 0.5</td>
</tr>
<tr>
<td>25,000</td>
<td>(g) 0/5</td>
<td>19.7 ± 0.4</td>
<td>(e)</td>
</tr>
<tr>
<td>50,000</td>
<td>(h) 0/5</td>
<td>19.5 ± 0.5</td>
<td>(e)</td>
</tr>
</tbody>
</table>

(a) Number surviving/number initially in the group
(b) Initial body weight ± standard error of the mean for all animals in the group
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Deaths were on days 10, 11, 12, 12, and 12.
(e) No data are presented due to the 100% mortality in this group.
(f) Deaths were on days 4, 6, 6, 6, and 7.
(g) Deaths were on days 11, 11, 11, 11, and 12.
(h) Deaths were on days 4, 4, 4, 4, and 5.
III. RESULTS: MICE

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred; all deaths were accidental (Table 10). Final mean body weights relative to controls were depressed 11% for male mice and 10% for female mice that received 6,000 ppm 8-hydroxyquinoline in feed. Feed consumption by mice that received 6,000 ppm 8-hydroxyquinoline was 82% that of controls for males and 74% that of controls for females. No compound-related histopathologic effects were observed in the high dose (6,000 ppm) male or female mice. Mice in lower dose groups were not examined.

Because of weight gain depression observed at 6,000 ppm, concentrations selected for mice for the 2-year studies were 1,500 and 3,000 ppm 8-hydroxyquinoline in feed.

**TABLE 10. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF 8-HYDROXYQUINOLINE**

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>Survival (a)</th>
<th>Mean Body Weight (grams)</th>
<th>Final Weight Relative to Controls (percent)</th>
<th>Feed Consumption (c)</th>
<th>Calculated Dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(d) 9/10</td>
<td>24.4 ± 0.8</td>
<td>35.4 ± 1.1</td>
<td>--</td>
<td>157</td>
</tr>
<tr>
<td>400</td>
<td>10/10</td>
<td>24.7 ± 0.7</td>
<td>36.7 ± 0.8</td>
<td>120.0 ± 0.7</td>
<td>103.7</td>
</tr>
<tr>
<td>800</td>
<td>10/10</td>
<td>24.3 ± 0.5</td>
<td>35.6 ± 0.9</td>
<td>113.3 ± 0.7</td>
<td>100.6</td>
</tr>
<tr>
<td>1,500</td>
<td>10/10</td>
<td>24.6 ± 0.6</td>
<td>34.3 ± 0.6</td>
<td>9.7 ± 0.8</td>
<td>96.9</td>
</tr>
<tr>
<td>3,000</td>
<td>10/10</td>
<td>24.8 ± 0.8</td>
<td>34.8 ± 0.7</td>
<td>10.0 ± 0.5</td>
<td>98.3</td>
</tr>
<tr>
<td>6,000</td>
<td>10/10</td>
<td>24.1 ± 0.6</td>
<td>31.4 ± 0.8</td>
<td>7.3 ± 0.6</td>
<td>88.7</td>
</tr>
</tbody>
</table>

(a) Number surviving/number per group
(b) Initial body weight ± standard error of the mean for all animals in the group. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Grams per kilogram body weight per day during week 12
(d) All deaths were accidental.
III. RESULTS: MICE

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were slightly lower than those of the controls throughout most of the study (Table 11 and Figure 3). Mean body weights of both low dose and high dose female mice were lower than those of the controls. The average daily feed consumption by low dose and high dose male mice was 81% and 72% that of the controls and by low dose and high dose female mice, 86% and 71% that of the controls (Appendix L, Tables L3 and L4). Approximate chemical consumption for low dose and high dose mice (mice were group housed) was 217 and 396 mg/kg for males and 349 and 619 mg/kg for females.

<table>
<thead>
<tr>
<th>Weeks on Study</th>
<th>Control Av. WL (grams)</th>
<th>1,500 ppm Av. WL (grams)</th>
<th>3,000 ppm Av. WL (grams)</th>
<th>Control No. of Survivors</th>
<th>1,500 ppm No. of Survivors</th>
<th>3,000 ppm No. of Survivors</th>
<th>Control WL (percent of controls)</th>
<th>1,500 ppm WL (percent of controls)</th>
<th>3,000 ppm WL (percent of controls)</th>
<th>Control No. of Survivors</th>
<th>1,500 ppm No. of Survivors</th>
<th>3,000 ppm No. of Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25</td>
<td>50</td>
<td>100.0</td>
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<td>25</td>
<td>100.0</td>
<td>50</td>
<td>100.0</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEMALE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>50</td>
<td>19</td>
<td>100.0</td>
<td>50</td>
<td>100.0</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8-Hydroxyquinoline, NTP TR 276
FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED 8-HYDROXYQUINOLINE IN FEED FOR TWO YEARS

8-Hydroxyquinoline, NTP TR 276
III. RESULTS: MICE

Survival

Estimates of the probabilities of survival of male and female mice fed diets containing 8-hydroxyquinoline at the concentrations used in these studies and those of the controls are shown in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex (Table 12).

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidences of animals with neoplastic or nonneoplastic lesions. Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Appendix E, Tables E3 and E4, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).

### TABLE 12. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALE (a)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals initially in study</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Nonaccidental deaths before termination (b)</td>
<td>21</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Killed at termination</td>
<td>29</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Survival P values (c)</td>
<td>0.208</td>
<td>0.171</td>
<td>0.267</td>
</tr>
<tr>
<td><strong>FEMALE (a)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals initially in study</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Nonaccidental deaths before termination (b)</td>
<td>26</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Killed at termination</td>
<td>24</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Died during termination period</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Survival P values (c)</td>
<td>0.181</td>
<td>0.381</td>
<td>0.236</td>
</tr>
</tbody>
</table>

(a) Terminal kill period: weeks 104-105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the life table exact pairwise comparisons with the controls are in the dosed columns.
FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 8-HYDROXYQUINOLINE IN FEED FOR TWO YEARS
Circulatory System: Hemangiomas and hemangiomas or hemangiosarcomas (combined) in male mice occurred with significant negative trends, and the incidences in the dosed groups were significantly lower than those in the controls (Table 13). The incidence of hemangiomas or hemangiosarcomas (combined) in low dose female mice was significantly greater than that in the controls by the Fisher exact test, but the difference was not significant by methods that adjusted for survival. The incidences of circulatory system tumors in the male control group were markedly greater than those observed in historical control groups, both at this laboratory and throughout the Program.

Other Tumor Effects: Marginal decreases in malignant lymphoma (control, 12/50; low dose, 6/50; high dose, 6/50) in dosed male mice and hepatocellular carcinomas (control, 3/49; low dose, 1/50; high dose, 0/49) in dosed female mice were not considered to be chemically related (Appendix E, Tables E3 and E4).

Multiple Organs: Necrotizing inflammation of the ovary, uterus, and thoracic or abdominal cavities was found in 20/26 control, 11/24 low dose, and 10/21 high dose female mice that died before the end of the study, primarily after week 80. The gross diagnosis of the necrotizing inflammation was based on the presence of thick yellow fluid. A microscopic review indicated that these lesions were consistent with Klebsiella infection, and overall 22/50 control, 13/50 low dose, and 12/50 high dose female mice were infected.
TABLE 13. ANALYSIS OF CIRCULATORY SYSTEM TUMORS IN MICE IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE (a)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1,500 ppm (b)</th>
<th>3,000 ppm (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangioma (c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>7/50 (14%)</td>
<td>1/50 (2%)</td>
<td>0/50 (0%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>21.0%</td>
<td>2.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>4/29 (14%)</td>
<td>1/35 (3%)</td>
<td>0/35 (0%)</td>
</tr>
<tr>
<td>Life Table Tests</td>
<td>P &lt; 0.001N</td>
<td>P = 0.019N</td>
<td>P = 0.006N</td>
</tr>
<tr>
<td>Incidental Tumor Tests</td>
<td>P = 0.002N</td>
<td>P = 0.026N</td>
<td>P = 0.010N</td>
</tr>
<tr>
<td>Hemangiosarcoma (d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>3/50 (6%)</td>
<td>1/50 (2%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Hemangiomia or Hemangiosarcoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates</td>
<td>10/50 (20%)</td>
<td>2/50 (4%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Adjusted Rates</td>
<td>29.3%</td>
<td>6.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Terminal Rates</td>
<td>6/29 (21%)</td>
<td>1/55 (3%)</td>
<td>0/35 (0%)</td>
</tr>
<tr>
<td>Life Table Tests</td>
<td>P &lt; 0.001N</td>
<td>P = 0.007N</td>
<td>P = 0.003N</td>
</tr>
<tr>
<td>Incidental Tumor Tests</td>
<td>P = 0.002N</td>
<td>P = 0.010N</td>
<td>P = 0.006N</td>
</tr>
</tbody>
</table>

| **FEMALE**               |         |               |               |
| Hemangioma (e)           |         |               |               |
| Overall Rates            | 0/50 (0%) | 4/50 (8%)     | 1/50 (2%)     |
| Adjusted Rates           | 0.0%    | 11.6%         | 3.2%          |
| Terminal Rates           | 0/24 (0%) | 1/27 (4%)     | 1/31 (3%)     |
| Life Table Tests         | P = 0.487 | P = 0.096     | P = 0.551     |
| Incidental Tumor Tests   | P = 0.351 | P = 0.112     | P = 0.551     |
| Hemangiosarcoma (f)      |         |               |               |
| Overall Rates            | 0/50 (0%) | 1/50 (2%)     | 0/50 (0%)     |
| Hemangiomia or Hemangiosarcoma |         |               |               |
| Overall Rates            | 0/50 (0%) | 5/50 (10%)    | 1/50 (2%)     |
| Adjusted Rates           | 0.0%    | 14.9%         | 3.2%          |
| Terminal Rates           | 0/24 (0%) | 2/27 (7%)     | 1/31 (3%)     |
| Life Table Tests         | P = 0.487 | P = 0.055     | P = 0.551     |
| Incidental Tumor Tests   | P = 0.384 | P = 0.079     | P = 0.551     |

(a) The statistical analyses used are described in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) The equivalent dose in milligrams per kilograms per day is given in Chapter III (Body Weights and Clinical Signs) and in Appendix L.
(c) Historical incidence for hemangioma: testing laboratory--17/745 (2.3%); NTP laboratories--34/2,395 (1.4%)
(d) Historical incidence for hemangiosarcoma or angiosarcoma: testing laboratory--31/745 (4.2%); NTP laboratories--65/2,395 (2.7%)
(e) Historical incidence for hemangioma: testing laboratory--15/748 (2.0%); NTP laboratories--39/2,537 (1.5%)
(f) Historical incidence for hemangiosarcoma or angiosarcoma: testing laboratory--14/748 (1.9%); NTP laboratories--51/2,537 (2.0%)
IV. DISCUSSION AND CONCLUSIONS
IV. DISCUSSION AND CONCLUSIONS

Studies were conducted by administering 8-hydroxyquinoline in feed to rats and mice for 15 days (0, 3,000-50,000 ppm) and 13 weeks (rats: 0, 800-12,000 ppm; mice: 0, 400-6,000 ppm). The 25,000- or 50,000-ppm diets produced emaciation, weight loss, and death. Weight gain depression and reduced feed consumption also occurred at the highest concentrations used in the 13-week studies. Decreased feed consumption and body weight depression were previously reported for rats and mice given diets containing 8-hydroxyquinoline (Yamamoto et al., 1971; Galea and Popa, 1972; Fukushima et al., 1981). No compound-related gross or microscopic pathologic lesions were observed in the studies.

Administration of 8-hydroxyquinoline in feed for 2 years (0, 1,500, or 3,000 ppm) did not affect survival of rats or mice. The slight reductions in mean body weight gains that occurred in the high dose groups were probably related to reduced feed consumption. Results of the 13-week and 2-year studies indicate that higher concentrations of 8-hydroxyquinoline in feed would not be palatable.

No evidence of compound-related nonneoplastic or neoplastic lesions was found in female rats. In male rats, alveolar/bronchiolar adenomas or carcinomas (combined) occurred with a positive trend in the dosed groups, and the incidence in the high dose group was significantly greater than that in the concurrent controls (Tables 7 and 14). The proportion of high dose animals with lung tumors (8%) was above the average in controls at this laboratory (2%) and throughout the Carcinogenesis Program (2.4%); neither the individual nor the combined incidences of adenomas and carcinomas were greater than those previously observed (Appendix F, Table F3). Most of these lesions did not appear to differ from lung tumors observed in control animals, and the adenomas were lesions that were borderline between focal epithelial hyperplasias and small adenomas. Epithelial hyperplasia was not increased in the dosed males. The difference between this lesion and alveolar/bronchiolar adenoma is one of degree. Dosed male and female mice also showed increased incidences of lung tumors (Table 14); however, these increases were not statistically significant and were within the range of historical values. Hence, none of these marginal effects in the lungs of rats or mice was regarded as being associated with the administration of 8-hydroxyquinoline.

Thyroid gland C-cell adenomas and C-cell adenomas or carcinomas (combined) in male rats and C-cell adenomas in female rats occurred with positive trends (Tables 8 and 14). The incidences of these neoplasms in the high dose groups were not statistically significant compared with the controls. For both sexes, C-cell hyperplasia decreased with dose. Proliferation of C-cells in the thyroid gland of aging rats is not uncommon and appears to begin as mild, diffuse, or small focal collections of C-cells adjacent to the follicular epithelium. As the proliferation continues, the follicular epithelium is compressed and contiguous follicles become involved. Lesions smaller than three follicles are arbitrarily classified as hyperplasia. Lesions that are larger and restricted to one lobe are adenomas; and lesions involving the thyroid capsule, invading adjacent tissue, or having obvious malignant characteristics (such as metastases) are classified as C-cell carcinomas. Since these lesions occur in about 9% of F344/N rats (Appendix F, Tables F4 and F5) and the distinction between hyperplasia and adenoma is one of degree, the marginally increased incidences of these neoplastic lesions are not considered to be chemically related.

Neoplastic nodules or carcinomas of the liver decreased in low dose male rats, but the incidence in the high dose group was not significantly different from that in the controls. Mononuclear cell leukemia occurred with a negative trend in male rats, and the incidences in the dosed groups were lower than that in the controls. Neither of these decreases was considered to be related to administration of 8-hydroxyquinoline. Quinoline, the parent compound of 8-hydroxyquinoline, was found to produce increased incidences of hepatocellular carcinomas and hemangioendotheliomas when incorporated into the diet of male Sprague-Dawley rats at a concentration of 500 ppm for 40 weeks (Hirao et al., 1976). No such effects were observed in the present study.
### TABLE 14. INCIDENCES OF LESIONS IN RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALE RATS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Lung
  epithelial hyperplasia       | 5/50    | 5/50      | 3/50      |
  alveolar/bronchiolar adenoma/carcinoma | 0/50    | 3/50      | 4/50      |
| thyroid
  c-cell hyperplasia          | 4/50    | 3/49      | 1/47      |
  c-cell adenoma/carcinoma       | 1/50    | 1/49      | 6/47      |
| liver
  neoplastic nodule            | 6/49    | 1/50      | 3/48      |
  carcinoma                      | 1/49    | 0/50      | 0/48      |
| hematopoietic system
  mononuclear cell leukemia     | 17/50   | 8/50      | 9/50      |
| **FEMALE RATS**                |         |           |           |
| thyroid
  c-cell hyperplasia          | 9/48    | 6/50      | 1/49      |
  c-cell adenoma/carcinoma       | 3/48    | 2/50      | 6/49      |
| **MALE MICE**                  |         |           |           |
| circulatory system
  hemangioma                    | 7/50    | 1/50      | 0/50      |
  hemangiosarcoma                | 3/50    | 1/50      | 1/50      |
| hematopoietic system
  malignant lymphoma            | 12/50   | 6/50      | 6/50      |
| lung
  epithelial hyperplasia       | 1/50    | 0/49      | 5/50      |
  alveolar/bronchiolar adenoma/carcinoma | 6/50    | 10/49     | 10/50     |
| **FEMALE MICE**                |         |           |           |
| circulatory system
  hemangioma                    | 0/50    | 4/50      | 1/50      |
  hemangiosarcoma                | 0/50    | 1/50      | 0/50      |
| hematopoietic system
  malignant lymphocytic lymphoma | 1/50    | 1/50      | 6/50      |
  malignant lymphoma (all types) | 13/50   | 13/50     | 12/50     |
| liver
  carcinoma                    | 3/49    | 1/50      | 0/49      |
| lung
  epithelial hyperplasia       | 1/49    | 0/50      | 0/50      |
  alveolar/bronchiolar adenoma/carcinoma | 2/49    | 5/50      | 5/50      |
IV. DISCUSSION AND CONCLUSIONS

In mice, incidences of hemangiomas and hemangiosarcomas or hemangiomas were decreased in dosed males. The incidences in the control group were notably greater than the highest incidence previously observed in the historical controls (Appendix F, Table F6). The combined incidence of these lesions was marginally increased in low dose female mice, and the incidence in the high dose group was not significantly greater than that in the controls. The decrease in circulatory system tumors in mice is considered to be unrelated to 8-hydroxyquinoline administration. No explanation is readily apparent for the increased incidence of circulatory system tumors in the concurrent controls relative to NTP historical control values.

Marginal decreases were observed in malignant lymphoma in dosed male mice and hepatocellular carcinoma in dosed female mice, but neither of these effects was considered to be chemically related.

In female mice, the incidence of necrotizing inflammation of multiple organs (uterine-ovarian and thoracic or abdominal cavities) correlated with Klebsiella infection. The lesions were similar to those found in female mice in other NTP studies in which a diagnosis of Klebsiella was made.

Neurologic or neuropathologic lesions induced in humans or animals by halogenated derivatives of 8-hydroxyquinoline (Oakley, 1973; Murayama et al., 1974) were not observed in this study with 8-hydroxyquinoline.

8-Hydroxyquinoline is mutagenic in strain TA100 of Salmonella typhimurium and causes chromosomal aberrations in the bean plant Vicia faba; however, the compound gave equivocal or inconclusive results in a variety of other short-term tests (see Introduction). In NTP in vitro tests, 8-hydroxyquinoline did not induce either unscheduled DNA synthesis in rat hepatocytes or transformation of BALB/c-3T3 cells (Appendix M). These results are consistent with the lack of carcinogenicity in the present studies.

Conclusions: Under the conditions of these studies, there was no evidence of carcinogenicity* for male and female F344/N rats or for male and female B6C3F1 mice given 8-hydroxyquinoline in feed at concentrations of 1,500 or 3,000 ppm for 103 weeks.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
V. REFERENCES
V. REFERENCES


42. NCI/SRI Mark II. Data Base on Category E Drug Exposure (1978) National Cancer Institute, Contract No. N01-CP-33285.


47. Sadler Standard Spectra, IR No. 187, UV No. 76, NMR No. 24M.


APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE
### TABLE AI. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Segment</th>
<th>Control (U)</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANIMALS INITIALLY IN STUDY</strong></td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>ANIMALS NECROSIED</strong></td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>ANIMALS EXAMINED HISTOPATHOLOGICALLY</strong></td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>INTEGUMENTARY SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>SKIN</em></td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Squamous Cell Papilloma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Basal-Cell Carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>SUBCUT TISSUE</em></td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Carcinoma, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Sarcoma, NOS</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fibroma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RESPIRATORY SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUNG</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Carcinoma, NOS, Metastatic</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma, Metastatic</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Alveolar/Brachyoliar Adenoma</td>
<td>2 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar/Brachyoliar Carcinoma</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>C-Cell Carcinoma, Metastatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma, NOS, Metastatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma, NOS, Unc Prim or Meta</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma, Metastatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEMATOPOIETIC SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>MULTIPLE ORGANS</em></td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Malignant Lymphoma, NOS</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Malig. Lymphoma, Lymphocytic Type</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Malig. Lymphoma, Histiocytic Type</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia, Mononuclear Cell</td>
<td>17 (34%)</td>
<td>8 (16%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Spleen</td>
<td>(50)</td>
<td>(48)</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma, Invasive</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant Lymphoma, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandibular L. Node</td>
<td>(48)</td>
<td>(48)</td>
<td>(48)</td>
</tr>
<tr>
<td>Sarcoma, NOS, Unc Prim or Meta</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CIRCULATORY SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>(50)</td>
<td>(49)</td>
<td>(49)</td>
</tr>
<tr>
<td>Hemaniosarcoma</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Hemaniosarcoma, Metastatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>(49)</td>
<td>(48)</td>
<td>(48)</td>
</tr>
<tr>
<td>Hemaniosarcoma, Metastatic</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIGESTIVE SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary Gland</td>
<td>(49)</td>
<td>(46)</td>
<td>(49)</td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>(49)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td>Neoplastic Nodule</td>
<td>6 (12%)</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma, NOS, Metastatic</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

8-Hydroxyquinoline, NTP TR 276
<table>
<thead>
<tr>
<th>System</th>
<th>CONTROL (UNTR)</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIGESTIVE SYSTEM (Continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Pancreas</td>
<td>(47)</td>
<td>(48)</td>
<td>(45)</td>
</tr>
<tr>
<td># Acinar-Cell Adenoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Stomach</td>
<td>(50)</td>
<td>(49)</td>
<td>(46)</td>
</tr>
<tr>
<td>Mesothelioma, Invasive</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIGESTIVE SYSTEM (Continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Glandular Stomach</td>
<td>(50)</td>
<td>(49)</td>
<td>(46)</td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>URINARY SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Kidney</td>
<td>(50)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td>Tubular-Cell Adenoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ENDOCRINE SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Pituitary Adenoma, NOS</td>
<td>(48)</td>
<td>(50)</td>
<td>(47)</td>
</tr>
<tr>
<td># Pituitary Intermedia Adenoma, NOS</td>
<td>(48)</td>
<td>(50)</td>
<td>(47)</td>
</tr>
<tr>
<td># Adrenal Cortical Adenoma</td>
<td>(50)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td># Thyroid Adenoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>12 (24%)</td>
<td>8 (16%)</td>
<td>13 (27%)</td>
</tr>
<tr>
<td># Thyroid C-Cell Adenoma</td>
<td>(50)</td>
<td>(49)</td>
<td>(47)</td>
</tr>
<tr>
<td>C-Cell Carcinoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td># Parathyroid Adenoma, NOS</td>
<td>(18)</td>
<td>(20)</td>
<td>(20)</td>
</tr>
<tr>
<td># Pancreatic Islets</td>
<td>(47)</td>
<td>(48)</td>
<td>(45)</td>
</tr>
<tr>
<td>Islet-Cell Adenoma</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Islet-Cell Carcinoma</td>
<td>1 (2%)</td>
<td></td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>REPRODUCTIVE SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Mammary Gland</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>* Preputial Gland</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Carcinoma, NOS</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td># Testis</td>
<td>(47)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td>Interstitial-Cell Tumor</td>
<td>39 (83%)</td>
<td>42 (84%)</td>
<td>44 (92%)</td>
</tr>
<tr>
<td><strong>NERVOUS SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Brain</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Carcinoma, NOS, Invasive Astrocytoma</td>
<td>1 (2%)</td>
<td></td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>SPECIAL SENSE ORGANS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Zymbal Gland</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Carcinoma, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Skull</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

55 8-Hydroxyquinoline, NTP TR 276
**TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)**

<table>
<thead>
<tr>
<th>Body Cavities</th>
<th>Control (UNTR)</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Abdominal Cavity</em></td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><em>Tunica Vaginalis</em></td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Mesothelioma, NOS</td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma, Malignant</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| All Other Systems                    |                |            |            |
| Base of tail                         |                |            |            |
| Keratoacanthoma                      | 1              |            |            |

* Number of animals with tissue examined microscopically
*+ Number of animals necropsied

**Animal Disposition Summary**

<table>
<thead>
<tr>
<th>Animal Disposition</th>
<th>Control (UNTR)</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals initially in study</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Natural death</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Moribund sacrifice</td>
<td>12</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Scheduled sacrifice</td>
<td>28</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Terminal sacrifice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing accident</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidentally killed, NDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidentally killed, NOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal missing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal missexed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tumor Summary**

<table>
<thead>
<tr>
<th>Tumor Summary</th>
<th>Control (UNTR)</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total animals with primary tumors**</td>
<td>47</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Total primary tumors</td>
<td>120</td>
<td>112</td>
<td>113</td>
</tr>
<tr>
<td>Total animals with benign tumors</td>
<td>44</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Total benign tumors</td>
<td>82</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>Total animals with malignant tumors</td>
<td>27</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Total malignant tumors</td>
<td>32</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Total animals with secondary tumors##</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total secondary tumors</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Total animals with tumors uncertain-benign or malignant</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total uncertain tumors</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total animals with tumors uncertain-primary or metastatic</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total uncertain tumors</td>
<td></td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Tumors: All tumors except secondary tumors
Secondary Tumors: Metastatic tumors or tumors invasive into an adjacent organ**
<table>
<thead>
<tr>
<th>TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL (UNTR)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>ANIMALS INITIALLY IN STUDY</td>
</tr>
<tr>
<td>ANIMALS NECROPSIED</td>
</tr>
<tr>
<td>ANIMALS EXAMINED HISTOPATHOLOGICALLY</td>
</tr>
<tr>
<td><strong>INTEGUMENTARY SYSTEM</strong></td>
</tr>
<tr>
<td><em>SUBCUT TISSUE</em></td>
</tr>
<tr>
<td>SARCOMA, NOS</td>
</tr>
<tr>
<td>FIBROMA</td>
</tr>
<tr>
<td>FIBROSARCOMA</td>
</tr>
<tr>
<td>LEIOMYOSARCOMA</td>
</tr>
<tr>
<td><strong>RESPIRATORY SYSTEM</strong></td>
</tr>
<tr>
<td>LUNG</td>
</tr>
<tr>
<td>ALVEOLAR/BRONCHIOLAR ADENOMA</td>
</tr>
<tr>
<td>SARCOMA, NOS, METASTATIC</td>
</tr>
<tr>
<td>FIBROSARCOMA, METASTATIC</td>
</tr>
<tr>
<td><strong>HEMATOPOIETIC SYSTEM</strong></td>
</tr>
<tr>
<td><em>MULTIPLE ORGANS</em></td>
</tr>
<tr>
<td>MALIGNANT LYMPHOMA, NOS</td>
</tr>
<tr>
<td>LEUKEMIA, NOS</td>
</tr>
<tr>
<td>LEUKEMIA, MONONUCLEAR CELL</td>
</tr>
<tr>
<td><strong>CIRCULATORY SYSTEM</strong></td>
</tr>
<tr>
<td>NONE</td>
</tr>
<tr>
<td><strong>DIGESTIVE SYSTEM</strong></td>
</tr>
<tr>
<td>LIVER</td>
</tr>
<tr>
<td>NEOPLASTIC NODULE</td>
</tr>
<tr>
<td>HEPATOCELLULAR CARCINOMA</td>
</tr>
<tr>
<td>#ILEAL SUBMUCOSA</td>
</tr>
<tr>
<td>SARCOMA, NOS</td>
</tr>
<tr>
<td>#CECUM</td>
</tr>
<tr>
<td>SARCOMA, NOS</td>
</tr>
<tr>
<td><strong>URINARY SYSTEM</strong></td>
</tr>
<tr>
<td>#KIDNEY</td>
</tr>
<tr>
<td>SARCOMA, NOS, METASTATIC</td>
</tr>
<tr>
<td>#URINARY BLADDER</td>
</tr>
<tr>
<td>TRANSITIONAL-CELL PAPILLOMA</td>
</tr>
<tr>
<td><strong>ENDOCRINE SYSTEM</strong></td>
</tr>
<tr>
<td>#PITUITARY</td>
</tr>
<tr>
<td>CARCINOMA, NOS</td>
</tr>
<tr>
<td>ADENOMA, NOS</td>
</tr>
<tr>
<td>#ADRENAL</td>
</tr>
<tr>
<td>CORTICAL ADENOMA</td>
</tr>
<tr>
<td>CORTICAL CARCINOMA</td>
</tr>
<tr>
<td>PHEOCHROMOCYTOMA</td>
</tr>
<tr>
<td>GANGLIONEUROMA</td>
</tr>
<tr>
<td>#THYROID</td>
</tr>
<tr>
<td>C-CELL ADENOMA</td>
</tr>
<tr>
<td>C-CELL CARCINOMA</td>
</tr>
<tr>
<td>#PARATHYROID</td>
</tr>
<tr>
<td>ADENOMA, NOS</td>
</tr>
<tr>
<td>TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>REPRODUCTIVE SYSTEM</strong></td>
</tr>
<tr>
<td>*MAMMARY GLAND</td>
</tr>
<tr>
<td>ADENOMA, NOS</td>
</tr>
<tr>
<td>FIBROADENOMA</td>
</tr>
<tr>
<td>*CLITORAL GLAND</td>
</tr>
<tr>
<td>ADENOMA, NOS</td>
</tr>
<tr>
<td>UTERUS</td>
</tr>
<tr>
<td>ENDOMETRIAL STROMAL POLYP</td>
</tr>
<tr>
<td>ENDOMETRIAL STROMAL SARCOMA</td>
</tr>
<tr>
<td>OVARY</td>
</tr>
<tr>
<td>GRANULOSA-CELL TUMOR</td>
</tr>
<tr>
<td>SERTOLI-CELL TUMOR</td>
</tr>
<tr>
<td><strong>NERVOUS SYSTEM</strong></td>
</tr>
<tr>
<td>BRAIN</td>
</tr>
<tr>
<td>ASTROCYTOMA</td>
</tr>
<tr>
<td><strong>SPECIAL SENSE ORGANS</strong></td>
</tr>
<tr>
<td>*EAR</td>
</tr>
<tr>
<td>FIBROSARCOMA</td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL SYSTEM</strong></td>
</tr>
<tr>
<td><strong>BODY CAVITIES</strong></td>
</tr>
<tr>
<td><strong>ALL OTHER SYSTEMS</strong></td>
</tr>
<tr>
<td><strong>NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY</strong></td>
</tr>
<tr>
<td><strong>NUMBER OF ANIMALS NECROPSIED</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONTROL (UNTR)</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>19 (38%)</td>
<td>15 (30%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>11 (22%)</td>
<td>13 (27%)</td>
<td>14 (29%)</td>
</tr>
<tr>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>(49)</td>
<td>(49)</td>
<td>(49)</td>
</tr>
<tr>
<td>2 (4%)</td>
<td>13 (26%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>2 (4%)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

8-Hydroxyquinoline, NTP TR 276  58
<table>
<thead>
<tr>
<th>ANIMAL DISPOSITION SUMMARY</th>
<th>CONTROL (UNTR)</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANIMALS INITIALLY IN STUDY</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>NATURAL DEATH</td>
<td>5</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>MORIBUND SACRIFICE</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>SCHEDULED SACRIFICE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TERMINAL SACRIFICE</td>
<td>36</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>DOSING ACCIDENT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCIDENTALLY KILLED, NDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCIDENTALLY KILLED, NOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANIMAL MISSING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANIMAL MISSEXED</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TUMOR SUMMARY</th>
<th>CONTROL (UNTR)</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL ANIMALS WITH PRIMARY TUMORS**</td>
<td>40</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>TOTAL PRIMARY TUMORS</td>
<td>79</td>
<td>76</td>
<td>90</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH BENIGN TUMORS</td>
<td>37</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>TOTAL BENIGN TUMORS</td>
<td>62</td>
<td>65</td>
<td>71</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH MALIGNANT TUMORS</td>
<td>12</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>TOTAL MALIGNANT TUMORS</td>
<td>13</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH SECONDARY TUMORS##</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL SECONDARY TUMORS</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL UNCERTAIN TUMORS</td>
<td>4</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL UNCERTAIN TUMORS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
## SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
### TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE: UNTREATED CONTROL

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Tumors</th>
<th>Untreated Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
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<tr>
<td>Lungs and</td>
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</tr>
<tr>
<td>Bronchi</td>
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</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td></td>
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</tr>
<tr>
<td>Liver</td>
<td></td>
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</tr>
<tr>
<td>Gallbladder</td>
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<tr>
<td>Bile duct</td>
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<tr>
<td>Gallbladder &amp; common bile duct</td>
<td></td>
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<tr>
<td>Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
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<tr>
<td>Stomach</td>
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<td>Intestine</td>
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<td>Orphan</td>
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<td>Urinary bladder</td>
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<td>Pituitary</td>
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<td>Reproductive</td>
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<td>Mammary gland</td>
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<td>All Other Systems</td>
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</tbody>
</table>

*Note: Table shows tumor incidence in specific organs and tissues for male rats in the two-year feed study of 8-hydroxyquinoline.*
TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL

(Continued)

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>HISTOLOGY</th>
<th>ANIMAL</th>
<th>HISTOLOGY</th>
<th>ANIMAL</th>
<th>HISTOLOGY</th>
<th>ANIMAL</th>
<th>HISTOLOGY</th>
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<td>4</td>
<td></td>
<td>5</td>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**INTEROCULAR SYSTEM**
- BOTH:
  - **SQUAMOUS CELL CARCINOMA**: 0
  - **BASAL-CELL CARCINOMA**: 0
- **SUBCUTANEOUS TISSUE**:
  - **SQUAMOUS**: 0
  - **BASAL**: 0

**RESPIRATORY SYSTEM**
- LUNG:
  - **SQUAMOUS CELL CARCINOMA, METASTASIS**: 0
  - **TRACHEA**: 0

**HEMATOPOietic SYSTEM**
- **BONE MARROW**: 0
- **SPLEEN**:
  - **METASTASIS, INVASIVE HODGKIN'S CARCINOMA**: 0
- **LYMPH NODE**: 0
- **THYMUS**: 0

**CIRCULATORY SYSTEM**
- **HEART**: 0

**Gastrointestinal System**
- **SALIVARY GLAND**:
  - **NEOPLASMS**:
    - **HYPOPHYSIOPATHIC**: 0
- **LIVER**:
  - **HEPATOCELLULAR CARCINOMA**: 0
- **BILE DUCT**:
  - **HEPATOCELLULAR CARCINOMA**: 0
- **GALLBLADDER & COMMON BILE DUCT**:
  - **CARCINOMA**: 0
- **PANCREAS**:
  - **MALIGNANT CYSTIC NEOPLASM**: 0
- **ESOPHAGUS**: 0
- **STOMACH**:
  - **MALIGNANT CYSTIC NEOPLASM**: 0
  - **MALIGNANT CYSTIC NEOPLASM, INVASIVE**: 0
- **SMALL INTESTINE**: 0
- **LARGE INTESTINE**: 0

**Urinary System**
- **URINARY TUBULAR-CELL ADENOMA**: 0
- **URINARY BLADDER**: 0

**Endocrine System**
- **PITUITARY**:
  - **ADENOMA, NOS**: 0
- **ADRENAL**:
  - **CORTICAL ADENOMA**: 0
  - **PHAEOMELANOTIC**: 0
  - **THYMID C-CELL ADENOMA**: 0
- **PARATHYROID**:
  - **PARATHYROID ADENOMA**: 0
  - **PARATHYROID ADENOMA, NOS**: 0

**Reproductive System**
- **REPRODUCTIVE SYSTEM**:
  - **TESTIS**:
    - **NEOPLASM, INTESTINAL-CELL TUMOR**: 0
  - **PROSTATE**: 0
  - **PREPUTIAL/CLITORAL GLAND**:
    - **CARCINOMA, NOS**: 0
    - **ADENOMA, NOS**: 0

**Nervous System**
- **BRAIN**: 0

**Special Sensitive Organs**
- **BRAIN**: 0

**Miscellaneous System**
- **BONE**:
  - **OSTEOCARCINOMA**: 0

**Body Cavities**
- **PERITONEUM**: 0

**Other Systems**
- **MULTIPLE ORGANS NOS**:
  - **LYMPHOMA, NON-HODGKIN'S**:
    - **MALIGNANT, HISTIOCYTIC TYPE**:
      - **MALIGNANT, HISTIOCYTIC TYPE LEUKEMIA, MONONUCLEAR CELL**:
      - **MALIGNANT, CLEAN, NOS**: 0

**Side Effects**
- **THYMUS**: 0

**Animals Necropsied**: 0

---

*Animals Necropsied*
TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE: LOW DOSE

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<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
</tr>
</thead>
</table>

**INTERMEDIAN SYSTEM**
- NEXUS: BASAL-CELL CARCINOMA
- SUBSTANTOEUS TISSUE: BASAL-CELL CARCINOMA
- NOE: BASAL-CELL CARCINOMA

**NEPHROEPITHELIAL SYSTEM**
- BONE MARROW: SALLARY GLAND
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**RENAL SYSTEM**
- BONE MARROW: ADRENAL CARCINOMA
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**CONDUCTOR SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**NERVOUS SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**EXTRA-ADRENAL SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**ADRENAL SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**CIRCULATORY SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**LIVER SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**BONE MARROW**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**LYMPH SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**THYROID SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**HEAD SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**NECK SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**BRAIN SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**SPECIAL SENSE BLAST**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**SPECIAL NERVE BLAST**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**GENETIC SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

**UROGENITAL SYSTEM**
- NEXUS: ADRENAL CARCINOMA
- SUBSTANTOEUS TISSUE: ADRENAL CARCINOMA

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### Table A3. Individual Animal Tumor Pathology of Male Rats: Low Dose (Continued)

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Tumor Type</th>
<th>Male Rats</th>
<th>Female Rats</th>
<th>Total Rats</th>
</tr>
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<tbody>
<tr>
<td>Integumentary System</td>
<td>Squamous Cell Papilloma</td>
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<td>1</td>
<td>2</td>
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<tr>
<td>Respiratory System</td>
<td>Lungs and Bronchi: Carcinoma, Malignant, Metastatic</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Hematopoietic System</td>
<td>Spleen: Hemangiosarcoma</td>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Circulatory System</td>
<td>Heart</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Digestive System</td>
<td>Salivary Gland</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Liver: Hepatoma, Hepatocellular Carcinoma, Metastatic</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomach: Eosinophilic Gastritis</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
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<td>Pancreas</td>
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<td>2</td>
</tr>
<tr>
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<td>Large Intestine</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Urogenital System</td>
<td>Bladder</td>
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<td>Uterus</td>
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</tr>
<tr>
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<td>Testis</td>
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<td>2</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
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<td>1</td>
<td>2</td>
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<tr>
<td></td>
<td>Reproductive System</td>
<td>Urethra</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Special Senses System</td>
<td>Ears, Nerve, and Retina</td>
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<td>1</td>
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<tr>
<td></td>
<td>Body Cavities</td>
<td>Peritoneum: Mesothelioma</td>
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<tr>
<td></td>
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<td>Osteosarcoma</td>
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<td>1</td>
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<tr>
<td></td>
<td></td>
<td>Soft Tissue: Hemangiopericytoma</td>
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</tr>
<tr>
<td></td>
<td>All Other Systems</td>
<td>Nerve, Ovarian, Male Germ Cells</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Numbers indicate the number of animals affected by each type of tumor.
TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE: HIGH DOSE

<table>
<thead>
<tr>
<th>ANIMAL NUMBER</th>
<th>TOTAL TISSUE TUMORS</th>
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</thead>
<tbody>
<tr>
<td></td>
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</table>

**TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)**

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>ANIMAL NUMBER</th>
<th>TOTAL TISSUE TUMORS</th>
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</thead>
<tbody>
<tr>
<td>Integumentary System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-Cell Carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma, HGS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleomastoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs and Bronchial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar/Bronchiolar adenoma</td>
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<td></td>
</tr>
<tr>
<td>Small airway/bronchiolar</td>
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<td></td>
</tr>
<tr>
<td>Sarcoma, HGS</td>
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</tr>
<tr>
<td>Metastatic</td>
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<tr>
<td>Bones and cartilage</td>
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<tr>
<td>Osteosarcoma, Metastatic</td>
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</tr>
<tr>
<td>Mammary Gland</td>
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</tr>
<tr>
<td>Mammary Gland</td>
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<tr>
<td>Thyroid</td>
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</tr>
<tr>
<td>C-Cell Carcinoma</td>
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</tr>
<tr>
<td>Adenoma, HGS</td>
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<tr>
<td>Adrenal</td>
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<td>Phaeochromocytoma</td>
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<td>Intestine</td>
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</tr>
<tr>
<td>Spleen</td>
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<td>Lymph Nodes</td>
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<td>Thymus</td>
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<tr>
<td>Circulatory System</td>
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</tr>
<tr>
<td>Heart</td>
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</tr>
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<td>Salivary Gland</td>
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</tr>
<tr>
<td>Liver</td>
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</tr>
<tr>
<td>Neoepithelial Nodule</td>
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<td>Duodenum</td>
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<td>Gallbladder &amp; common bile duct</td>
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<td>Pancreas</td>
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<td>Acinar-Cell adenoma</td>
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<td>Stomach</td>
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</tr>
<tr>
<td>Renal System</td>
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</tr>
<tr>
<td>Kidney</td>
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</tr>
<tr>
<td>Urinary Bladder</td>
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<td>Endocrine System</td>
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</tr>
<tr>
<td>Pituitary</td>
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<td></td>
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<tr>
<td>Adenoma, HGS</td>
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<tr>
<td>Adrenal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasms</td>
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<tr>
<td>Thyroid</td>
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<td>C-Cell Carcinoma</td>
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<td>Neoplasms</td>
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<td>Reproductive System</td>
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<td>Neoplasms</td>
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<td>Spinal cord</td>
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<tr>
<td>All other systems</td>
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</tr>
<tr>
<td>Multiple organs</td>
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<tr>
<td>Kidney, bladder</td>
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<tr>
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<td>All other systems</td>
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</tbody>
</table>

* Animals necropsied

8-Hydroxyquinoline, NTP TR 276
### TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE: UNTREATED CONTROL

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<tr>
<td>SUBCUTANEOUS TISSUE</td>
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- **T** Tissue examined microscopically
- **T** Tissue not examined microscopically
- **H** Tissue examined histologically
- **H** Tissue not histologically due to protocol
- **T** Tumor incidence
- **T** Tumor incidence
- **H** Necropsy, no autolysis, no microscopic examination
- **H** Animal missing
- **S** Animal mis-sexed

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* ANIMALS HECROSPIED

8-Hydroxyquinoline, NTP TR 276
<p>| ANIMAL NUMBER | WEEKS ON STUDY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
|---------------|----------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| INTEROCYANIC SYSTEM | SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | X | + | + | + | + | + | + | + | + | + | + |
| | SARCOMA, NOS | X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | LEIOMYSARCOMA | X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| RESPIRATORY SYSTEM | LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | ALVEolar-BRONCHIOLAR ADENoMA | X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | SARCOMA, NOS, METASTATIC | X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATIC SYSTEM | BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | LYMPH NODES | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | THYME | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CIRCULATORY SYSTEM | HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| DIGESTIVE SYSTEM | SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | NESPLOMATIC MODULE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | GALLBLADDER &amp; COMMON BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | SARCOCMA, NOS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY SYSTEM | URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | TRANSITIONAL-CELL PAPILLOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ENDOCRINE SYSTEM | PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | PARATHYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| REPRODUCTIVE SYSTEM | UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | HEMORRHoidal POLYP | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | ENDOMETRIAL STROMAL SARCOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GYNECOLOGICAL SYSTEM | UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | HEMORRHoidal POLYP | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | ENDOMETRIAL STROMAL SARCOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | BONE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | SKIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | MULTIPLE ORGANS NOS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | NOS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | LEUKEMIA, LYMPHOCYTIC CELL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |</p>
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</table>

8-Hydroxyquinoline, NTP TR 276
# TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

| ANIMAL NUMBER | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | TOTAL TISSUES |
|---------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|--------------------------------------------------|
| 1. INTEGUMENTARY SYSTEM | FIBROMA | X | | | | | | | | | | | | | | | | | | | | |
| 2. RESPIRATORY SYSTEM | LUNG AND BRONCHI | ALVEOLAR/BRONCHIOLEAR ADENOMA | | | | | | | | | | | | | | | | | | | | |
| 3. TRACHEA | | | | | | | | | | | | | | | | | | | | | | |
| 4. HEMATOPOIETIC SYSTEM | BONE MARROW | | | | | | | | | | | | | | | | | | | | |
| 5. DIGESTIVE SYSTEM | LIVER | NEOPLASTIC MODULE | BILE DUCT | | | | | | | | | | | | | | | | | | |
| 6. PANCREAS | | | | | | | | | | | | | | | | | | | | |
| 7. Spleen | | | | | | | | | | | | | | | | | | | | |
| 8. LYMPH NODES | | | | | | | | | | | | | | | | | | | | |
| 9. THYMUS | | | | | | | | | | | | | | | | | | | | |
| 10. CIRCULATORY SYSTEM | HEART | | | | | | | | | | | | | | | | | | | | |
| 11. URINARY SYSTEM | KIDNEY | | | | | | | | | | | | | | | | | | | | |
| 12. URETER | | | | | | | | | | | | | | | | | | | | |
| 13. BLADDER | | | | | | | | | | | | | | | | | | | | |
| 14. REPRODUCTIVE SYSTEM | OVARY | | | | | | | | | | | | | | | | | | | | |
| 15. UTERUS | | | | | | | | | | | | | | | | | | | | |
| 16. UTERUS | | | | | | | | | | | | | | | | | | | | |
| 17. NERVOUS SYSTEM | BRAIN | | | | | | | | | | | | | | | | | | | | |
| 18. ALL OTHER SYSTEMS | | | | | | | | | | | | | | | | | | | | |

- Animals necropsied

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*8-Hydroxyquinoline, NTP TR 276*
APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE
<p>| TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE |
|-------------------------------------------------|-----------------|-----------------|
| CONTROL (UNTR) | LOW DOSE | HIGH DOSE |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| <strong>SKIN</strong> | (50) | (50) | (50) |
| KERATOACANTHOMA | 1 (2%) | 1 (2%) | |
| SARCOMA, NOS | 1 (2%) | 1 (2%) | |
| <strong>SUBCUT TISSUE</strong> | (50) | (50) | (50) |
| SARCOMA, NOS | 6 (12%) | 7 (14%) | 9 (18%) |
| FIBROMA | 1 (2%) | 2 (4%) | |
| FIBROSARCOMA | 1 (2%) | 1 (2%) | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| <strong>LUNG</strong> | (50) | (49) | (50) |
| NEOPLASM, NOS, METASTATIC | 1 (2%) | 1 (2%) | 1 (2%) |
| NEOPLASM, NOS, UNC PRIM OR META | | | |
| HEPATOCELLULAR CARCINOMA, METAST | 1 (2%) | 2 (4%) | |
| ALVEOLAR/BRONCHIOCARCINOMA, ADENOMA | 5 (10%) | 9 (18%) | 9 (18%) |
| ALVEOLAR/BRONCHIOCARCINOMA | 1 (2%) | 1 (2%) | 1 (2%) |
| SARCOMA, NOS, METASTATIC | 1 (2%) | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| <strong>MULTIPLE ORGANS</strong> | (50) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 7 (14%) | 1 (2%) | 3 (6%) |
| MALIGNANT LYMPHOMA, UNDIFFER-TYPE | | | |
| MALIGNANT LYMPHOMA, LYMPHOCYTIC TYPE | | 3 (6%) | 1 (2%) |
| MALIGNANT LYMPHOMA, HISTIOCYTIC TYPE | 1 (2%) | 1 (2%) | |
| <strong>SPLAEN</strong> | (49) | (48) | (50) |
| MALIGNANT LYMPHOMA, NOS | 1 (2%) | | |
| <strong>LYMPH NODE</strong> | (44) | (45) | (42) |
| HEPATOCELLULAR CARCINOMA, METAST | | | |
| MALIGNANT LYMPHOMA, NOS | 2 (5%) | | |
| <strong>LIVER</strong> | (50) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 1 (2%) | | |
| <strong>GASTRIC SEROSA</strong> | (47) | (49) | (50) |
| MAST-CELL TUMOR | 1 (2%) | 1 (2%) | |
| PEYERS PATCH | (43) | (45) | (47) |
| MALIGNANT LYMPHOMA, NOS | 1 (2%) | 1 (2%) | |
| <strong>THYMUS</strong> | (20) | (27) | (26) |
| MALIGNANT LYMPHOMA, NOS | 1 (2%) | | |
| CIRCULATORY SYSTEM | | | |
| <strong>ABDOMINAL CAVITY</strong> | (50) | (50) | (50) |
| HEMANGIOMA | 1 (2%) | 1 (2%) | |
| <strong>SUBCUT TISSUE</strong> | (50) | (50) | (50) |
| HEMANGIOMA | 1 (2%) | 1 (2%) | |
| HEMANGIOSARCOMA | 1 (2%) | 1 (2%) | |
| <strong>SPLAEN</strong> | (49) | (48) | (50) |
| HEMANGIOMA | 3 (6%) | 1 (2%) | |
| HEMANGIOSARCOMA | 1 (2%) | 1 (2%) | 1 (2%) |
| <strong>LYMPH NODE</strong> | (44) | (45) | (42) |
| HEMANGIOMA | 1 (2%) | | |
| <strong>HEART</strong> | (50) | (50) | (49) |
| ALVEOLAR/BRONCHIOCARCINOMA, METAST | 1 (2%) | | |
| <strong>LIVER</strong> | (50) | (50) | (50) |
| HEMANGIOMA | 2 (4%) | | |
| HEMANGIOSARCOMA | 2 (4%) | | |</p>
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<td>7 (14%)</td>
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<td>Sarcoma, Nos, Unc Prim Or Meta</td>
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<td>(49)</td>
<td>(50)</td>
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<td>(50)</td>
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<td>Alveolar/bronchiolar ca, metastasis</td>
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<td>Tubular-cell adenocarcinoma</td>
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<td>(46)</td>
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<td>(46)</td>
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<td>Cortical Adenoma</td>
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<td>4 (8%)</td>
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TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

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<td>SARCOMA, NOS</td>
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# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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<th>ANIMALS INITIALLY IN STUDY</th>
<th>NATURAL DEATH</th>
<th>MORIBUND SACRIFICE</th>
<th>SCHEDULED SACRIFICE</th>
<th>TERMINAL SACRIFICE</th>
<th>DOSSING ACCIDENT</th>
<th>ACCIDENTALLY KILLED, NDA</th>
<th>ACCIDENTALLY KILLED, NOS</th>
<th>ANIMAL MISSING</th>
<th>ANIMAL MISSEXED</th>
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<td>29</td>
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</table>

TUMOR SUMMARY

| TOTAL ANIMALS WITH PRIMARY TUMORS** | 35 | 35 | 35 |
| TOTAL PRIMARY TUMORS               | 56 | 67 | 55 |
| TOTAL ANIMALS WITH BENIGN TUMORS   | 25 | 21 | 25 |
| TOTAL BENIGN TUMORS                | 29 | 34 | 31 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS| 22 | 22 | 21 |
| TOTAL MALIGNANT TUMORS             | 27 | 31 | 23 |
| TOTAL ANIMALS WITH SECONDARY TUMORS## | 2 | 4 | 1 |
| TOTAL SECONDARY TUMORS             | 2 | 8 | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | 1 |   |   |
| TOTAL UNCERTAIN TUMORS             | 1 |   |   |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | 1 |   |   |
| TOTAL UNCERTAIN TUMORS             | 1 |   |   |

** 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 IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

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<th>CONTROL (UNTR)</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANIMALS INITIALLY IN STUDY</td>
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<td>50</td>
<td>50</td>
</tr>
<tr>
<td>ANIMALS NECROPSIED</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>ANIMALS EXAMINED HISTOPATHOLOGICALLY</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>INTEGUMENTARY SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*SUBCUT TISSUE</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>SARCOMA, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>RESPIRATORY SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#LUNG</td>
<td>(49)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>NEOPLASM, NOS, UNC PRIM OR META</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEPATOCELLULAR CARCINOMA, METAST</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>ALVEOLAR/BRONCHIOHAR ADENOMA</td>
<td>1 (2%)</td>
<td>5 (10%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>ADENOSQUAMOUS CARCINOMA, METAST</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>PHEOCHROMOCYTOMA, METASTATIC</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SARCOMA, NOS, METASTATIC</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSTEOSARCOMA, METASTATIC</td>
<td></td>
<td></td>
<td>1 (2%)</td>
</tr>
<tr>
<td>HEMATOPOIETIC SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*MULTIPLE ORGANS</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>SARCOMA, NOS</td>
<td>8 (16%)</td>
<td>10 (20%)</td>
<td>6 (12%)</td>
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<tr>
<td>MALIG. LYMPHOMA, UNDIFFER-TYPE</td>
<td>2 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALIG. LYMPHOMA, HISTIOCYTIC TYPE</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>MALIG. LYMPHOMA, AUTOLOGOUS TYPE</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>#SPLICE</td>
<td>(49)</td>
<td>(48)</td>
<td>(47)</td>
</tr>
<tr>
<td>MALIG. LYMPHOMA, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>#UTERUS</td>
<td>(50)</td>
<td>(47)</td>
<td>(49)</td>
</tr>
<tr>
<td>MALIG. LYMPHOMA, HISTIOCYTIC TYPE</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CIRCULATORY SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*SUBCUT TISSUE</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>HEMANGIOSARCOMA</td>
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<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>#Lymph Node</td>
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<td>(47)</td>
<td>(44)</td>
</tr>
<tr>
<td>HEMANGIOMA</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>#LIVER</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>HEMANGIOMA</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>#OVARY</td>
<td>(43)</td>
<td>(46)</td>
<td>(43)</td>
</tr>
<tr>
<td>HEMANGIOMA</td>
<td>2 (4%)</td>
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<td></td>
</tr>
<tr>
<td>DIGESTIVE SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#SALIVARY GLAND</td>
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<td>(46)</td>
<td>(48)</td>
</tr>
<tr>
<td>SARCOMA, NOS, INVASIVE</td>
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<td></td>
</tr>
<tr>
<td>#LIVER</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>HEPATOCELLULAR ADENOMA</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
</tr>
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<td>HEPATOCELLULAR CARCINOMA</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
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</tr>
<tr>
<td>#DUODENUM</td>
<td>(43)</td>
<td>(44)</td>
<td>(45)</td>
</tr>
<tr>
<td>ADENOMATOUS POLYP, NOS</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>URINARY SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#KIDNEY</td>
<td>(49)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td>TUBULAR-CELL ADENOMA</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>SARCOMA, NOS, METASTATIC</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
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77 8-Hydroxyquinoline, NTP TR 276
TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>CONTROL (UNTR)</th>
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<th>HIGH DOSE</th>
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<tbody>
<tr>
<td>ENDOCRINE SYSTEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma, NOS</td>
<td>(40)</td>
<td>(44)</td>
<td>(37)</td>
</tr>
<tr>
<td>Adrenal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>12 (30%)</td>
<td>14 (32%)</td>
<td>11 (30%)</td>
</tr>
<tr>
<td>Pheochromocytoma, Malignant</td>
<td>(49)</td>
<td>(48)</td>
<td>(47)</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>(48)</td>
<td>(48)</td>
<td>(47)</td>
</tr>
<tr>
<td>Follicular-cell Adenoma</td>
<td>4 (8%)</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Follicular-cell Carcinoma</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic islets</td>
<td>(47)</td>
<td>(47)</td>
<td>(45)</td>
</tr>
<tr>
<td>Islet-cell Adenoma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammary gland</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Adenosquamous Carcinoma</td>
<td>(50)</td>
<td>(47)</td>
<td>(49)</td>
</tr>
<tr>
<td>Uterus</td>
<td>1 (2%)</td>
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<td></td>
</tr>
<tr>
<td>Endometrial stromal polyp</td>
<td>(43)</td>
<td>(46)</td>
<td>(43)</td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystadenoma, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary Cystadenoma, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulosa-cell tumor</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>(49)</td>
<td>(50)</td>
<td>(47)</td>
</tr>
<tr>
<td>Meningioma</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special sense organs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harderian gland</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Adenoma, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Squamous cell papilloma</td>
<td>1 (2%)</td>
<td></td>
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</tr>
<tr>
<td>Musculoskeletal system</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body cavities</td>
<td>None</td>
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</tr>
<tr>
<td>All other systems</td>
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<td></td>
</tr>
<tr>
<td>Leg</td>
<td></td>
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</tr>
<tr>
<td>Osteosarcoma</td>
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# Number of animals with tissue examined microscopically
* Number of animals necropsied

8-Hydroxyquinoline, NTP TR 276 78
### Table B2. Summary of the Incidence of Neoplasms in Female Mice in the Two-Year Feed Study of 8-Hydroxyquinoline (Continued)

<table>
<thead>
<tr>
<th>ANIMAL DISPOSITION SUMMARY</th>
<th>CONTROL (UNTR)</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
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<td>ANIMALS INITIALLY IN STUDY</td>
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<td>50</td>
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<tr>
<td>NATURAL DEATH</td>
<td>25</td>
<td>22</td>
<td>21</td>
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<tr>
<td>MORIBUND SACRIFICE</td>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>SCHEDULED SACRIFICE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TERMINAL SACRIFICE</td>
<td>24</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>DOSING ACCIDENT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCIDENTALLY KILLED, NDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCIDENTALLY KILLED, NOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANIMAL MISSING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANIMAL MISSEXED</td>
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</table>

<table>
<thead>
<tr>
<th>TUMOR SUMMARY</th>
<th>CONTROL (UNTR)</th>
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<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL ANIMALS WITH PRIMARY TUMORS**</td>
<td>33</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>TOTAL PRIMARY TUMORS</td>
<td>46</td>
<td>49</td>
<td>41</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH BENIGN TUMORS</td>
<td>19</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>TOTAL BENIGN TUMORS</td>
<td>25</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH MALIGNANT TUMORS</td>
<td>19</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>TOTAL MALIGNANT TUMORS</td>
<td>21</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>TOTAL ANIMALS WITH SECONDARY TUMORS##</td>
<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>TOTAL SECONDARY TUMORS</td>
<td>4</td>
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<td>3</td>
</tr>
</tbody>
</table>

** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
## SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE: UNTREATED CONTROL

<table>
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<tr>
<th>Tissue Type</th>
<th>Male Mice</th>
<th>Female Mice</th>
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<tr>
<td>INTERDIGITANT SYSTEM</td>
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<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SARCOMA, MGB</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EPHEDRINUM</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>RESPIRATORY SYSTEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUNG AND TRACHEA</td>
<td>X</td>
<td>X</td>
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<tr>
<td>NEUROECTODERMAL CARCINOMA, METASTATIC</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NEOPLASTIC ELEMENTARY CARCINOMA</td>
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<td></td>
</tr>
<tr>
<td>LYMPHOCYTIC ABDOMINAL EDEMA</td>
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</tr>
<tr>
<td>SARCINA, MGB, METASTATIC</td>
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<td></td>
</tr>
<tr>
<td>TRACHEA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EOSINOPHILIC SYSTEM</td>
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<td></td>
</tr>
<tr>
<td>BONE MARROW</td>
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</tr>
<tr>
<td>EPHEDRINUM</td>
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<td></td>
</tr>
<tr>
<td>CORTICAL CARCINOMA</td>
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<td></td>
</tr>
<tr>
<td>MALIGNANT LYMPHOMA, MGB</td>
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<td></td>
</tr>
<tr>
<td>LYMPH NODES</td>
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</tr>
<tr>
<td>CYANIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALIGNANT LYMPHOMA, MGB</td>
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<td>X</td>
</tr>
<tr>
<td>THYMUS</td>
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<td>CIRCULATORY SYSTEM</td>
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<td></td>
</tr>
<tr>
<td>HEART</td>
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<td></td>
</tr>
<tr>
<td>DIGESTIVE SYSTEM</td>
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<td></td>
</tr>
<tr>
<td>SALIVARY GLAND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIVER</td>
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<td></td>
</tr>
<tr>
<td>NEUROECTODERMAL CARCINOMA, METASTATIC</td>
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<tr>
<td>NEOPLASTIC ELEMENTARY CARCINOMA</td>
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<td>GALLBLADDER &amp; COMMON BILE DUCT</td>
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<td>ESOPHAGUS</td>
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<td>STOMACH</td>
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<td>SMALL INTESTINE</td>
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<td>LARGE INTESTINE</td>
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<tr>
<td>URINARY SYSTEM</td>
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</tr>
<tr>
<td>KIDNEY</td>
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<tr>
<td>URETHRAL GLAND</td>
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<td>ENDOCRINE SYSTEM</td>
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<td>ADRENAL</td>
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<td>GONADAL, MGB</td>
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<td>MAMMARY GLAND</td>
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<tr>
<td>TESTIS</td>
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<td>PROSTATE</td>
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<td>CNS SYSTEM</td>
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<tr>
<td>MALIGNANT LYMPHOMA, MGB</td>
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</tr>
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</table>

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### TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE: LOW DOSE

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</tr>
</tbody>
</table>

**Respiratory System**
- Lungs and bronchi: hepatocellular carcinoma, metastatic
- Bronchus: adenocarcinoma
- Lungs: adenocarcinoma, metastatic
- Bronchi: melanoma, metastatic

**Gastrointestinal System**
- Stomach: adenocarcinoma
- Liver: hepatocellular carcinoma, metastatic
- Stomach: adenocarcinoma
- Liver: hepatocellular carcinoma, metastatic
- Gallbladder and cystic bile duct: adenocarcinoma
- Pancreas: adenocarcinoma
- Stomach: adenocarcinoma
- Liver: hepatocellular carcinoma, metastatic
- Spleen: adenocarcinoma
- Lung: adenocarcinoma
- Stomach: adenocarcinoma
- Spleen: adenocarcinoma
- Lung: adenocarcinoma

**Urinary System**
- Kidney: renal-cell adenocarcinoma
- Urinary bladder: adenocarcinoma
- Prostate: adenocarcinoma

**Endocrine System**
- Hypothalamus: adenoma
- Adrenal: adenoma
- Brain: adenoma
- Pituitary: adenoma
- Thyroid: adenoma
- Parathyroid: adenoma

**Reproductive System**
- Testes
- Uterus

**Eye**
- Cataract

**Bone Marrow**
- Aplasia

**Lymph Nodes**
- Metastatic

**Adrenal Gland**
- Melanoma, metastatic

**Other Sites**
- Skin: melanoma, metastatic
- Adrenal gland: melanoma, metastatic
- Skin: melanoma, metastatic
- Skin: melanoma, metastatic

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TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

<table>
<thead>
<tr>
<th>ANIMAL HUMOR</th>
<th>WEEKS OF STUDY</th>
<th>TOTAL TUMORS</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>INTERMEDIATE SYSTEM</td>
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<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ependymoma, HNS, metastatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma, HNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary gland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcina, HNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma, HNS</td>
<td></td>
<td>583</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
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</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs and Bronchi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial epithe-mal hyperplasia, HNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial adenoma, HNS, metastatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma, HNS</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Adenocarcinoma, HNS, metastatic</td>
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<tr>
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<tr>
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<td>Circulatory System</td>
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<td>Heart</td>
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<tr>
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</tr>
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<td>Sarcoma, HNS</td>
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<td>Objective System</td>
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<tr>
<td>Salivary gland</td>
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</tr>
<tr>
<td>Liver</td>
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</tr>
<tr>
<td>Hepatocellular adenoma</td>
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</tr>
<tr>
<td>Hepatocellular adenoma, HNS</td>
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</tr>
<tr>
<td>Hepatocellular adenoma, HNS, or meta</td>
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<tr>
<td>Malignant lymphoma, HNS</td>
<td></td>
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<tr>
<td>Bile duct</td>
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<td></td>
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<tr>
<td>Gallbladder &amp; common bile duct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethra</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, HNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular adenoma, HNS, metastatic</td>
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<tr>
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<tr>
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<td>Adenocarcinoma, HNS</td>
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<tr>
<td>Large intestine</td>
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</tr>
<tr>
<td>Bladder</td>
<td></td>
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</tr>
<tr>
<td>Urethra</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, HNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical System</td>
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<tr>
<td>Brain</td>
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<td></td>
</tr>
<tr>
<td>Astrocytoma</td>
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<tr>
<td>Pituitary gland</td>
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<tr>
<td>Adrenal gland</td>
<td></td>
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<tr>
<td>Isletoma, HNS</td>
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<tr>
<td>Cortical adenoma</td>
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<tr>
<td>Parathyroid gland</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Parathyroid gland</td>
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</tr>
<tr>
<td>Reproductive System</td>
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<td></td>
</tr>
<tr>
<td>Mammary gland</td>
<td></td>
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</tr>
<tr>
<td>Testis</td>
<td></td>
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</tr>
<tr>
<td>Genital System</td>
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</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma</td>
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</tr>
<tr>
<td>Special sense organs</td>
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</tr>
<tr>
<td>Ear</td>
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<tr>
<td>Isletoma, HNS</td>
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<tr>
<td>Adrenal gland</td>
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<tr>
<td>Body cavities</td>
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<tr>
<td>Peritoneum</td>
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<tr>
<td>Sarcina, HNS</td>
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<tr>
<td>Bone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcina, HNS</td>
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<tr>
<td>Multiple organs</td>
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<td>Testis, lymphoma</td>
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<td>Male, lymphoma, histiocytic type</td>
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<tr>
<td>Liver, lymphoma</td>
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<tr>
<td># Animals necropsied</td>
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83 8-Hydroxyquinoline, NTP TR 276
| ANIMAL NUMBER | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|---------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|
| STUDY NUMBER  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| INTERMENTARY SYSTEM | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | | | | | | | | | | | | | | | | | | | | | |
| INDOX | | | | | | | | | | | | | | | | | | | | | |
| INDOX | | | | | | | | | | | | | | | | | | | | | |
| INDOX | | | | | | | | | | | | | | | | | | | | | |
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| INDOX | | | | | | | | | | | | | | | | | | | | | |
| INDOX | | | | | | | | | | | | | | | | | | | | | |
TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

<table>
<thead>
<tr>
<th>Animal ID</th>
<th>Tumor Site</th>
<th>Tumor Type</th>
<th>Pathology</th>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>A123</td>
<td>Lungs</td>
<td>Carcinoma</td>
<td>Well</td>
<td>2</td>
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<tr>
<td>B456</td>
<td>Liver</td>
<td>Sarcoma</td>
<td>Poor</td>
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<tr>
<td>C789</td>
<td>Kidney</td>
<td>Adenoma</td>
<td>Moderate</td>
<td>2.5</td>
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</table>

*Hydroxyquinoline, NTP TR 276*
<table>
<thead>
<tr>
<th>Table B4. Individual Animal Tumor Pathology of Female Mice in the Two-Year Feed Study of 8-Hydroxyquinoline: Untreated Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal Number</strong></td>
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<tr>
<td><strong>Weeks in Study</strong></td>
</tr>
<tr>
<td><strong>Integumentary System</strong></td>
</tr>
<tr>
<td>Subcutaneous Tissue Sarcoma, NOS</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
</tr>
<tr>
<td>Lungs and Bronchi Hepatocellular Carcinoma, Metastatic Alveolar-Acinar Adenoma, NOS Alveolar-Bradnewich Adenoma, NOS Sarcoma, NOS, Metastatic Trachea</td>
</tr>
<tr>
<td><strong>Hematopoietic System</strong></td>
</tr>
<tr>
<td>Bone Marrow</td>
</tr>
<tr>
<td>Spleen</td>
</tr>
<tr>
<td>LympH Nodes</td>
</tr>
<tr>
<td>Thymus</td>
</tr>
<tr>
<td><strong>Circulatory System</strong></td>
</tr>
<tr>
<td>Heart</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
</tr>
<tr>
<td>Salivary Gland Sarcoma, NOS, Invasive</td>
</tr>
<tr>
<td>Liver Hepatocellular Adenoma Hepatocellular Carcinoma Lipoma</td>
</tr>
<tr>
<td>Bile Duct Gallbladder &amp; Common Bile Duct Pancreas</td>
</tr>
<tr>
<td>Esophagus</td>
</tr>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Small Intestine</td>
</tr>
<tr>
<td>Large Intestine</td>
</tr>
<tr>
<td><strong>Urinary System</strong></td>
</tr>
<tr>
<td>Kidney Sarcoma, NOS, Metastatic</td>
</tr>
<tr>
<td>Urinary Bladder</td>
</tr>
<tr>
<td><strong>Endocrine System</strong></td>
</tr>
<tr>
<td>Pituitary Adenoma, NOS</td>
</tr>
<tr>
<td>Adrenal Pheochromocytoma</td>
</tr>
<tr>
<td>Thyroid Follicular-Cell Adenoma Follicular-Cell Carcinoma</td>
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<tr>
<td>Parathyroid</td>
</tr>
<tr>
<td><strong>Reproductive System</strong></td>
</tr>
<tr>
<td>Mammary Gland Adenocarcinoma</td>
</tr>
<tr>
<td>Uterus Endometrial Stromal Polyp Malignant Lymphoma, Histiocytic Type</td>
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<tr>
<td>Ovary Cystadenoma, NOS Papillary Cystadenoma, NOS</td>
</tr>
<tr>
<td>Brain Meningioma</td>
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<tr>
<td><strong>Special Sense Organs</strong></td>
</tr>
<tr>
<td>Harderian Gland Adenoma, NOS</td>
</tr>
<tr>
<td><strong>All Other Systems</strong></td>
</tr>
<tr>
<td>Multiple Organs NOS Malignant Lymphoma, NOS Malignant Lymphoma, Undifferentiated Malignant Lymphoma, Lymphoid Type Malignant Lymphoma, Lymphocytic Type</td>
</tr>
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</table>

8-Hydroxyquinoline, NTP TR 276
## TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL
(Continued)

<table>
<thead>
<tr>
<th>ANIMAL NUMBER</th>
<th>TOTAL TISSUES</th>
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</thead>
<tbody>
<tr>
<td>WEKS ON STUDY</td>
<td>TUMORS</td>
</tr>
</tbody>
</table>

### INTESTINAL SYSTEM
- **SALIVARY GLAND**
  - Carcinoma, invasive: 48
- **LIVER**
  - Hepatocellular adenoma: 1
  - Hepatocellular carcinoma: 1
  - Lipoma: 1
- **BILE DUCT**
- **GALLBLADDER & COMMON BILE DUCT**
- **PANCREAS**
- **ESOPHAGUS**
- **STOMACH**
  - Ulcers: 44
- **SMALL INTESTINE**
- **LARGE INTESTINE**
- **URINARY SYSTEM**
  - **KIDNEY**
    - Carcinoma, invasive: 49
  - **URETHRA**
  - **BLADDER**
- **ENDOCRINE SYSTEM**
  - **PITUITARY**
    - Adenoma, NOS: 49
  - **ADRENAL**
    - Phaeochromocytoma: 49
  - **THYROID**
    - Follicular-cell adenoma: 46
    - Follicular-cell carcinoma: 4
  - **PARATHYROID**
    - Adenoma, NOS: 26
- **REPRODUCTIVE SYSTEM**
  - **MAMMARY GLAND**
    - Carcinoma: 58
  - **UTERUS**
    - Endometrial stromal polyp: 58
  - **OVARY**
    - cystadenoma, NOS: 43
  - **EPITHELIAL CYSTADENOMA, NOS**
  - **NERVOUS SYSTEM**
    - None: 49
- **SPECIAL SENSE ORGANS**
  - **HARDERIAN GLAND**
    - Adenoma, NOS: 58
  - **ALL OTHER SYSTEMS**
    - Multiple organs NOS: 58
    - Multiple lymphoma, NOS: 2
    - Multiple lymphoma, undifferentiated-type: 1
    - Multiple lymphoma, histiocytic type: 1

*Animals necropsied.*
TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE: LOW DOSE

<table>
<thead>
<tr>
<th>System</th>
<th>Male Numbers</th>
<th>Female Numbers</th>
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<tr>
<td>Intestinal System</td>
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<tr>
<td>Spleen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulatory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammary gland</td>
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<td></td>
</tr>
<tr>
<td>Germline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special Sense Organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
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</tr>
</tbody>
</table>

8-Hydroxyquinoline, NTP TR 276 88
<table>
<thead>
<tr>
<th>TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERNAL TUMORS</td>
</tr>
<tr>
<td>Carcinomas &amp; Sarcomas</td>
</tr>
<tr>
<td>(continued)</td>
</tr>
<tr>
<td><strong>Tissue</strong></td>
</tr>
<tr>
<td>Subcutaneous Tissue</td>
</tr>
<tr>
<td>Hemangioendothelioma</td>
</tr>
<tr>
<td>Respiratory System</td>
</tr>
<tr>
<td>Lungs and Bronchi</td>
</tr>
<tr>
<td>Bronchial Adenoma &amp; Metastasis</td>
</tr>
<tr>
<td>Trachea</td>
</tr>
<tr>
<td>Hematopoietic System</td>
</tr>
<tr>
<td>Bone Marrow</td>
</tr>
<tr>
<td>Spleen</td>
</tr>
<tr>
<td>Leukemic Lymphoma, MDS</td>
</tr>
<tr>
<td>Thymus</td>
</tr>
<tr>
<td>Circulatory System</td>
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<tr>
<td>Heart</td>
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<tr>
<td>Digestive System</td>
</tr>
<tr>
<td>Salivary Gland</td>
</tr>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Small Intestine</td>
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<tr>
<td>Large Intestine</td>
</tr>
<tr>
<td>Liver</td>
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<tr>
<td>Hepatocellular Adenoma</td>
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<td>Bile Duct</td>
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<td>Gallbladder &amp; Common Bile Duct</td>
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<tr>
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<tr>
<td>Stomach</td>
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<td>Small Intestine</td>
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<tr>
<td>Large Intestine</td>
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<tr>
<td>Urogenital System</td>
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# TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE: HIGH DOSE

| ANIMAL NUMBER | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
| WEEKS ON STUDY | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
| RESPIRATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ALVEOLARY BRONCHIAL ADENOMA | 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 | X |
| ALVEOLARY BRONCHOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADENOSQUAMOUS CARCINOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNG, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SPLEEN | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LYMPH NODES | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| CIRCULATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LIVER | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEPATOCELLMAL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEPATOCellular CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BILE DUCT | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| COMMON BILE DUCT | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PANCREAS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ESOPhAGUS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| STOMACH | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SMALL INTESTINE | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADENOMATOUS POLYP, HOS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LARGE INTESTINE | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| URINARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| URINARY BLADDER | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ENDOCRINE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADENOMA, HOS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADRENAL | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PHAEOMONODCITOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PHAEOMONOCYTOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYROID | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| FOLLICULAR-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PARATHYROID | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| REPRODUCTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADENOSQUAMOUS CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| UTERUS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| OVARY | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NERVOUS SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SPECIAL SENSE ORGANS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ALL OTHER SYSTEMS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS, HOS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIGANT LYMPHOMA, HOS | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphocytic Type | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| OTHERS | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

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* ANIMALS NECROSIZED
APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE
<table>
<thead>
<tr>
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8-Hydroxyquinoline, NTP TR 276
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<th>High Dose</th>
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<td>12 (26%)</td>
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<td>43 (38)</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
<td>Necrosis, Nos</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
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</tr>
<tr>
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<td>(49)</td>
<td>(47)</td>
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<tr>
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<td>(50)</td>
<td>(50)</td>
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<td>1 (2%)</td>
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<td>1 (2%)</td>
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<td>Fibrosis</td>
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<td>(50)</td>
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<td>1 (2%)</td>
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</tr>
<tr>
<td># Pancreatic Artery</td>
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<td>(50)</td>
<td>(50)</td>
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<td>1 (2%)</td>
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<tr>
<td>Perivasculitis</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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</tr>
<tr>
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<td>(48)</td>
<td>(45)</td>
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<td>1 (2%)</td>
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<td>1 (2%)</td>
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<tr>
<td>* Gum</td>
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<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
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<td>(50)</td>
<td>(48)</td>
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</tr>
<tr>
<td>Fibrosis</td>
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<td>1 (2%)</td>
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<td>Degeneration, Cystic</td>
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<td>(48)</td>
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95  8-Hydroxyquinoline, NTP TR 276
TABLE CI. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

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<tr>
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TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

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*NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
*NUMBER OF ANIMALS NECROPSIED
TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

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8-Hydroxyquinoline, NTP TR 276
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<td>2 (4%)</td>
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8-Hydroxyquinoline, NTP TR 276  100
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<td>1 (2%)</td>
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<td>(49)</td>
<td>(49)</td>
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<tr>
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<td>1 (2%)</td>
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<tr>
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101 8-Hydroxyquinoline, NTP TR 276
### TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

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<td>INFLAMMATION, ACUTE/CHRONIC</td>
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<tr>
<td>FIBROSIS</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>NECROSIS, NOS</td>
<td></td>
<td>1</td>
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<tr>
<td>OMENTUM</td>
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<td>NECROSIS, FAT</td>
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<td>4</td>
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**SPECIAL MORPHOLOGY SUMMARY**

NONE

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED
APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE
TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

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<tr>
<td>ANIMALS NECROPSIED</td>
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<td>50</td>
</tr>
<tr>
<td>ANIMALS EXAMINED HISTOPATHOLOGICALLY</td>
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**INTEGUMENTARY SYSTEM**

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<td>Inflammation, NOS</td>
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<td>6 (12%)</td>
<td>6 (12%)</td>
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<tr>
<td>Fibrosis</td>
<td>1 (2%)</td>
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<td></td>
</tr>
<tr>
<td>Necrosis, NOS</td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td></td>
<td>1 (2%)</td>
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<td>Metaplasia, Osseous</td>
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**Subcut Tissue**

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<td>Mineralization</td>
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<td>1 (2%)</td>
</tr>
<tr>
<td>Dilatation, NOS</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Inflammation, NOS</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Abscess, NOS</td>
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</tr>
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<td>Inflammation, Acute/Chronic</td>
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<td>3 (6%)</td>
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<td>Granuloma, NOS</td>
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<tr>
<td>Fibrosis</td>
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<td>1 (2%)</td>
</tr>
<tr>
<td>Infection, Fungal</td>
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</tr>
<tr>
<td>Necrosis, NOS</td>
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<td>6 (12%)</td>
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**Respiratory System**

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<td>2 (4%)</td>
</tr>
<tr>
<td>Inflammation, Acute</td>
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</table>

<table>
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<td>Hemorrhage</td>
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<td>2 (4%)</td>
</tr>
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<td>Inflammation, NOS</td>
<td>9 (18%)</td>
<td>11 (22%)</td>
<td>7 (14%)</td>
</tr>
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</tr>
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<td>Inflammation, Acute</td>
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<td>1 (2%)</td>
<td>3 (6%)</td>
</tr>
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<td>Inflammation, Acute/Chronic</td>
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<td>Alveolar Macrophages</td>
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<td>Hyperplasia, Epithelial</td>
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**Hematopoietic System**

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<td>Hemorrhage</td>
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<td></td>
</tr>
<tr>
<td>Inflammation, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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</tr>
<tr>
<td>Necrosis, NOS</td>
<td>1 (2%)</td>
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<td>Necrosis, Focal</td>
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<td>1 (2%)</td>
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8-Hydroxyquinoline, NTP TR 276 104
TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE  
TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

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<tr>
<td>NECROSIS, NOS</td>
<td>2 (5%)</td>
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<td>4 (9%)</td>
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<td>1 (2%)</td>
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TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

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<td>2 (4%)</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
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<td>2 (4%)</td>
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NERVOUS SYSTEM
NONE

SPECIAL SENSE ORGANS
NONE

MUSCULOSKELETAL SYSTEM
NONE

BODY CAVITIES
*ABDOMINAL CAVITY
MINERALIZATION
HEMORRHAGE

ALL OTHER SYSTEMS
*MULTIPLE ORGANS
INFLAMMATION, NOS 4 (8%) 2 (4%) 2 (4%)
INFLAMMATION, ACUTE 1 (2%)
TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE
TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

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* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

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<td>3 (6%)</td>
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<td>HYPERPLASIA, LYMPHOID</td>
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</tr>
<tr>
<td>HEMATOPOIESIS</td>
<td>2 (5%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>#LIVER</td>
<td>(49)</td>
<td>(50)</td>
<td>(49)</td>
</tr>
<tr>
<td>HEMATOPOIESIS</td>
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<tr>
<td>#PEYER’S PATCH</td>
<td>(43)</td>
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<td>(45)</td>
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<td>3 (7%)</td>
<td>3 (7%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>#THYMUS</td>
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<td>(25)</td>
<td>(27)</td>
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<td><strong>CIRCULATORY SYSTEM</strong></td>
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<td><em>MULTIPLE ORGANS</em></td>
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<td>(50)</td>
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<td>PERIVASCULITIS</td>
<td>1 (2%)</td>
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<td>#HEART</td>
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<td>(50)</td>
<td>(50)</td>
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<tr>
<td>INFLAMMATION, NOS</td>
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<tr>
<td>#MYOCARDIUM</td>
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<td>(50)</td>
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<tr>
<td>DEGENERATION, NOS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>DIGESTIVE SYSTEM</strong></td>
<td></td>
<td></td>
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<tr>
<td>#SALIVARY GLAND</td>
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<td>(46)</td>
<td>(48)</td>
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<tr>
<td>INFLAMMATION, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NECROSIS, FOCAL</td>
<td>1 (2%)</td>
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</tr>
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8-Hydroxyquinoline, NTP TR 276
TABLE D3. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

<table>
<thead>
<tr>
<th></th>
<th>CONTROL (UNTR)</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>DIGESTIVE SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#LIVER</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>MINERALIZATION</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>DILATATION, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>DEGENERATION, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>NECROSIS, NOS</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
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<td>NECROSIS, ISCHEMIC</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>METAMORPHOSIS FATTY</td>
<td>11 (22%)</td>
<td>11 (22%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>CYTOPLASMIC CHANGE, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>CLEAR-CELL CHANGE</td>
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</tr>
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<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>*GALLBLADDER</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
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<td>1 (2%)</td>
<td>1 (2%)</td>
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<td>#PANCREATIC ACINUS</td>
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<td>(47)</td>
<td>(45)</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
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<td>1 (2%)</td>
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</tr>
<tr>
<td>#STOMACH</td>
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<td>(48)</td>
<td>(48)</td>
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<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>NECROSIS, NOS</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>HYPERPLASIA, EPITHELIAL</td>
<td></td>
<td></td>
<td>1 (2%)</td>
</tr>
<tr>
<td>HYPERKERATOSIS</td>
<td>9 (19%)</td>
<td>7 (15%)</td>
<td>10 (21%)</td>
</tr>
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<td><strong>URINARY SYSTEM</strong></td>
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<td></td>
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</tr>
<tr>
<td>#KIDNEY</td>
<td>(49)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td>MINERALIZATION</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>HYDRONEPHROSIS</td>
<td></td>
<td></td>
<td>1 (2%)</td>
</tr>
<tr>
<td>INFLAMMATION, NOS</td>
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<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>NEPHROTICIS</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
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<tr>
<td>GLOMERULOSCLEROSIS, NOS</td>
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<td></td>
<td>1 (2%)</td>
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<tr>
<td>NECROSIS, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>#RENAL PAPILLA</td>
<td>(49)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td>MINERALIZATION</td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>#KIDNEY/TUBULE</td>
<td>(49)</td>
<td>(50)</td>
<td>(48)</td>
</tr>
<tr>
<td>DEGENERATION, NOS</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
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<tr>
<td>#URINARY BLADDER</td>
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<td>(48)</td>
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<td>HYPERPLASIA, EPITHELIAL</td>
<td>2 (4%)</td>
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</tr>
<tr>
<td><strong>ENDOCRINE SYSTEM</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>#PITUITARY</td>
<td>(40)</td>
<td>(44)</td>
<td>(37)</td>
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<td>DILATATION, NOS</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>HYPERPLASIA, NOS</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>#PITUITARY INTERMEDIA</td>
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<td>(44)</td>
<td>(37)</td>
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<tr>
<td>HYPERPLASIA, NOS</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#ADRENAL</td>
<td>(49)</td>
<td>(48)</td>
<td>(47)</td>
</tr>
<tr>
<td>NECROSIS, NOS</td>
<td></td>
<td></td>
<td>1 (2%)</td>
</tr>
<tr>
<td>METAMORPHOSIS FATTY</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYPERPLASIA, NOS</td>
<td>21 (43%)</td>
<td>23 (48%)</td>
<td>25 (53%)</td>
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<tr>
<td>#ADRENAL/CAPSULE</td>
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<td>(48)</td>
<td>(47)</td>
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<td>HYPERPLASIA, NOS</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
</tr>
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<td>#ADRENAL CORTEX</td>
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<td>(48)</td>
<td>(47)</td>
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<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#ADRENAL MEDULLA</td>
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<td>(48)</td>
<td>(47)</td>
</tr>
<tr>
<td>HYPERPLASIA, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>#THYROID</td>
<td>(48)</td>
<td>(48)</td>
<td>(47)</td>
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<td>HYPERPLASIA, FOLLICULAR-CELL</td>
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<td>3 (6%)</td>
<td>4 (9%)</td>
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8-Hydroxyquinoline, NTP TR 276 110
### Table D2. Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the Two-Year Feed Study of 8-Hydroxyquinoline (Continued)

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<thead>
<tr>
<th>System</th>
<th>CONTROL (UNTR)</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
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<tbody>
<tr>
<td><strong>Reproductive System</strong></td>
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</tr>
<tr>
<td>* Mammary Gland</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Necrosis, Nos</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td>(50)</td>
<td>(47)</td>
<td>(49)</td>
</tr>
<tr>
<td>Hydrometra</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Inflammation, NOS</td>
<td>2 (4%)</td>
<td>6 (12%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Inflammation, Fibrous</td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Inflammation, Necrotizing</td>
<td>9 (18%)</td>
<td>4 (9%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Angiectasis</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Uterus/Endometrium</td>
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<td>(47)</td>
<td>(49)</td>
</tr>
<tr>
<td>Hyperplasia, NOS</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Hyperplasia, Cystic</td>
<td>10 (20%)</td>
<td>19 (40%)</td>
<td>15 (31%)</td>
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<td>Ovary</td>
<td>(43)</td>
<td>(46)</td>
<td>(43)</td>
</tr>
<tr>
<td>Mineralization</td>
<td>1 (2%)</td>
<td>3 (7%)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Inflammation, NOS</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Inflammation, Necrotizing</td>
<td>16 (37%)</td>
<td>7 (15%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Inflammation, Acute</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Necrosis, Nos</td>
<td>2 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiectasis</td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
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<td>Brain</td>
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<td>(50)</td>
<td>(47)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Special Sense Organs</strong></td>
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</tr>
<tr>
<td>Ear</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
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<tr>
<td>Necrosis, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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</tr>
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<td><strong>Musculoskeletal System</strong></td>
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<td>Mandible</td>
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<td>(50)</td>
</tr>
<tr>
<td>Mineralization</td>
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<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Inflammation, Acute</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Abscess, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Necrosis, NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Body Cavities</strong></td>
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</tr>
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<td>Thoracic Cavity</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Inflammation, Necrotizing</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Abdominal Cavity</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Inflammation, Necrotizing</td>
<td>7 (14%)</td>
<td>6 (12%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td></td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Peritoneum</td>
<td>(50)</td>
<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Inflammation, NOS</td>
<td>3 (6%)</td>
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<td></td>
</tr>
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<td><strong>All Other Systems</strong></td>
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</tr>
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<td>(50)</td>
<td>(50)</td>
</tr>
<tr>
<td>Inflammation, NOS</td>
<td>16 (32%)</td>
<td>12 (24%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Inflammation, Acute</td>
<td></td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Omentum</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Necrosis, Fat</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

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111 8-Hydroxyquinoline, NTP TR 276
### TABLE D3. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

<table>
<thead>
<tr>
<th>Special Morphology Summary</th>
<th>Control (UNTR)</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTO/NECROPSY/HISTO PERF</td>
<td></td>
<td></td>
<td>3</td>
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</table>

* NUMBER OF ANIMALS NECROPSIED
APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE

IN THE TWO-YEAR FEED STUDIES OF

8-HYDROXYQUINOLINE
# TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

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<thead>
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<th></th>
<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
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<tbody>
<tr>
<td><strong>Subcutaneous Tissue: Fibroma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>2/50 (4%)</td>
<td>4/50 (8%)</td>
<td>5/50 (10%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>6.9%</td>
<td>11.1%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/29 (7%)</td>
<td>3/34 (9%)</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.210</td>
<td>P = 0.411</td>
<td>P = 0.267</td>
</tr>
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<td>Incidental Tumor Tests (d)</td>
<td>P = 0.198</td>
<td>P = 0.400</td>
<td>P = 0.250</td>
</tr>
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<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.169</td>
<td></td>
<td></td>
</tr>
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<td>Fisher Exact Tests</td>
<td></td>
<td>P = 0.339</td>
<td>P = 0.218</td>
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<tr>
<td><strong>Subcutaneous Tissue: Fibroma or Fibrosarcoma</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>2/50 (4%)</td>
<td>4/50 (8%)</td>
<td>6/50 (12%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>6.9%</td>
<td>11.1%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/29 (7%)</td>
<td>3/34 (9%)</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.132</td>
<td>P = 0.411</td>
<td>P = 0.182</td>
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<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.118</td>
<td>P = 0.400</td>
<td>P = 0.159</td>
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<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.099</td>
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<tr>
<td>Fisher Exact Tests</td>
<td></td>
<td>P = 0.339</td>
<td>P = 0.134</td>
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<td><strong>Lung: Alveolar/Bronchiolar Adenoma</strong></td>
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<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>0/50 (0%)</td>
<td>2/50 (4%)</td>
<td>3/50 (6%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>0.0%</td>
<td>5.9%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
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<td>2/34 (6%)</td>
<td>2/33 (6%)</td>
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<td>Life Table Tests (d)</td>
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<td>P = 0.143</td>
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<td>4/50 (8%)</td>
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<td>2/33 (6%)</td>
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<td>P = 0.080</td>
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<td>Cochran-Armitage Trend Test (d)</td>
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<td>Fisher Exact Tests</td>
<td></td>
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<td>P = 0.059</td>
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<td>8/50 (16%)</td>
<td>9/50 (18%)</td>
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<td>20.4%</td>
<td>22.9%</td>
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<td>5/34 (15%)</td>
<td>4/33 (12%)</td>
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<tr>
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<td>3/60 (6%)</td>
<td>3/50 (6%)</td>
<td>3/50 (6%)</td>
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<td>9.0%</td>
<td>6.4%</td>
<td>4.5%</td>
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<tr>
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<td>2/29 (7%)</td>
<td>0/34 (0%)</td>
<td>0/33 (0%)</td>
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<td>P = 0.661N</td>
<td>P = 0.500N</td>
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<td><strong>Liver: Neoplastic Nodule</strong></td>
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<tr>
<td>Overall Rates (a)</td>
<td>6/49 (12%)</td>
<td>1/50 (2%)</td>
<td>3/48 (6%)</td>
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<tr>
<td>Adjusted Rates (b)</td>
<td>18.7%</td>
<td>2.9%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>4/29 (14%)</td>
<td>1/34 (3%)</td>
<td>2/33 (6%)</td>
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<td>P = 0.233N</td>
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<td>Fisher Exact Tests</td>
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<td>P = 0.254N</td>
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<td>Table E1. Analysis of Primary Tumors in Male Rats in the Two-Year Feed Study of 8-Hydroxyquinoline (Continued)</td>
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<td>3,000 ppm</td>
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<tr>
<td><strong>Liver: Neoplastic Nodule or Carcinoma</strong></td>
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</tr>
<tr>
<td>Overall Rates (a)</td>
<td>7/49 (14%)</td>
<td>1/50 (2%)</td>
<td>3/48 (6%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>20.4%</td>
<td>2.9%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>4/29 (14%)</td>
<td>1/34 (3%)</td>
<td>2/33 (6%)</td>
</tr>
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<td>P = 0.032N</td>
<td>P = 0.122N</td>
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<td>P = 0.037N</td>
<td>P = 0.151N</td>
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<td>P = 0.028N</td>
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<tr>
<td><strong>Pituitary: Adenoma</strong></td>
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<tr>
<td>Overall Rates (a)</td>
<td>18/48 (38%)</td>
<td>17/50 (34%)</td>
<td>12/47 (26%)</td>
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<td>Adjusted Rates (b)</td>
<td>42.1%</td>
<td>40.9%</td>
<td>32.7%</td>
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<td>13/29 (45%)</td>
<td>10/34 (29%)</td>
<td>9/33 (27%)</td>
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<td>P = 0.306N</td>
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<td>P = 0.403N</td>
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<td>Cochran-Armitage Trend Test (d)</td>
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<td>P = 0.440N</td>
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<td><strong>Adrenal: Pheochromocytoma</strong></td>
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<td>Overall Rates (a)</td>
<td>12/50 (24%)</td>
<td>8/50 (16%)</td>
<td>13/48 (27%)</td>
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<td>Adjusted Rates (b)</td>
<td>34.5%</td>
<td>20.6%</td>
<td>35.9%</td>
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<tr>
<td>Terminal Rates (c)</td>
<td>7/29 (24%)</td>
<td>4/34 (12%)</td>
<td>10/33 (30%)</td>
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<td>Fisher Exact Tests</td>
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<tr>
<td><strong>Thyroid: C-Cell Carcinoma</strong></td>
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<tr>
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<td>0/50 (0%)</td>
<td>0/49 (0%)</td>
<td>4/47 (9%)</td>
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<td>Adjusted Rates (b)</td>
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<td>0.0%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>0/29 (0%)</td>
<td>0/34 (0%)</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.018</td>
<td>(e)</td>
<td>P = 0.080</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.018</td>
<td>(e)</td>
<td>P = 0.068</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.013</td>
<td>(e)</td>
<td>P = 0.051</td>
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<tr>
<td>Fisher Exact Tests</td>
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<tr>
<td><strong>Thyroid: C-Cell Adenoma or Carcinoma</strong></td>
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</tr>
<tr>
<td>Overall Rates (a)</td>
<td>1/50 (2%)</td>
<td>1/49 (2%)</td>
<td>6/47 (13%)</td>
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<td>Adjusted Rates (b)</td>
<td>2.5%</td>
<td>2.9%</td>
<td>17.1%</td>
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<td>Terminal Rates (c)</td>
<td>0/29 (0%)</td>
<td>1/34 (3%)</td>
<td>5/33 (15%)</td>
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<td>Life Table Tests (d)</td>
<td>P = 0.030</td>
<td>P = 0.736N</td>
<td>P = 0.080</td>
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<td>Incidental Tumor Tests (d)</td>
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<td>P = 0.717</td>
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<td>P = 0.747</td>
<td>P = 0.047</td>
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<tr>
<td>Fisher Exact Tests</td>
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<tr>
<td><strong>Pancreatic Islets: Islet Cell Adenoma</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>3/47 (6%)</td>
<td>5/48 (10%)</td>
<td>1/45 (2%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>10.3%</td>
<td>13.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>3/29 (10%)</td>
<td>3/34 (9%)</td>
<td>1/33 (3%)</td>
</tr>
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<tr>
<td><strong>Pancreatic Islets: Islet Cell Adenoma or Carcinoma</strong></td>
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<tr>
<td>Overall Rates (a)</td>
<td>4/47 (9%)</td>
<td>5/48 (10%)</td>
<td>2/45 (4%)</td>
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<td>Adjusted Rates (b)</td>
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<td>13.3%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>3/29 (10%)</td>
<td>3/34 (9%)</td>
<td>1/33 (3%)</td>
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<td>Life Table Tests (d)</td>
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<td>P = 0.507</td>
<td>P = 0.329N</td>
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<td>P = 0.301N</td>
<td>P = 0.514</td>
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115 8-Hydroxyquinoline, NTP TR 276
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<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
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<td>Overall Rates (a)</td>
<td>2/50 (4%)</td>
<td>3/50 (6%)</td>
<td>4/50 (8%)</td>
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<tr>
<td>Adjusted Rates (b)</td>
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<td>8.2%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/29 (7%)</td>
<td>2/34 (6%)</td>
<td>2/33 (6%)</td>
</tr>
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<td>Life Table Tests (d)</td>
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<td>Fisher Exact Tests</td>
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<td>P = 0.339</td>
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<td><strong>Preputial Gland: Carcinoma</strong></td>
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</tr>
<tr>
<td>Overall Rates (a)</td>
<td>1/50 (2%)</td>
<td>3/50 (6%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>2.7%</td>
<td>8.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>0/29 (0%)</td>
<td>2/34 (6%)</td>
<td>1/33 (3%)</td>
</tr>
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<tr>
<td><strong>Preputial Gland: Adenoma or Carcinoma</strong></td>
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<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>2/50 (4%)</td>
<td>4/50 (8%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>6.1%</td>
<td>11.2%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>1/29 (3%)</td>
<td>3/34 (9%)</td>
<td>1/33 (3%)</td>
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<td>P = 0.500N</td>
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</tr>
<tr>
<td><strong>Testis: Interstitial Cell Tumor</strong></td>
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<tr>
<td>Overall Rates (a)</td>
<td>39/47 (83%)</td>
<td>42/50 (84%)</td>
<td>44/48 (92%)</td>
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<td>Adjusted Rates (b)</td>
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<td>100.0%</td>
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<td>24/29 (83%)</td>
<td>33/34 (97%)</td>
<td>33/33 (100%)</td>
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<td>P = 0.565</td>
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<td>P = 0.167</td>
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<tr>
<td>Fisher Exact Tests</td>
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</table>

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study 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's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is presented because no tumors were observed in the 1,500 ppm and control groups.
### TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Hematopoietic System: Mononuclear Cell Leukemia</th>
<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Rates (a)</td>
<td>6/50 (12%)</td>
<td>3/50 (6%)</td>
<td>9/50 (18%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>13.5%</td>
<td>7.2%</td>
<td>21.1%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/37 (5%)</td>
<td>2/40 (5%)</td>
<td>5/37 (14%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.211</td>
<td>P = 0.240N</td>
<td>P = 0.276</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.240</td>
<td>P = 0.299N</td>
<td>P = 0.345</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.221</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P = 0.244N</td>
<td></td>
<td>P = 0.288</td>
</tr>
</tbody>
</table>

| Liver: Neoplastic Nodule                       |         |           |           |
| Overall Rates (a)                              | 3/50 (6%) | 2/50 (4%) | 4/49 (8%)  |
| Adjusted Rates (b)                             | 8.1%     | 5.0%      | 10.8%     |
| Terminal Rates (c)                             | 3/37 (8%) | 2/40 (5%) | 4/37 (11%) |
| Life Table Tests (d)                           | P = 0.415 | P = 0.464N | P = 0.500 |
| Incidental Tumor Tests (d)                     | P = 0.415 | P = 0.464N | P = 0.500 |
| Cochran-Armitage Trend Test (d)                | P = 0.407 |            |           |
| Fisher Exact Tests                             | P = 0.500N |           | P = 0.489 |

| Liver: Neoplastic Nodule or Carcinoma          |         |           |           |
| Overall Rates (a)                              | 4/50 (8%) | 2/50 (4%) | 4/49 (8%)  |
| Adjusted Rates (b)                             | 10.8%    | 5.0%      | 10.8%     |
| Terminal Rates (c)                             | 4/37 (11%) | 2/40 (5%) | 4/37 (11%) |
| Life Table Tests (d)                           | P = 0.581 | P = 0.301N | P = 0.645 |
| Incidental Tumor Tests (d)                     | P = 0.581 | P = 0.301N | P = 0.645 |
| Cochran-Armitage Trend Test (d)                | P = 0.559 |            |           |
| Fisher Exact Tests                             | P = 0.339N |           | P = 0.631 |

| Pituitary: Adenoma                             |         |           |           |
| Overall Rates (a)                              | 23/47 (49%) | 27/49 (55%) | 25/46 (54%) |
| Adjusted Rates (b)                             | 55.5%    | 59.9%     | 56.2%     |
| Terminal Rates (c)                             | 18/36 (50%) | 22/40 (55%) | 17/36 (47%) |
| Life Table Tests (d)                           | P = 0.356 | P = 0.421 | P = 0.392 |
| Incidental Tumor Tests (d)                     | P = 0.246 | P = 0.271 | P = 0.336 |
| Cochran-Armitage Trend Test (d)                | P = 0.337 |            |           |
| Fisher Exact Tests                             | P = 0.344 |           | P = 0.377 |

| Pituitary: Adenoma or Carcinoma                |         |           |           |
| Overall Rates (a)                              | 23/47 (49%) | 25/49 (57%) | 25/46 (54%) |
| Adjusted Rates (b)                             | 55.5%    | 62.1%     | 56.2%     |
| Terminal Rates (c)                             | 18/36 (50%) | 23/40 (58%) | 17/36 (47%) |
| Life Table Tests (d)                           | P = 0.356 | P = 0.354 | P = 0.392 |
| Incidental Tumor Tests (d)                     | P = 0.246 | P = 0.209 | P = 0.356 |
| Cochran-Armitage Trend Test (d)                | P = 0.336 |            |           |
| Fisher Exact Tests                             | P = 0.274 |           | P = 0.377 |

| Adrenal: Pheochromocytoma                      |         |           |           |
| Overall Rates (a)                              | 1/49 (2%) | 4/50 (8%) | 2/49 (4%)  |
| Adjusted Rates (b)                             | 2.7%     | 9.4%      | 5.4%      |
| Terminal Rates (c)                             | 1/37 (3%) | 3/40 (7%) | 2/37 (5%) |
| Life Table Tests (d)                           | P = 0.402 | P = 0.204 | P = 0.500 |
| Incidental Tumor Tests (d)                     | P = 0.451 | P = 0.278 | P = 0.500 |
| Cochran-Armitage Trend Test (d)                | P = 0.406 |            |           |
| Fisher Exact Tests                             | P = 0.187 |           | P = 0.500 |

| Thyroid: C-Cell Adenoma                        |         |           |           |
| Overall Rates (a)                              | 1/48 (2%) | 2/50 (4%) | 5/49 (10%) |
| Adjusted Rates (b)                             | 2.2%     | 4.8%      | 13.3%     |
| Terminal Rates (c)                             | 0/37 (0%) | 1/40 (3%) | 4/36 (11%) |
| Life Table Tests (d)                           | P = 0.054 | P = 0.501 | P = 0.097 |
| Incidental Tumor Tests (d)                     | P = 0.041 | P = 0.350 | P = 0.076 |
| Cochran-Armitage Trend Test (d)                | P = 0.062 |            |           |
| Fisher Exact Tests                             | P = 0.515 |           | P = 0.107 |
TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid: C-Cell Adenoma or Carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>3/48 (6%)</td>
<td>2/50 (4%)</td>
<td>6/49 (12%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>7.5%</td>
<td>4.8%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/37 (5%)</td>
<td>1/40 (3%)</td>
<td>5/36 (14%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P=0.154</td>
<td>P=0.485N</td>
<td>P=0.227</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.128</td>
<td>P=0.602N</td>
<td>P=0.197</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.480N</td>
<td></td>
<td>P=0.254</td>
</tr>
<tr>
<td><strong>Mammary Gland: Fibroadenoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>19/60 (38%)</td>
<td>15/50 (30%)</td>
<td>13/50 (26%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>42.0%</td>
<td>35.7%</td>
<td>29.6%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>11/37 (30%)</td>
<td>13/40 (33%)</td>
<td>7/37 (19%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P=0.166N</td>
<td>P=0.232N</td>
<td>P=0.200N</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.166N</td>
<td>P=0.391N</td>
<td>P=0.178N</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.118N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.264N</td>
<td></td>
<td>P=0.142N</td>
</tr>
<tr>
<td><strong>Clitoral Gland: Adenoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>3/50 (6%)</td>
<td>0/50 (0%)</td>
<td>3/50 (6%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>7.7%</td>
<td>0.0%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/37 (5%)</td>
<td>0/40 (0%)</td>
<td>3/37 (8%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P=0.595</td>
<td>P=0.116N</td>
<td>P=0.654</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.573</td>
<td>P=0.151N</td>
<td>P=0.635</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.601</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.121N</td>
<td></td>
<td>P=0.661</td>
</tr>
<tr>
<td><strong>Uterus: Endometrial Stromal Polyp</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>11/49 (22%)</td>
<td>13/49 (27%)</td>
<td>14/49 (29%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>26.8%</td>
<td>30.4%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>8/37 (22%)</td>
<td>11/40 (28%)</td>
<td>11/37 (30%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P=0.275</td>
<td>P=0.474</td>
<td>P=0.313</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.324</td>
<td>P=0.430</td>
<td>P=0.334</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.292</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.407</td>
<td></td>
<td>P=0.322</td>
</tr>
<tr>
<td><strong>Uterus: Endometrial Stromal Polyp or Sarcoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>11/49 (22%)</td>
<td>14/49 (29%)</td>
<td>14/49 (29%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>26.8%</td>
<td>32.0%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>8/37 (22%)</td>
<td>11/40 (28%)</td>
<td>11/37 (30%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P=0.376</td>
<td>P=0.387</td>
<td>P=0.313</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.315</td>
<td>P=0.316</td>
<td>P=0.334</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.284</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.322</td>
<td></td>
<td>P=0.322</td>
</tr>
</tbody>
</table>

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study 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's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
### TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subcutaneous Tissue: Sarcoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>6/50 (12%)</td>
<td>7/50 (14%)</td>
<td>9/50 (18%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>16.9%</td>
<td>16.3%</td>
<td>23.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/29 (7%)</td>
<td>2/35 (6%)</td>
<td>6/35 (17%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.353</td>
<td>P = 0.568N</td>
<td>P = 0.419</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.195</td>
<td>P = 0.581</td>
<td>P = 0.282</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P = 0.500</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Integumentary System: Sarcoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>6/50 (12%)</td>
<td>8/50 (16%)</td>
<td>9/50 (18%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>16.9%</td>
<td>18.3%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/29 (7%)</td>
<td>2/35 (6%)</td>
<td>6/35 (17%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.360</td>
<td>P = 0.558</td>
<td>P = 0.419</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.197</td>
<td>P = 0.454</td>
<td>P = 0.282</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.244</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P = 0.387</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subcutaneous Tissue: Fibroma or Fibrosarcoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>1/50 (2%)</td>
<td>1/50 (2%)</td>
<td>3/50 (6%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>3.4%</td>
<td>2.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>1/29 (3%)</td>
<td>1/35 (3%)</td>
<td>1/35 (3%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.217</td>
<td>P = 0.720N</td>
<td>P = 0.359</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.213</td>
<td>P = 0.720N</td>
<td>P = 0.315</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P = 0.753</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lung: Alveolar/Bronchiolar Adenoma**

| Overall Rates (a)                    | 5/50 (10%)      | 9/49 (18%)      | 9/50 (18%)      |
| Adjusted Rates (b)                   | 20.0%           | 20.8%           | 29.2%           |
| Terminal Rates (c)                   | 3/29 (10%)      | 3/35 (9%)       | 7/35 (20%)      |
| Life Table Tests (d)                 | P = 0.224       | P = 0.544N      | P = 0.276       |
| Incidental Tumor Tests (d)           | P = 0.096       | P = 0.597       | P = 0.151       |
| Cochran-Armitage Trend Test (d)      | P = 0.121       |                 |                 |
| Fisher Exact Tests                   | P = 0.353       |                 |                 |

**Lung: Alveolar/Bronchiolar Adenoma or Carcinoma**

| Overall Rates (a)                    | 6/50 (12%)      | 10/49 (20%)     | 10/50 (20%)     |
| Adjusted Rates (b)                   | 19.1%           | 27.4%           | 28.1%           |
| Terminal Rates (c)                   | 5/29 (17%)      | 9/35 (26%)      | 6/35 (17%)      |
| Life Table Tests (d)                 | P = 0.295       | P = 0.359       | P = 0.332       |
| Incidental Tumor Tests (d)           | P = 0.243       | P = 0.278       | P = 0.261       |
| Cochran-Armitage Trend Test (d)      | P = 0.178       |                 |                 |
| Fisher Exact Tests                   | P = 0.194       |                 |                 |

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### TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

<table>
<thead>
<tr>
<th>System</th>
<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematopoietic System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant Lymphoma, Lymphocytic Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>0/60 (0%)</td>
<td>3/60 (6%)</td>
<td>0/60 (0%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>0.0%</td>
<td>8.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>0/29 (0%)</td>
<td>3/35 (9%)</td>
<td>0/35 (0%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.592N</td>
<td>P = 0.156</td>
<td>(e)</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.592N</td>
<td>P = 0.156</td>
<td>(e)</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.540</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Test</td>
<td>P = 0.121</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematopoietic System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma, All Malignant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>12/50 (24%)</td>
<td>6/50 (12%)</td>
<td>6/50 (12%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>34.1%</td>
<td>16.5%</td>
<td>16.3%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>7/29 (24%)</td>
<td>5/35 (14%)</td>
<td>5/35 (14%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P = 0.032N</td>
<td>P = 0.046N</td>
<td>P = 0.022N</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.047N</td>
<td>P = 0.055N</td>
<td>P = 0.073N</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.087N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Test</td>
<td>P = 0.097N</td>
<td>P = 0.097N</td>
<td></td>
</tr>
<tr>
<td><strong>Circulatory System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>7/50 (14%)</td>
<td>1/50 (2%)</td>
<td>0/50 (0%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>21.0%</td>
<td>2.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>4/29 (14%)</td>
<td>1/35 (3%)</td>
<td>0/35 (0%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P &lt; 0.001N</td>
<td>P = 0.019N</td>
<td>P = 0.006N</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P = 0.022N</td>
<td>P = 0.026N</td>
<td>P = 0.010N</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P = 0.025N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Test</td>
<td>P = 0.030N</td>
<td>P = 0.030N</td>
<td></td>
</tr>
<tr>
<td><strong>Circulatory System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>3/60 (6%)</td>
<td>1/50 (2%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>9.4%</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/29 (7%)</td>
<td>0/35 (0%)</td>
<td>0/35 (0%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
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<td>P = 0.347N</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Test</td>
<td>P = 0.030N</td>
<td>P = 0.030N</td>
<td></td>
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<tr>
<td><strong>Circulatory System</strong></td>
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<tr>
<td>Hemangioma or Hemangiosarcoma</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>10/50 (23%)</td>
<td>2/50 (4%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>29.3%</td>
<td>2.1%</td>
<td>2.1%</td>
</tr>
<tr>
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<td>0/35 (0%)</td>
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<tr>
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<td>Fisher Exact Test</td>
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<td>P = 0.009N</td>
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<tr>
<td><strong>Liver: Hepaticellular Adenoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>9/50 (18%)</td>
<td>8/50 (16%)</td>
<td>14/50 (28%)</td>
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<tr>
<td>Adjusted Rates (b)</td>
<td>27.9%</td>
<td>21.7%</td>
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<td>7/35 (20%)</td>
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<td>P = 0.477N</td>
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<td></td>
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<td>Fisher Exact Test</td>
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<td>P = 0.171</td>
<td></td>
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<tr>
<td><strong>Liver: Hepaticellular Carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>5/50 (10%)</td>
<td>7/50 (14%)</td>
<td>3/50 (6%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>16.0%</td>
<td>20.0%</td>
<td>7.7%</td>
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<tr>
<td>Terminal Rates (c)</td>
<td>4/29 (14%)</td>
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<td>1/35 (3%)</td>
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<td>Life Table Tests (d)</td>
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8-Hydroxyquinoline, NTP TR 276  120
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<tbody>
<tr>
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<td>Liver: Hepatocellular Adenoma or Carcinoma</td>
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<td>3,000 ppm</td>
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<tr>
<td>14/50 (28%)</td>
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<tr>
<td>17/50 (34%)</td>
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<td>Adjusted Rates (b)</td>
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<td>42.2%</td>
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<td>12/35 (34%)</td>
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<td>P = 0.500</td>
</tr>
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<td>Adrenal Cortexial Adenoma</td>
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<td>Overall Rates (a)</td>
</tr>
<tr>
<td>Control:</td>
</tr>
<tr>
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</tr>
<tr>
<td>3,000 ppm</td>
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<td>2/28 (6%)</td>
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</tr>
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<tr>
<td>P = 0.558</td>
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<td>Incidental Tumor Tests (d)</td>
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</tr>
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<td>P = 0.187</td>
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<td>Adrenal Adenoma or Cortical Adenoma</td>
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<tr>
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<tr>
<td>Control:</td>
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<tr>
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</tr>
<tr>
<td>3,000 ppm</td>
</tr>
<tr>
<td>2/49 (4%)</td>
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<td>3/46 (7%)</td>
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<tr>
<td>Adjusted Rates (b)</td>
</tr>
<tr>
<td>7.1%</td>
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<tr>
<td>9.1%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
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<td>2/28 (7%)</td>
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<td>3/33 (9%)</td>
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<tr>
<td>Life Table Tests (d)</td>
</tr>
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<td>P = 0.575</td>
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<td>Incidental Tumor Tests (d)</td>
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<tr>
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<td>Control:</td>
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<tr>
<td>3,000 ppm</td>
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<tr>
<td>2/49 (4%)</td>
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<tr>
<td>0/46 (0%)</td>
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<tr>
<td>Adjusted Rates (b)</td>
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<tr>
<td>0.0%</td>
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<tr>
<td>Terminal Rates (c)</td>
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<tr>
<td>0/35 (0%)</td>
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<tr>
<td>Cochran-Armitage Trend Test (d)</td>
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<td>P = 0.216N</td>
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<td>Fisher Exact Tests</td>
</tr>
<tr>
<td>P = 0.510</td>
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<td>Harderian Gland: Adenoma</td>
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<tr>
<td>Control:</td>
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<tr>
<td>3,000 ppm</td>
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<tr>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>1/50 (2%)</td>
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<td>Adjusted Rates (b)</td>
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<tr>
<td>1/35 (3%)</td>
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<td>P = 0.720N</td>
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<td>Cochran-Armitage Trend Test (d)</td>
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<td>P = 0.601</td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
</tr>
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<td>P = 0.181</td>
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<td>Harderian Gland: Adenoma or Cystadenoma</td>
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<tr>
<td>Control:</td>
</tr>
<tr>
<td>1,500 ppm</td>
</tr>
<tr>
<td>3,000 ppm</td>
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<tr>
<td>2/50 (4%)</td>
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<td>2/50 (4%)</td>
</tr>
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<td>Adjusted Rates (b)</td>
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<td>5.7%</td>
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<td>Terminal Rates (c)</td>
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<td>2/29 (7%)</td>
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<td>2/35 (6%)</td>
</tr>
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<td>Life Table Tests (d)</td>
</tr>
<tr>
<td>P = 0.506N</td>
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<td>P = 0.626N</td>
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<tr>
<td>Incidental Tumor Tests (d)</td>
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<td>P = 0.525N</td>
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<td>Cochran-Armitage Trend Test (d)</td>
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<td>P = 0.588</td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
</tr>
<tr>
<td>P = 0.339</td>
</tr>
</tbody>
</table>

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TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study 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's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is presented because no tumors were observed in the 3,000 ppm and control groups.
<table>
<thead>
<tr>
<th>Table E4. Analysis of Primary Tumors in Female Mice in the Two-Year Feed Study of 8-Hydroxyquinoline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
</tbody>
</table>

### Lung: Alveolar/Bronchiolar Adenoma

| Overall Rates (a) | 1/49 (2%) | 5/50 (10%) | 4/50 (8%) |
| Adjusted Rates (b) | 2.1% | 17.0% | 12.4% |
| Terminal Rates (c) | 0/23 (0%) | 4/27 (15%) | 3/31 (10%) |
| Life Table Tests (d) | P = 0.250 | P = 0.145 | P = 0.254 |
| Incidental Tumor Tests (d) | P = 0.210 | P = 0.057 | P = 0.211 |
| Cochran-Armitage Trend Test (d) | P = 0.164 | | |
| Fisher Exact Tests | P = 0.107 | | P = 0.187 |

### Lung: Alveolar/Bronchiolar Adenoma or Carcinoma

| Overall Rates (a) | 2/49 (4%) | 5/50 (10%) | 5/50 (10%) |
| Adjusted Rates (b) | 6.3% | 17.0% | 15.5% |
| Terminal Rates (c) | 1/23 (4%) | 4/27 (15%) | 4/31 (13%) |
| Life Table Tests (d) | P = 0.292 | P = 0.286 | P = 0.325 |
| Incidental Tumor Tests (d) | P = 0.251 | P = 0.161 | P = 0.283 |
| Cochran-Armitage Trend Test (d) | P = 0.186 | | |
| Fisher Exact Tests | P = 0.226 | | P = 0.226 |

### Hematopoietic System: Malignant Lymphoma, Lymphocytic Type

| Overall Rates (a) | 1/50 (2%) | 1/50 (2%) | 6/50 (12%) |
| Adjusted Rates (b) | 4.2% | 3.4% | 16.4% |
| Terminal Rates (c) | 0/24 (0%) | 0/27 (0%) | 4/31 (13%) |
| Life Table Tests (d) | P = 0.039 | P = 0.731N | P = 0.096 |
| Incidental Tumor Tests (d) | P = 0.094 | P = 0.683N | P = 0.094 |
| Cochran-Armitage Trend Test (d) | P = 0.226 | | P = 0.753N |
| Fisher Exact Tests | P = 0.556 | | |

### Hematopoietic System: Lymphoma, All Malignant

| Overall Rates (a) | 13/60 (26%) | 13/60 (26%) | 12/50 (24%) |
| Adjusted Rates (b) | 44.1% | 37.5% | 32.7% |
| Terminal Rates (c) | 9/24 (38%) | 7/27 (26%) | 8/31 (26%) |
| Life Table Tests (d) | P = 0.241N | P = 0.424N | P = 0.228N |
| Incidental Tumor Tests (d) | P = 0.408N | P = 0.407N | | |
| Cochran-Armitage Trend Test (d) | P = 0.454N | | |
| Fisher Exact Tests | P = 0.500N | | |

### Circulatory System: Hemangioma

| Overall Rates (a) | 0/50 (0%) | 4/50 (8%) | 1/50 (2%) |
| Adjusted Rates (b) | 0.0% | 11.5% | 3.2% |
| Terminal Rates (c) | 0/24 (0%) | 1/27 (4%) | 1/31 (3%) |
| Life Table Tests (d) | P = 0.467 | P = 0.096 | P = 0.511 |
| Incidental Tumor Tests (d) | P = 0.551 | P = 0.551 | | |
| Cochran-Armitage Trend Test (d) | P = 0.390 | | |
| Fisher Exact Tests | P = 0.059 | | P = 0.500 |

### Circulatory System: Hemangiosarcoma

| Overall Rates (a) | 0/50 (0%) | 5/50 (10%) | 1/50 (2%) |
| Adjusted Rates (b) | 0.0% | 14.9% | 3.2% |
| Terminal Rates (c) | 0/24 (0%) | 2/27 (7%) | 1/31 (3%) |
| Life Table Tests (d) | P = 0.487 | P = 0.055 | P = 0.511 |
| Incidental Tumor Tests (d) | P = 0.584 | P = 0.075 | P = 0.511 |
| Cochran-Armitage Trend Test (d) | P = 0.399 | | |
| Fisher Exact Tests | P = 0.028 | | P = 0.500 |

### Liver: Hepatocellular Adenoma

| Overall Rates (a) | 2/49 (4%) | 1/50 (2%) | 4/49 (8%) |
| Adjusted Rates (b) | 6.6% | 3.7% | 12.9% |
| Terminal Rates (c) | 1/24 (4%) | 1/27 (4%) | 4/31 (13%) |
| Life Table Tests (d) | P = 0.320 | P = 0.457N | P = 0.441 |
| Incidental Tumor Tests (d) | P = 0.295 | P = 0.534N | P = 0.405 |
| Cochran-Armitage Trend Test (d) | P = 0.238 | | |
| Fisher Exact Tests | P = 0.492N | | P = 0.339 |

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TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE (Continued)

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<th>Control</th>
<th>1,500 ppm</th>
<th>3,000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver: Hepatocellular Carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>3/49 (6%)</td>
<td>1/50 (2%)</td>
<td>0/49 (0%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>10.6%</td>
<td>3.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/24 (8%)</td>
<td>1/27 (4%)</td>
<td>0/31 (0%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
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<td>P=0.285N</td>
<td>P=0.084N</td>
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<td>Incidental Tumor Tests (d)</td>
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<td>P=0.320N</td>
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<td>Cochran-Armitage Trend Test (d)</td>
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<tr>
<td>Fisher Exact Tests</td>
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<td><strong>Liver: Hepatocellular Adenoma or Carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>5/49 (10%)</td>
<td>2/50 (4%)</td>
<td>4/49 (8%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>16.8%</td>
<td>7.4%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/24 (13%)</td>
<td>2/27 (7%)</td>
<td>4/31 (13%)</td>
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</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.354N</td>
<td>P=0.241N</td>
<td>P=0.431N</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.424N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.210N</td>
<td></td>
<td>P=0.500N</td>
</tr>
<tr>
<td><strong>Pituitary: Adenoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>12/40 (30%)</td>
<td>14/44 (32%)</td>
<td>11/27 (30%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>40.7%</td>
<td>47.3%</td>
<td>40.4%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>7/22 (32%)</td>
<td>10/24 (42%)</td>
<td>10/26 (38%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P=0.288N</td>
<td>P=0.550</td>
<td>P=0.346N</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.451N</td>
<td>P=0.524</td>
<td>P=0.518N</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.541N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.523</td>
<td></td>
<td>P=0.589N</td>
</tr>
<tr>
<td><strong>Thyroid: Follicular Cell Adenoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>4/48 (8%)</td>
<td>2/48 (4%)</td>
<td>2/47 (4%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>15.7%</td>
<td>7.4%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>2/23 (9%)</td>
<td>2/27 (7%)</td>
<td>2/31 (6%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P=0.159N</td>
<td>P=0.270N</td>
<td>P=0.224N</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.190N</td>
<td>P=0.219N</td>
<td>P=0.305N</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.260N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.339N</td>
<td></td>
<td>P=0.349N</td>
</tr>
<tr>
<td><strong>Thyroid: Follicular Cell Adenoma or Carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Rates (a)</td>
<td>5/48 (10%)</td>
<td>2/48 (4%)</td>
<td>2/47 (4%)</td>
</tr>
<tr>
<td>Adjusted Rates (b)</td>
<td>19.7%</td>
<td>7.4%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Terminal Rates (c)</td>
<td>3/23 (13%)</td>
<td>2/27 (7%)</td>
<td>2/31 (6%)</td>
</tr>
<tr>
<td>Life Table Tests (d)</td>
<td>P=0.079N</td>
<td>P=0.160N</td>
<td>P=0.123N</td>
</tr>
<tr>
<td>Incidental Tumor Tests (d)</td>
<td>P=0.095N</td>
<td>P=0.125N</td>
<td>P=0.176N</td>
</tr>
<tr>
<td>Cochran-Armitage Trend Test (d)</td>
<td>P=0.152N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher Exact Tests</td>
<td>P=0.218N</td>
<td></td>
<td>P=0.226N</td>
</tr>
</tbody>
</table>

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study 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's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
APPENDIX F

HISTORICAL INCIDENCES OF TUMORS

IN F344/N RATS AND B6C3F1 MICE

RECEIVING NO TREATMENT
**TABLE F1. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of Leukemia in Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical Incidence at EG&amp;G Mason Research Institute (b)</td>
<td></td>
</tr>
<tr>
<td>4,4'-Methylenedianiline • 2 HCl</td>
<td>12/50</td>
</tr>
<tr>
<td>Monuron</td>
<td>5/50</td>
</tr>
<tr>
<td>8-Hydroxyquinoline</td>
<td>17/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)phthlate</td>
<td>13/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)adipate</td>
<td>9/49</td>
</tr>
<tr>
<td>Guar gum</td>
<td>13/50</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>21/50</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>10/50</td>
</tr>
<tr>
<td>Agar</td>
<td>9/50</td>
</tr>
<tr>
<td>Tara gum</td>
<td>14/50</td>
</tr>
<tr>
<td>2,6-Toluenediamine • 2 HCl</td>
<td>9/50</td>
</tr>
<tr>
<td>4,4'-Oxydianiline</td>
<td>23/50</td>
</tr>
<tr>
<td>2-Biphenylamine • HCl</td>
<td>15/50</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>(b) 10/50</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>170/699 (24.3%)</td>
</tr>
<tr>
<td><strong>SD (c)</strong></td>
<td>11.96%</td>
</tr>
<tr>
<td><strong>Range (d)</strong></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>23/50</td>
</tr>
<tr>
<td>Low</td>
<td>(e) 0/50</td>
</tr>
</tbody>
</table>

**Overall Historical Incidence at All Laboratories**

| TOTAL                    | 648/2,320 (27.9%) |
| SD (c)                   | 10.67%            |
| **Range (d)**            |                   |
| High                     | 23/50              |
| Low                      | (f) 0/50           |

(a) Data as of March 16, 1983, for NTP carcinogenesis studies of at least 104 weeks.
(b) 7/50 malignant lymphoma were observed, possibly representing a difference in nomenclature.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Second lowest: 9/50
(f) Second lowest: 5/50

8-Hydroxyquinoline, NTP TR 276  126
### TABLE F2: HISTORICAL INCIDENCE OF LIVER TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoplastic Nodule</th>
<th>Hepatocellular Carcinoma</th>
<th>Neoplastic Nodule or Hepatocellular Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical Incidence at EG&amp;G Mason Research Institute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4,4’-Methylenedianiline · 2HCl</td>
<td>1/50 (2%)</td>
<td>0/50 (0%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Monuron</td>
<td>1/50 (2%)</td>
<td>0/50 (0%)</td>
<td>1/50 (0%)</td>
</tr>
<tr>
<td>3-Hydroxyquinoline</td>
<td>6/49 (12%)</td>
<td>1/49 (2%)</td>
<td>7/49 (14%)</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)phthalate</td>
<td>2/50 (4%)</td>
<td>1/50 (2%)</td>
<td>3/50 (6%)</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)adipate</td>
<td>2/60 (4%)</td>
<td>0/49 (0%)</td>
<td>0/60 (0%)</td>
</tr>
<tr>
<td>Guar gum</td>
<td>2/50 (4%)</td>
<td>1/50 (2%)</td>
<td>3/50 (6%)</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>0/50 (0%)</td>
<td>1/50 (2%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>3/49 (6%)</td>
<td>1/49 (2%)</td>
<td>4/49 (8%)</td>
</tr>
<tr>
<td>Agar</td>
<td>0/50 (0%)</td>
<td>0/50 (0%)</td>
<td>0/50 (0%)</td>
</tr>
<tr>
<td>Tara gum</td>
<td>1/49 (2%)</td>
<td>0/49 (0%)</td>
<td>1/49 (2%)</td>
</tr>
<tr>
<td>2,6-Toluenediame · 2HCl</td>
<td>0/50 (0%)</td>
<td>0/50 (0%)</td>
<td>0/50 (0%)</td>
</tr>
<tr>
<td>4,4’-Oxydianiline</td>
<td>1/50 (2%)</td>
<td>0/50 (0%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>2-Biphenylamine · HCl</td>
<td>0/49 (0%)</td>
<td>0/49 (0%)</td>
<td>0/49 (0%)</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>1/48 (2%)</td>
<td>0/48 (0%)</td>
<td>1/48 (0%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>20/693 (3%)</td>
<td>5/693 (1%)</td>
<td>25/693 (4%)</td>
</tr>
<tr>
<td>SD (b)</td>
<td>3.27%</td>
<td>1.00%</td>
<td>3.93%</td>
</tr>
<tr>
<td>Range (c)</td>
<td>0%-8%</td>
<td>0%-2%</td>
<td>0%-14%</td>
</tr>
</tbody>
</table>

| Overall Historical Incidence at All Laboratories                  |                   |                          |                                               |
| TOTAL                                                             | 78/2,306 (3%)     | 18/2,306 (1%)            | 96/2,306 (4%)                                 |
| SD (b)                                                           | 4.47%             | 1.16%                    | 5.06%                                         |
| Range (c)                                                        | 0%-12%            | 0%-4%                    | 0%-14%                                        |

(a) Data as of March 16, 1983, for studies of at least 104 weeks  
(b) Standard deviation  
(c) Range and SD are presented for groups of 35 or more animals.
### TABLE F5. HISTORICAL INCIDENCE OF LUNG TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence in Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alveolar/Bronchiolar</td>
</tr>
<tr>
<td></td>
<td>Adenoma</td>
</tr>
<tr>
<td>4,4'-Methylenedianiline · 2HCl</td>
<td>2/60</td>
</tr>
<tr>
<td>Monuron</td>
<td>1/60</td>
</tr>
<tr>
<td>8-Hydroxyquinoline</td>
<td>0/60</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)phthalate</td>
<td>1/60</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)adipate</td>
<td>0/49</td>
</tr>
<tr>
<td>Guar gum</td>
<td>0/50</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>0/50</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>0/50</td>
</tr>
<tr>
<td>Agar</td>
<td>0/60</td>
</tr>
<tr>
<td>Tara gum</td>
<td>2/50</td>
</tr>
<tr>
<td>2,6-Toludenediamine dihydrochloride</td>
<td>3/49</td>
</tr>
<tr>
<td>4,4'-Oxydianiline</td>
<td>1/50</td>
</tr>
<tr>
<td>2-Biphenylaniline · HCl</td>
<td>2/50</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>0/48</td>
</tr>
<tr>
<td>TOTAL</td>
<td>12/696 (1.7%)</td>
</tr>
<tr>
<td>SD (b)</td>
<td>2.07%</td>
</tr>
</tbody>
</table>

Range (c)

| High | 3/49 | 1/50 | 3/49 |
| Low | 0/50 | 0/50 | 0/50 |

Overall Historical Incidence

| TOTAL | 36/2,357 (1.5%) | 23/2,357 (1.0%) | 57/2,357 (2.4%) |
| SD (b) | 2.05% | 1.71% | 2.38% |

Range (c)

| High | 3/47 | 3/50 | 4/49 |
| Low | 0/89 | 0/50 | 0/50 |

(a) Data as of March 18, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence in Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-Cell Adenoma</td>
</tr>
<tr>
<td>4,4'-Methylenedianiline · 2HCl</td>
<td>1/49</td>
</tr>
<tr>
<td>Monuron</td>
<td>4/49</td>
</tr>
<tr>
<td>8-Hydroxyquinoline</td>
<td>1/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)phthalate</td>
<td>1/48</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)adipate</td>
<td>1/49</td>
</tr>
<tr>
<td>Guar gum</td>
<td>0/50</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>1/49</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>0/47</td>
</tr>
<tr>
<td>Agar</td>
<td>2/49</td>
</tr>
<tr>
<td>Tara gum</td>
<td>3/45</td>
</tr>
<tr>
<td>2,6-Toluidinediamine dihydrochloride</td>
<td>5/44</td>
</tr>
<tr>
<td>4,4'-Oxydianiline</td>
<td>3/46</td>
</tr>
<tr>
<td>2-Biphenylamine · HCl</td>
<td>2/47</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>2/42</td>
</tr>
<tr>
<td>TOTAL</td>
<td>27/664 (4.1%)</td>
</tr>
<tr>
<td>SD (b)</td>
<td>3.31%</td>
</tr>
<tr>
<td>Range (c)</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>0/50</td>
</tr>
<tr>
<td>Overall Historical Incidence</td>
<td>TOTAL</td>
</tr>
<tr>
<td>SD (b)</td>
<td>4.49%</td>
</tr>
<tr>
<td>Range (c)</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>0/50</td>
</tr>
</tbody>
</table>

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
### TABLE F5. HISTORICAL INCIDENCE OF THYROID GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT(a)

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence in Controls</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-Cell Adenoma</td>
<td>C-Cell Carcinoma</td>
<td>C-Cell Adenoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>or Carcinoma</td>
</tr>
<tr>
<td><strong>Historical Incidence at EG&amp;G Mason Research Institute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4,4'-Methylenedianiline · 2HCl</td>
<td>0/47</td>
<td>1/47</td>
<td>1/47</td>
</tr>
<tr>
<td>Monuron</td>
<td>2/49</td>
<td>0/49</td>
<td>2/49</td>
</tr>
<tr>
<td>8-Hydroxyquinoline</td>
<td>1/48</td>
<td>2/48</td>
<td>3/48</td>
</tr>
<tr>
<td>Butyl benzyl phthalate</td>
<td>0/47</td>
<td>2/47</td>
<td>2/47</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)phthalate</td>
<td>0/48</td>
<td>1/48</td>
<td>1/48</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)adipate</td>
<td>1/50</td>
<td>3/50</td>
<td>4/50</td>
</tr>
<tr>
<td>Guar gum</td>
<td>2/48</td>
<td>1/48</td>
<td>3/48</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>1/50</td>
<td>5/50</td>
<td>6/50</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>3/49</td>
<td>1/49</td>
<td>4/49</td>
</tr>
<tr>
<td>Agar</td>
<td>0/49</td>
<td>4/49</td>
<td>4/49</td>
</tr>
<tr>
<td>Tara gum</td>
<td>3/46</td>
<td>1/46</td>
<td>4/46</td>
</tr>
<tr>
<td>2,6-Toluenediamine dihydrochloride</td>
<td>2/49</td>
<td>1/49</td>
<td>3/49</td>
</tr>
<tr>
<td>4,4'-Oxydianiline</td>
<td>2/49</td>
<td>0/49</td>
<td>2/49</td>
</tr>
<tr>
<td>2-Biphenylamine · HCl</td>
<td>2/49</td>
<td>3/49</td>
<td>5/49</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>2/46</td>
<td>0/46</td>
<td>2/46</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>21/724 (2.9%)</td>
<td>25/724 (3.5%)</td>
<td>46/724 (6.4%)</td>
</tr>
<tr>
<td>SD (b)</td>
<td>2.22%</td>
<td>3.01%</td>
<td>2.88%</td>
</tr>
<tr>
<td>Range (c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3/46</td>
<td>5/50</td>
<td>6/50</td>
</tr>
<tr>
<td>Low</td>
<td>0/49</td>
<td>0/49</td>
<td>1/48</td>
</tr>
<tr>
<td><strong>Overall Historical Incidence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>119/2,317 (6.1%)</td>
<td>81/2,317 (3.5%)</td>
<td>197/2,317 (8.5%)</td>
</tr>
<tr>
<td>SD (b)</td>
<td>4.34%</td>
<td>2.99%</td>
<td>4.74%</td>
</tr>
<tr>
<td>Range (c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8/52</td>
<td>6/48</td>
<td>9/50</td>
</tr>
<tr>
<td>Low</td>
<td>0/86</td>
<td>0/82</td>
<td>0/50</td>
</tr>
</tbody>
</table>

(a) Data as of March 16, 1983, for studies of at least 104 weeks  
(b) Standard deviation  
(c) Range and SD are presented for groups of 35 or more animals.
**TABLE F8. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN MALE B6C3F1 MICE RECEIVING NO TREATMENT**

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one diagnosis of angioma
(e) Includes 17 diagnoses of angiosarcoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Hemangioma</th>
<th>Hemangiosarcoma</th>
<th>Hemangioma or Hemangiosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence in Controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Historical Incidence at EG&amp;G Mason Research Institute</strong></td>
<td>3/49</td>
<td>5/49</td>
<td>7/49</td>
</tr>
<tr>
<td>4,4'-Methyleneedianiline · 2HCl</td>
<td>0/50</td>
<td>2/50</td>
<td>2/50</td>
</tr>
<tr>
<td>Monuron</td>
<td>7/50</td>
<td>3/50</td>
<td>10/60</td>
</tr>
<tr>
<td>Butyl benzyl phthalate</td>
<td>0/50</td>
<td>1/50</td>
<td>1/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)phthalate</td>
<td>0/50</td>
<td>1/50</td>
<td>1/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)adipate</td>
<td>0/50</td>
<td>2/50</td>
<td>2/50</td>
</tr>
<tr>
<td>Guar gum</td>
<td>1/50</td>
<td>4/50</td>
<td>5/50</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>1/50</td>
<td>3/50</td>
<td>4/50</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>0/49</td>
<td>2/49</td>
<td>2/49</td>
</tr>
<tr>
<td>Tara gum</td>
<td>3/50</td>
<td>1/50</td>
<td>4/50</td>
</tr>
<tr>
<td>Agar</td>
<td>0/49</td>
<td>1/49</td>
<td>1/49</td>
</tr>
<tr>
<td>2,6-Toluenediamine · 2HCl</td>
<td>1/50</td>
<td>0/50</td>
<td>1/50</td>
</tr>
<tr>
<td>4,4'-Oxydianiline</td>
<td>0/50</td>
<td>4/50</td>
<td>4/50</td>
</tr>
<tr>
<td>2-Biphenylamine · HCl</td>
<td>0/50</td>
<td>0/50</td>
<td>0/50</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>1/48</td>
<td>2/48</td>
<td>3/48</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>17/745 (2.3%)</td>
<td>31/745 (4.2%)</td>
<td>47/745 (6.3%)</td>
</tr>
<tr>
<td><strong>SD (b)</strong></td>
<td>3.85%</td>
<td>3.00%</td>
<td>5.36%</td>
</tr>
<tr>
<td><strong>Range (c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>7/50</td>
<td>5/49</td>
<td>10/50</td>
</tr>
<tr>
<td>Low</td>
<td>0/50</td>
<td>0/50</td>
<td>0/50</td>
</tr>
<tr>
<td><strong>Overall Historical Incidence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>(d) 34/2,395 (1.4%)</td>
<td>(e) 65/2,395 (2.7%)</td>
<td>98/2,395 (4.1%)</td>
</tr>
<tr>
<td><strong>SD (b)</strong></td>
<td>2.45%</td>
<td>2.55%</td>
<td>3.85%</td>
</tr>
<tr>
<td><strong>Range (c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>7/50</td>
<td>5/49</td>
<td>10/50</td>
</tr>
<tr>
<td>Low</td>
<td>0/52</td>
<td>0/50</td>
<td>0/50</td>
</tr>
</tbody>
</table>
# TABLE F7. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F1 MICE RECEIVING NO TREATMENT (a)

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence in Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malignant Lymphoma</td>
<td>Lymphoma or Leukemia</td>
</tr>
<tr>
<td>historical incidence at EG&amp;G mason research institute (b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4,4'-Methylenedianiline · 2 HCl</td>
<td>10/49</td>
<td>10/49</td>
</tr>
<tr>
<td>Monuron</td>
<td>3/50</td>
<td>3/50</td>
</tr>
<tr>
<td>8-Hydroxyquinoline</td>
<td>12/50</td>
<td>12/50</td>
</tr>
<tr>
<td>Butyl benzyl phthalate</td>
<td>13/50</td>
<td>14/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl) phthalate</td>
<td>8/50</td>
<td>9/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl) adipate</td>
<td>16/50</td>
<td>15/50</td>
</tr>
<tr>
<td>Guar gum</td>
<td>7/50</td>
<td>7/50</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>12/50</td>
<td>12/50</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>9/49</td>
<td>9/49</td>
</tr>
<tr>
<td>Tara gum</td>
<td>6/50</td>
<td>6/50</td>
</tr>
<tr>
<td>Agar</td>
<td>2/49</td>
<td>3/49</td>
</tr>
<tr>
<td>2,6-Toluenediamine · 2 HCl</td>
<td>2/50</td>
<td>2/50</td>
</tr>
<tr>
<td>4,4'-Oxydianiline</td>
<td>9/50</td>
<td>9/50</td>
</tr>
<tr>
<td>2,3-Biphenylamine · HCl</td>
<td>6/50</td>
<td>6/50</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>4/48</td>
<td>4/48</td>
</tr>
<tr>
<td>TOTAL</td>
<td>119/745 (16%)</td>
<td>121/745 (16.2%)</td>
</tr>
<tr>
<td>SD (b)</td>
<td>8.43%</td>
<td>8.42%</td>
</tr>
<tr>
<td>Range (c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>16/50</td>
<td>16/50</td>
</tr>
<tr>
<td>Low</td>
<td>2/50</td>
<td>2/50</td>
</tr>
<tr>
<td>overall historical incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>281/2,395 (11.7%)</td>
<td>298/2,395 (12.4%)</td>
</tr>
<tr>
<td>SD (b)</td>
<td>6.81%</td>
<td>7.05%</td>
</tr>
<tr>
<td>Range (c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>16/50</td>
<td>16/50</td>
</tr>
<tr>
<td>Low</td>
<td>1/52</td>
<td>1/52</td>
</tr>
</tbody>
</table>

(a) Data as of March 16, 1983, studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

8-Hydroxyquinoline, NTP TR 276
<table>
<thead>
<tr>
<th>Study</th>
<th>Hemangioma in Controls</th>
<th>Hemangiosarcoma</th>
<th>Hemangioma or Hemangiosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,4'-Methylenedianiline - 2HCl</td>
<td>2/50</td>
<td>1/50</td>
<td>3/50</td>
</tr>
<tr>
<td>Monuron</td>
<td>1/50</td>
<td>1/50</td>
<td>2/50</td>
</tr>
<tr>
<td>8-Hydroxyquinoline</td>
<td>0/50</td>
<td>0/50</td>
<td>0/50</td>
</tr>
<tr>
<td>Butyl benzyl phthalate</td>
<td>1/50</td>
<td>1/50</td>
<td>2/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)phthalate</td>
<td>3/50</td>
<td>0/50</td>
<td>3/50</td>
</tr>
<tr>
<td>Di(2-ethylhexyl)adipate</td>
<td>3/50</td>
<td>3/50</td>
<td>3/50</td>
</tr>
<tr>
<td>Guar gum</td>
<td>3/50</td>
<td>0/50</td>
<td>3/50</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>0/50</td>
<td>3/50</td>
<td>3/50</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>1/49</td>
<td>0/49</td>
<td>1/49</td>
</tr>
<tr>
<td>Tara gum</td>
<td>1/50</td>
<td>1/50</td>
<td>2/50</td>
</tr>
<tr>
<td>Agar</td>
<td>0/50</td>
<td>1/50</td>
<td>1/50</td>
</tr>
<tr>
<td>2,6-Toluenediamine - 2HCl</td>
<td>2/50</td>
<td>0/50</td>
<td>2/50</td>
</tr>
<tr>
<td>4,4'-Oxydianiline</td>
<td>0/50</td>
<td>0/50</td>
<td>0/50</td>
</tr>
<tr>
<td>2-Biphenylamine - HCl</td>
<td>0/49</td>
<td>0/49</td>
<td>0/49</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>1/50</td>
<td>3/50</td>
<td>4/50</td>
</tr>
<tr>
<td>TOTAL</td>
<td>15/748 (2.0%)</td>
<td>14/748 (1.9%)</td>
<td>29/748 (3.9%)</td>
</tr>
<tr>
<td>SD (b)</td>
<td>2.14%</td>
<td>2.33%</td>
<td>2.56%</td>
</tr>
</tbody>
</table>

Range (c)

<table>
<thead>
<tr>
<th>Range</th>
<th>Hemangioma in Controls</th>
<th>Hemangiosarcoma</th>
<th>Hemangioma or Hemangiosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>3/50</td>
<td>3/50</td>
<td>4/50</td>
</tr>
<tr>
<td>Low</td>
<td>0/50</td>
<td>0/50</td>
<td>0/50</td>
</tr>
</tbody>
</table>

Overall Historical Incidence

| TOTAL | (d) 39/2,537 (1.5%) | (e) 51/2,537 (2.0%) | 90/2,537 (3.5%) |
| SD (b) | 1.87% | 2.37% | 2.81% |

Range (c)

<table>
<thead>
<tr>
<th>Range</th>
<th>Hemangioma in Controls</th>
<th>Hemangiosarcoma</th>
<th>Hemangioma or Hemangiosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>3/47</td>
<td>4/50</td>
<td>5/49</td>
</tr>
<tr>
<td>Low</td>
<td>0/51</td>
<td>0/50</td>
<td>0/50</td>
</tr>
</tbody>
</table>

(a) Data as of March 16, 1983, for studies of at least 104 weeks.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes three diagnoses of angioma
(e) Includes eight diagnoses of angiosarcoma
<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence in Controls</th>
<th>Malignant Lymphoma</th>
<th>Lymphoma or Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,4'-Methyleneedianiline · 2 HCl</td>
<td>13/50</td>
<td>13/50</td>
<td></td>
</tr>
<tr>
<td>Monuron</td>
<td>16/50</td>
<td>16/50</td>
<td></td>
</tr>
<tr>
<td>8-Hydroxyquinoline</td>
<td>13/50</td>
<td>13/50</td>
<td></td>
</tr>
<tr>
<td>Butyl benzyl phthalate</td>
<td>17/50</td>
<td>17/50</td>
<td></td>
</tr>
<tr>
<td>Di(2-ethylhexyl)phthalate</td>
<td>10/50</td>
<td>10/50</td>
<td></td>
</tr>
<tr>
<td>Di(2-ethylhexyl)adipate</td>
<td>23/50</td>
<td>23/50</td>
<td></td>
</tr>
<tr>
<td>Guar gum</td>
<td>19/50</td>
<td>19/50</td>
<td></td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>31/50</td>
<td>31/50</td>
<td></td>
</tr>
<tr>
<td>Gum arabic</td>
<td>18/49</td>
<td>19/49</td>
<td></td>
</tr>
<tr>
<td>Tara gum</td>
<td>18/50</td>
<td>18/50</td>
<td></td>
</tr>
<tr>
<td>Agar</td>
<td>9/50</td>
<td>9/50</td>
<td></td>
</tr>
<tr>
<td>2,6-Toluenediamine · 2 HCl</td>
<td>4/50</td>
<td>4/50</td>
<td></td>
</tr>
<tr>
<td>4,4'-Oxydianiline</td>
<td>15/50</td>
<td>15/50</td>
<td></td>
</tr>
<tr>
<td>2-Biphenylamine · HCl</td>
<td>10/49</td>
<td>10/49</td>
<td></td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>18/50</td>
<td>18/50</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>232/748 (31%)</td>
<td>232/748 (31.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>SD (b)</strong></td>
<td>12.78%</td>
<td>12.85%</td>
<td></td>
</tr>
<tr>
<td><strong>Range (c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>31/50</td>
<td>31/50</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4/50</td>
<td>4/50</td>
<td></td>
</tr>
<tr>
<td><strong>Overall Historical Incidence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>637/2,537 (25.1%)</td>
<td>689/2,537 (27.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>SD (b)</strong></td>
<td>10.03%</td>
<td>9.87%</td>
<td></td>
</tr>
<tr>
<td><strong>Range (c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>31/50</td>
<td>31/50</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4/50</td>
<td>4/50</td>
<td></td>
</tr>
</tbody>
</table>

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

8-Hydroxyquinoline, NTP TR 276 134
APPENDIX G

CHEMICAL CHARACTERIZATION OF

8-HYDROXYQUINOLINE
APPENDIX G. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Lot No. 7223-J Performed by the Analytical Chemistry Laboratory

A. Physical Properties

1. Appearance: Cream-colored powder

2. Melting Point: Determined

<table>
<thead>
<tr>
<th>Determined</th>
<th>Literature Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>73°-74°C (visual, capillary)</td>
<td>76°C (Merck Index, 1976)</td>
</tr>
</tbody>
</table>

B. Spectral Data

1. Infrared

a. Instrument: Beckman IR-12

b. Phase: 2% Potassium bromide pellet

c. Results: See Figure 5 Consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible

a. Instrument: Cary 118

b. Solvent: Methanol

Cyclohexane

c. Results: No absorbance seen in visible region (300-350 nm) at a concentration of 3 mg/ml in methanol. Two maxima observed in ultraviolet region (350-228 nm)

<table>
<thead>
<tr>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>$\varepsilon \times 10^{-3}$</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>$\varepsilon \times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>311</td>
<td>2.56 ± 0.003 (S)</td>
<td>318</td>
<td>2.30</td>
</tr>
<tr>
<td>241</td>
<td>40.00 ± 0.02 (S)</td>
<td>243</td>
<td>43.04</td>
</tr>
</tbody>
</table>

(Sadtler Standard Spectra)
FIGURE 5. INFRARED ABSORPTION SPECTRUM OF 8-HYDROXYQUINOLINE (LOT NO. 7223-J)
APPENDIX G. CHEMICAL CHARACTERIZATION

3. Nuclear Magnetic Resonance

<table>
<thead>
<tr>
<th>Determined</th>
<th>Literature Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Instrument:</td>
<td>Varian EM 360-A</td>
</tr>
<tr>
<td>b. Solvent:</td>
<td>Methanol-d₄ with internal tetramethylsilane</td>
</tr>
<tr>
<td>c. Assignments:</td>
<td>See Figure 6</td>
</tr>
<tr>
<td>d. Chemical Shift (δ):</td>
<td>Consistent with literature spectrum (Sadtler Standard Spectra)</td>
</tr>
<tr>
<td>a</td>
<td>m, 7.00-7.63 ppm</td>
</tr>
<tr>
<td>b</td>
<td>dd, 8.10 ppm</td>
</tr>
<tr>
<td>c</td>
<td>dd, 8.73 ppm</td>
</tr>
<tr>
<td>e. Coupling Constant:</td>
<td>Jbd = 4 Hz</td>
</tr>
<tr>
<td></td>
<td>Jcb = 8 Hz</td>
</tr>
<tr>
<td></td>
<td>Jcd = 2 Hz</td>
</tr>
<tr>
<td>f. Integration Ratios:</td>
<td>4.03</td>
</tr>
<tr>
<td>a</td>
<td>1.0</td>
</tr>
<tr>
<td>b</td>
<td>0.96</td>
</tr>
</tbody>
</table>

C. Titration: Percent purity based on titration of one amine group per molecule with perchloric acid in an acetic acid medium, 101.6% ± 0.2(5)%

D. Water Analysis (Karl Fischer): 0.58% ± 0.06(5)%

E. Elemental Analysis:

<table>
<thead>
<tr>
<th>Element</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theory (T)</td>
<td>74.47</td>
<td>4.86</td>
<td>9.65</td>
</tr>
<tr>
<td>Determined (D)</td>
<td>74.57</td>
<td>4.79</td>
<td>9.61</td>
</tr>
<tr>
<td></td>
<td>74.25</td>
<td>4.88</td>
<td>9.92</td>
</tr>
<tr>
<td>Percent D/T</td>
<td>99.9</td>
<td>99.5</td>
<td>101.2</td>
</tr>
</tbody>
</table>
**FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 8-HYDROXYQUINOLINE (LOT NO. 7223-J)**

<table>
<thead>
<tr>
<th>Integration</th>
<th>$\delta$ (ppm)</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) $135/, 135$</td>
<td>4.03</td>
<td>200-7.68</td>
</tr>
<tr>
<td>(b) $135/, 73.5$</td>
<td>7.90</td>
<td></td>
</tr>
<tr>
<td>(c) $34/, 33.5$</td>
<td>10.01</td>
<td>8.10</td>
</tr>
<tr>
<td>(d) $32/, 33.5$</td>
<td>0.96</td>
<td>8.73</td>
</tr>
</tbody>
</table>
F. Chromatographic Analyses

1. Thin-Layer Chromatography

a. Plates: Silica Gel 60, F254, 0.25 mm layer
b. Reference Standard: 2-Methyl, 8-quinolinol (2 μl of a 10 μg/μl solution in chloroform)
c. Amount Spotted: 100 and 300 μg (10 and 30 μl of a 10 μg/μl solution in chloroform)
d. Visualization: Ultraviolet light (254 and 366 nm) and iodine vapor

System 1: Chloroform: methanol (90:10)

(1) Rf 0.60 (major), 0.40 (minor)
(2) Rst: 0.74, 0.50

System 2: Toluene:methanol (80:20)

(1) Rf 0.43 (major), 0.33 (minor)
(2) Rst: 0.69, 0.53

2. Gas Chromatography:

a. Instrument: Varian 3740
b. Detector: Flame ionization
c. Inlet Temperature: 200°C
d. Detector Temperature: 250°C
e. Carrier Gas: Nitrogen
f. Flow Rate: 70 cc/min
g. Sample Injected: 4 μl of a 10 mg/ml solution in methylene chloride to quantitate impurities and 4 μl of a 5 mg/ml solution in methylene chloride to check for detector overloading

System 1:

(1) Column: 3% OV-225 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass
(2) Oven Temperature Program: 5 min at 50°C; then 50°-220°C at 10°C/min
(3) Results: Major peak and two impurities before the major peak with a combined area of 0.15%, relative to the area of the major peak

<table>
<thead>
<tr>
<th>Peak</th>
<th>Retention Time (min.)</th>
<th>Retention Time Relative to Major Peak</th>
<th>Area (percent of major peak)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.3</td>
<td>0.87</td>
<td>0.09</td>
</tr>
<tr>
<td>2</td>
<td>13.9</td>
<td>0.91</td>
<td>0.06</td>
</tr>
<tr>
<td>3</td>
<td>16.3</td>
<td>1.00</td>
<td>100</td>
</tr>
</tbody>
</table>

8-Hydroxyquinoline, NTP TR 276
APPENDIX G. CHEMICAL CHARACTERIZATION

System 2:

(1) **Column**: 3% OV-17 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass

(2) **Oven Temperature Program**: 5 min at 50°C; then 50°C-250°C at 10°C/min

(3) **Results**: Major peak and one impurity after the major peak with an area of 0.07% relative to the major peak.

<table>
<thead>
<tr>
<th>Peak</th>
<th>Retention Time (min.)</th>
<th>Retention Time Relative to Major Peak</th>
<th>Area (percent of major peak)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.8</td>
<td>1.00</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>20.4</td>
<td>1.29</td>
<td>0.07</td>
</tr>
</tbody>
</table>

II. Heat Stability at the Analytical Chemistry Laboratory

A. **Sample Storage**: Samples of 8-hydroxyquinoline were stored in glass vials with Teflon®-lined screw caps at -20°C, 5°C, 25°C, and 60°C for 2 weeks.

B. **Analysis**: Samples from each storage temperature were weighed and dissolved in chloroform containing hexadecane as an internal standard, at a concentration of 5 μg/μl. The samples were analyzed on a gas chromatographic system, comparing the internal standard peak to the sample peak. The recovery of 8-hydroxyquinoline for each sample was compared with the recovery for the -20°C sample.

1. **Instrument**: Varian 3740
2. **Detection**: Flame ionization
3. **Column**: 3% OV-225 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass
4. **Inlet Temperature**: 200°C
5. **Oven Temperature Program**: 130°C, isothermal
6. **Detector Temperature**: 250°C
7. **Carrier Gas**: Nitrogen
8. **Carrier Flow Rate**: 70 cc/min
9. **Sample Injected**: 5 μl solutions of 8-hydroxyquinoline from each storage temperature (5 μg/μl) in chloroform containing 1.2 μg/μl hexadecane internal standard
10. **Retention times**: Hexadecane, 0.7 min; 8-hydroxyquinoline, 1.8 min

C. **Results**:

<table>
<thead>
<tr>
<th>Storage Temperature (degrees Celsius)</th>
<th>Percent Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>100.0 ± 2.9 (6)</td>
</tr>
<tr>
<td>5</td>
<td>103.1 ± 2.9 (6)</td>
</tr>
<tr>
<td>25</td>
<td>101.6 ± 2.9 (6)</td>
</tr>
<tr>
<td>60</td>
<td>103.7 ± 3.1 (6)</td>
</tr>
</tbody>
</table>

D. **Conclusion**: 8-hydroxyquinoline is stable when stored as the bulk chemical at temperatures up to 60°C for 2 weeks.
III. Test Chemical Stability at the Testing Laboratory

A. Methods:

1. Gas chromatography:
   a. Instrument: Varian 1440 or 3700
   b. Detection: Flame ionization
   c. Column: 3% SP2250 on 100/120 Supelcoport, 6 ft × 2 mm ID, glass
   d. Inlet Temperature: 190⁰-250⁰ C
   e. Oven Temperature Program: 70⁰-250⁰ C at 6⁰ C/min
   f. Detector Temperature: 230⁰-300⁰ C

2. Infrared Spectroscopy:
   a. Instrument: Perkin-Elmer Infracord® #137
   b. Phase: Potassium bromide

B. Results:

1. Purity:

<table>
<thead>
<tr>
<th>Date of Analysis</th>
<th>Percent Purity</th>
<th>Bulk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/05/79</td>
<td>99.9</td>
<td>&gt;99.9</td>
<td></td>
</tr>
<tr>
<td>12/26/79</td>
<td>99.8</td>
<td>99.8</td>
<td></td>
</tr>
<tr>
<td>02/25/79</td>
<td>99.8</td>
<td>99.8</td>
<td></td>
</tr>
<tr>
<td>06/12/80</td>
<td>99.7</td>
<td>99.7</td>
<td></td>
</tr>
<tr>
<td>10/09/80</td>
<td>99.8</td>
<td>99.8</td>
<td></td>
</tr>
<tr>
<td>02/08/81</td>
<td>99.7</td>
<td>99.8</td>
<td></td>
</tr>
<tr>
<td>06/18/81</td>
<td>99.7</td>
<td>99.7</td>
<td></td>
</tr>
<tr>
<td>10/08/81</td>
<td>99.7</td>
<td>99.7</td>
<td></td>
</tr>
<tr>
<td>12/30/81</td>
<td>99.8</td>
<td>99.7</td>
<td></td>
</tr>
</tbody>
</table>

2. Identity: Periodic reanalysis of test and reference samples of 8-hydroxyquinoline by infrared spectroscopy confirmed the identity of the chemical.

C. Conclusion: No notable degradation occurred throughout the studies.
APPENDIX H

PREPARATION AND CHARACTERIZATION

OF FORMULATED DIETS
I. Studies Conducted at the Analytical Chemistry Laboratory

A. Preparation Procedure

1. Premix: 8-Hydroxyquinoline (11.660 ± 0.001 g for 8,000 ppm preparation) was added directly to 100 g of Wayne Lab-Blox® rodent feed. This premixture was homogenized by rotating it in a 1-qt large-mouth glass jar for 15 min on a ball-mill type tumbler apparatus, with manual end-over-end tumbling every 5 min.

2. Bulk Mixing: The above premix and 1,400 g more feed were mixed in a Patterson-Kelly® Twin Shell Blender for 15 min. The blender was loaded from the top of the shells as follows: 700 g of feed was poured in and allowed to settle and level at the bottom (vertex of the "V"); then the premix was poured in on top of the feed from each side; this layer was covered with the remaining 700 g of feed poured in from each side. After 10- and 15-min mixing times, duplicate 5-g samples were removed from the top of each shell and the bottom trap of the blender for subsequent analysis. The target concentration of 8-hydroxyquinoline in feed was 7,770 ± 50 ppm.

3. Extraction and Analysis: Each sample was placed in a 200-ml centrifuge bottle (quantitative transfer), and 50 ml of absolute methanol was added. The mixture was placed in an ultrasonic vibratory bath for 30 sec and centrifuged for 10 min. The supernatant solution (40 ml) was removed by pipette; the feed residue was mixed with an additional 50 ml of methanol and extracted again as described above. The combined supernatant solutions (80 ml) were diluted 10/100 and 5/100 with methanol and then analyzed by ultraviolet absorption spectroscopy at 241.3 nm on a Cary 118 spectrophotometer.

4. Quality Control: Blank (undosed) feed samples and individual spiked (8,000 ppm level) mixtures were extracted and prepared for analysis in the same manner described for the test samples above. Standard solutions of 8-hydroxyquinoline in methanol (1.06, 1.48, 1.92, and 2.11 μg/ml) were used to determine the extinction coefficient for the compound at the analytical wavelength and to test the Beer-Lambert relationship. The system was found effectively linear with concentration, having a least-squares correlation coefficient of >0.999. Blank sample absorbance values were 0.019 ± 0.001 absorbance unit, or 3.2% of sample absorbance, and were subtracted from the absorbance values of samples containing 8-hydroxyquinoline.

B. Homogeneity

1. Results:

<table>
<thead>
<tr>
<th>Sample Time (min) and Location</th>
<th>Average Percent Found in Chemical/Vehicle Mixture (a,b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10, Right</td>
<td>0.76 ± 0.03</td>
</tr>
<tr>
<td>10, Left</td>
<td>0.89 ± 0.03</td>
</tr>
<tr>
<td>10, Bottom</td>
<td>0.71 ± 0.03</td>
</tr>
<tr>
<td>15, Right</td>
<td>0.70 ± 0.03</td>
</tr>
<tr>
<td>15, Left</td>
<td>0.68 ± 0.03</td>
</tr>
<tr>
<td>15, Bottom</td>
<td>0.74 ± 0.03</td>
</tr>
</tbody>
</table>

(a) Mean ± standard deviation. Corrected for a spiked recovery yield of 95.0% ± 0.9% (extraction efficiency, 102%; volume correction, 96.3%).
(b) Theoretical concentration of chemical in feed, 0.777 ± 0.006%
APPENDIX H. PREPARATION AND CHARACTERIZATION

2. Conclusion: The mixture of 8-hydroxyquinoline in stock rodent feed at 8,000 ppm was homogeneous after 10 min and 15 min mixing in a Patterson-Kelley® 4-qt, twin-shell blender with intensifier bar. The variations in the samples of the mixtures were within 10% of the target concentration of chemical in the feed.

C. Heat Stability (First Study: Extraction with Methanol)

1. Sample Mixing and Storage: Samples were prepared by weighing 5 g of Wayne Lab-Blox® rodent feed into 200-ml centrifuge bottles. 8-Hydroxyquinoline (40 mg, individual samples accurately weighed to ± 0.1 mg) was added to each feed sample, and the contents of the bottles were mixed on a vortex mixer for 15 sec. Duplicate samples were used as spikes for recovery determinations and stored for 2 weeks at -20°, 5°, 25°, and 45° C. No attempt was made to protect the samples from light.

2. Extraction and Analysis: Each 5-g sample was equilibrated at room temperature and triturated with 60 ml of methanol for 30 sec using a Brinkmann Polytron® high-speed blender. The mixture was then placed in an ultrasonic vibratory bath for 30 sec and then centrifuged for 10 min. A portion of the supernatant solution (50 ml) was pipetted into a separate flask. The feed residue was mixed with an additional 25 ml of methanol and extracted again as described above. An 8-ml aliquot of the combined supernatant solutions (75 ml total) was transferred to a 10-ml volumetric flask, and 2 ml of a 2 mg/ml solution of 2-methoxy-naphthalene in methanol was added (as internal reference standard for chromatographic analysis). This solution was then used for gas chromatographic analysis.

   a. Instrument: Bendix 2500
   b. Column: 3% OV-1 on 80/100 mesh Supelcoport; 1.8 m × 2 mm ID, glass
   c. Detector: Flame ionization
   d. Carrier Gas: Nitrogen
   e. Flow Rate: 30 cc/min
   f. Temperatures: Oven, 130° C, isothermal; injector, 170° C; detector, 250° C
   g. Retention Times: 8-Hydroxyquinoline, 2.8 min; internal standard, 4.5 min

3. Quality Control: Analyses were performed in duplicate for each storage temperature. 2-Methoxynaphthalene was used as an internal reference standard. Room temperature recovery studies were performed in duplicate at the 8,000-ppm level. Blank (undosed) feed samples were extracted and prepared for analysis in the same manner described above for the test samples. Blanks showed no interference from feed at the retention time of the major component. Detector linearity was established using methanolic standard solutions of 25.2, 50.4, and 100.9 µg/ml for the 8-hydroxyquinoline and 25.4, 50.8, and 101.5 for the 2-methoxynaphthalene internal reference compound. Least-squares plot correlation coefficients for both compounds were >0.999 (effectively 1.0, linear).

145 8-Hydroxyquinoline, NTP TR 276
4. Results:

<table>
<thead>
<tr>
<th>Storage Temperature (°C)</th>
<th>Target Concentration (a) (percent wt/wt)</th>
<th>Determined Concentration (a,b) (percent wt/wt)</th>
<th>Percent of Theory (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>0.81 ± 0.01</td>
<td>0.80 ± 0.03</td>
<td>99 ± 3</td>
</tr>
<tr>
<td>5</td>
<td>0.82 ± 0.01</td>
<td>0.80 ± 0.03</td>
<td>98 ± 3</td>
</tr>
<tr>
<td>25</td>
<td>0.81 ± 0.01</td>
<td>0.64 ± 0.03</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>45</td>
<td>0.80 ± 0.01</td>
<td>0.47 ± 0.03</td>
<td>59 ± 3</td>
</tr>
</tbody>
</table>

(a) ± Standard deviation
(b) Corrected for spike recovery yield of 99 ± 3% (extraction efficiency, 103.8%; volume correction, 96.2%) 

5. Conclusions: 8-Hydroxyquinoline mixed with stock rodent feed at 8,000 ppm was stable when stored for 2 weeks at temperatures of 5°C and below. Samples stored at 25°C and 45°C for the 2-week period showed significant loss of the test chemical upon analysis.

D. Stability (Second Study: Extraction with Acidified Methanol)

1. Preparation and Storage of Experimental Feed Blend: A 1-kg batch of feed formulated with 8-hydroxyquinoline to a concentration of approximately 8,000 ppm was prepared for the new stability study and for evaluating the effectiveness of different extracting solutions to recover the chemical from aged feed blend. 8-Hydroxyquinoline (7.988 ± 0.001 g) was transferred to a 600-ml beaker and mixed with approximately 8 g of feed (NIH 07 Rat and Mouse Ration). More feed was added in 15- and 30-g amounts with mixing between additions; then a final weight of feed was added and mixed in, making the total weight of the premix 200.0 g.

A 350-g portion of feed was layered evenly into the bottom of a stainless steel 4-qt capacity Patterson-Kelly® twin-shell blender equipped with an intensifier bar. The 200-g premix was added in equal amounts to both sides of the blender; then the fine material adhering to the beaker walls was taken up by stirring 100 g of feed in the beaker for a few seconds and adding it to the blender. A final 350-g portion of feed was layered over the premix, and the blender ports were sealed.

Blending was conducted with the intensifier bar turned ON for the first 5 min and turned OFF for the next 10 min of mixing. The outside of the blender was given a firm tap periodically with a block of wood to dislodge any feed packed in the corners of the blender. At the end of the 15-min mixing period, the blend was divided equally into four screw-cap jars and tightly sealed. The individual jars were stored in the dark at -20°C, 5°C, 25°C, or 45°C for the 2-week stability study. The target concentration of the 8-hydroxyquinoline in the feed blend was 7.99 mg/g.

8-Hydroxyquinoline was completely recovered from freshly prepared feed blends using methanol alone as the extractant; however, when the feed blend had been stored for a period of time, recovery of the chemical was significantly reduced. Therefore, for evaluating the different extracting mixtures, the feed sample prepared above and stored 2 weeks at 45°C was used for the study.

A series of methanol solutions containing 0.05%, 0.1%, 0.5%, 1%, and 5% hydrochloric acid by volume were prepared and used for the analysis of the stored feed blend, following the procedure below.
2. Analysis Procedure: Feed samples (10.00 g in 200-ml centrifuge bottles) were extracted with 100 ml of the selected solvent mixture by shaking for 30 min on a Burrell Wrist Action® shaker.

Aliquots from the extracts (2 ml), clarified by centrifugation, were diluted to 200 ml with methanol-acetic acid solution (99:1). After thorough mixing, a few milliliters of the diluted solution were filtered through a 0.5-μ Millipore® filter into 5-ml septum vials. The 8-hydroxyquinoline content of the solution was determined by the high-performance liquid chromatography system described below.

a. Instrument: Varian 500 Liquid Chromatograph
b. Column: Waters Associates μBondapak C18, 300 mm × 4 mm ID
c. Guard Column: Whatman CO:PELL, 72 mm × 4 mm ID
d. Detector: Waters Associates Model 440, UV at 254 nm
e. Mobile Phase: 60% 2 mM ethylenediaminetetraacetic acid, disodium salt in water-acetic acid (99:1); 40% methanol-acetic acid (99:1)
f. Flow Rate: 1 ml/min
g. Retention Time: 4.1 min

3. Recovery Study Results:

<table>
<thead>
<tr>
<th>Hydrochloric Acid in Methanol Extracting Mixture (v/v)</th>
<th>8-Hydroxyquinoline in Feed (mg/g)</th>
<th>Percent Recovered (Detected/Target × 100) (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>59</td>
</tr>
<tr>
<td>0.05%</td>
<td>6.15</td>
<td>77</td>
</tr>
<tr>
<td>0.10%</td>
<td>6.15</td>
<td>77</td>
</tr>
<tr>
<td>0.50%</td>
<td>6.7</td>
<td>84</td>
</tr>
<tr>
<td>1.00%</td>
<td>6.5</td>
<td>81</td>
</tr>
<tr>
<td>5.00%</td>
<td>5.9</td>
<td>74</td>
</tr>
</tbody>
</table>

(a) Target concentration of 8-hydroxyquinoline in feed was 7.99 mg/g.

4. Conclusions: Highest recovery of 8-hydroxyquinoline (approximately 84%) was obtained from the feed stored 2 weeks at 45° C when methanol containing 0.5% hydrochloric acid by volume was used as the extractant. This contrasts with the 59% recovery previously reported when methanol alone was used as the extractant.
APPENDIX I

ANALYSIS OF FORMULATED DIETS: METHODS
I. Analysis at Analytical Chemistry Laboratory

A. Preparation of Standard Spiked Feed

Two working standard solutions of 8-hydroxyquinoline in acidified methanol (5 ml concentrated hydrochloric acid per liter of solution) were prepared independently at concentrations of 2.49 and 1.97 mg/ml. These solutions were further diluted with acidified methanol to concentrations of 1.25, 0.99, 0.62, or 0.49 mg/ml. Aliquots (20 ml) of the six standard solutions were pipetted into individual 200-ml centrifuge bottles containing 5 g of undosed feed to make spiked feed standards bracketing the specified dose range of the referee sample. One 200-ml centrifuge bottle containing 5 g of undosed feed was treated with 20 ml of acidified methanol for use as a blank. The spiked feeds and the feed blank were sealed and allowed to remain overnight at room temperature prior to analysis.

B. Preparation of the Referee Sample

Triplicate weights of the dosed feed sample (approximately 5 g weighed to the nearest 0.01 g) were transferred to individual 200-ml centrifuge bottles. Acidified methanol (20 ml) was pipetted on each sample; then the bottles were sealed and allowed to stand overnight at room temperature with the standards and feed blank.

C. Analysis Procedure

The next day, 80 ml of acidified methanol was pipetted into each blank, standard, and referee sample bottle. The bottles were sonicated in an ultrasonic vibratory bath for 1 min and shaken for 15 min at maximum stroke on a Burrell Model 75 Wrist-Action® shaker. The extraction mixtures were centrifuged for 10 min; then 10-ml aliquots of the supernatant solutions were diluted to 100 ml with acidified methanol. A 5-ml aliquot of each sample was further diluted to 100 ml with acidified methanol, and the absorbance of the solutions was read versus acidified methanol at 256 nm in 1-cm quartz cells on a Cary 118 spectrophotometer.

The total amount of 8-hydroxyquinoline in the dosed referee feed samples was computed from the linear regression equation obtained by plotting the absorbance of each spiked feed sample and blank versus the amount of chemical in the respective spiked feed sample and blank.

D. Quality Assurance Measures

The dosed referee feed sample was analyzed in triplicate, and the undosed feed sample was analyzed once. Individually spiked portions of undosed feed (six levels) prepared from two independently weighed standards were treated like the dosed referee feed samples for obtaining standard curve data. The linearity of the standard curve data was evaluated by the regression equation.
II. Analysis of Formulated Diets for Concentration of 8-Hydroxyquinoline at the Testing Laboratory

A. Method Used Until June 1980

Duplicate samples of 2 g each were extracted with 50 ml of absolute methanol in 100-ml ground-glass-stoppered graduated cylinders by repeated inversions of the cylinders for approximately 15 min. The feed particles were allowed to settle overnight in a refrigerator at 4° C, and the absorbances of the supernatants were measured at 241.5 nm in a Beckman DU® spectrophotometer after appropriate dilutions with methanol. Spiked feed samples and blank feed were extracted and analyzed in the same manner to provide a calibration curve that was used to determine the concentration of test compound in the submitted samples.

B. Method Used After June 1980

In the revised method, feed samples were extracted with 50 ml methanol containing 0.5% hydrochloric acid, rather than with absolute methanol.
APPENDIX J

ANALYSES OF FORMULATED DIETS: DATA
### TABLE J1. ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Date Mixed</th>
<th>Target Concentration (ppm)</th>
<th>Actual Concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/19/79</td>
<td>(a) 400</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>460</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>880</td>
</tr>
<tr>
<td></td>
<td>1,500</td>
<td>1,600</td>
</tr>
<tr>
<td></td>
<td>3,000</td>
<td>2,800</td>
</tr>
<tr>
<td></td>
<td>6,000</td>
<td>6,000</td>
</tr>
<tr>
<td>(a) 12,000</td>
<td></td>
<td>12,000</td>
</tr>
<tr>
<td>12,000</td>
<td></td>
<td>12,800</td>
</tr>
<tr>
<td>12,000</td>
<td></td>
<td>11,600</td>
</tr>
<tr>
<td>3/7/79</td>
<td>(a) 400</td>
<td>410</td>
</tr>
<tr>
<td>400</td>
<td></td>
<td>410</td>
</tr>
<tr>
<td>400</td>
<td></td>
<td>380</td>
</tr>
</tbody>
</table>

(a) Samples of the 400- and 1,200-ppm dose mixtures were taken from three different areas of the blender to confirm homogeneity of feed blends.

### TABLE J2. CONCENTRATIONS OF 8-HYDROXYQUINOLINE IN FEED IN THE TWO-YEAR STUDIES (a)

<table>
<thead>
<tr>
<th>Date Mixed</th>
<th>Determined Concentration for Target Concentration of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,500 ppm 3,000 ppm</td>
</tr>
<tr>
<td>12/18/79</td>
<td>1,550 3,000</td>
</tr>
<tr>
<td>02/08/80</td>
<td>1,480 3,000</td>
</tr>
<tr>
<td>04/18/80</td>
<td>1,480 2,950</td>
</tr>
<tr>
<td>06/27/80</td>
<td>1,550 3,100</td>
</tr>
<tr>
<td>07/18/80</td>
<td>1,500 2,830</td>
</tr>
<tr>
<td>09/19/80</td>
<td>1,400 2,850</td>
</tr>
<tr>
<td>12/19/80</td>
<td>1,560 3,000</td>
</tr>
<tr>
<td>01/23/81</td>
<td>1,560 3,050</td>
</tr>
<tr>
<td>03/13/81</td>
<td>1,500 2,850</td>
</tr>
<tr>
<td>06/05/81</td>
<td>(b) 1,300 2,760</td>
</tr>
<tr>
<td>06/09/81</td>
<td>(c) 1,460</td>
</tr>
<tr>
<td>07/02/81</td>
<td>1,440 3,230</td>
</tr>
<tr>
<td>09/11/81</td>
<td>1,580 3,100</td>
</tr>
<tr>
<td>11/06/81</td>
<td>1,570 3,050</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1,485 2,982</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (ppm)</td>
<td>89.0 131.6</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>6.0 4.4</td>
</tr>
<tr>
<td>Coefficient of variation (percent)</td>
<td>1,300-1,580 2,760-3,230</td>
</tr>
<tr>
<td>Range (ppm)</td>
<td>13 13</td>
</tr>
</tbody>
</table>

(a) The data presented are the average of the results of duplicate analyses.
(b) Out of tolerance. Not used in study.
(c) Remix. Not included in mean.
### TABLE J3. REFEREE SAMPLE DATA FOR THE TWO-YEAR FEED STUDIES OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Date Mixed</th>
<th>Target Concentration (ppm)</th>
<th>Testing Laboratory</th>
<th>Analytical Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/18/80</td>
<td>1,500</td>
<td>1,480</td>
<td>1,460</td>
</tr>
<tr>
<td>09/19/80</td>
<td>3,000</td>
<td>2,850</td>
<td>2,830</td>
</tr>
<tr>
<td>06/05/81</td>
<td>1,500</td>
<td>1,300</td>
<td>1,510</td>
</tr>
<tr>
<td>11/06/81</td>
<td>3,000</td>
<td>3,050</td>
<td>3,000</td>
</tr>
</tbody>
</table>
APPENDIX K

SENTINEL ANIMAL PROGRAM
APPENDIX K. SENTINEL ANIMAL PROGRAM

A. METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect test results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the test rooms. These animals are untreated, and these animals and the test animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F1 mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

<table>
<thead>
<tr>
<th>Hemagglutination Inhibition</th>
<th>Complement Fixation</th>
<th>ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVM (pneumonia virus of mice)</td>
<td>M.A. (mouse adenovirus)</td>
<td>MHV (mouse hepatitis virus)</td>
</tr>
<tr>
<td>Reo 3 (reovirus type 3)</td>
<td>LCM (lymphocytic choriomeningitis virus)</td>
<td>MHV (6, 12, and 18 months)</td>
</tr>
<tr>
<td>GDVII (Thieler's encephalomyelitis virus)</td>
<td>Sendai (6 months)</td>
<td></td>
</tr>
<tr>
<td>Poly (polyoma virus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVM (minute virus of mice)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectro (infectious ectromelia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sendai (12, 18, and 24 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>RCV (rat coronavirus)</td>
<td>Sendai (6 months)</td>
</tr>
<tr>
<td>PVM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRV (Kilham rat virus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-1 (Toolan's H-1 virus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sendai (12, 18, and 24 months)</td>
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<td></td>
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B. RESULTS

Results are presented in Table K1.
<table>
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<th>Interval</th>
<th>No. of Animals</th>
<th>Positive Serologic Reaction for</th>
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</thead>
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<td><strong>RATS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>10/10</td>
<td>PVM</td>
</tr>
<tr>
<td></td>
<td>10/10</td>
<td>RCV</td>
</tr>
<tr>
<td>12 months</td>
<td>10/10</td>
<td>PVM</td>
</tr>
<tr>
<td></td>
<td>9/10</td>
<td>Sendai</td>
</tr>
<tr>
<td></td>
<td>1/10</td>
<td>KRV</td>
</tr>
<tr>
<td>18 months</td>
<td>8/8</td>
<td>PVM</td>
</tr>
<tr>
<td></td>
<td>8/8</td>
<td>Sendai</td>
</tr>
<tr>
<td></td>
<td>8/8</td>
<td>RCV</td>
</tr>
<tr>
<td>24 months</td>
<td>9/10</td>
<td>PVM</td>
</tr>
<tr>
<td></td>
<td>10/10</td>
<td>Sendai</td>
</tr>
<tr>
<td></td>
<td>2/2</td>
<td>RCV</td>
</tr>
<tr>
<td><strong>MICE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>8/10</td>
<td>PVM</td>
</tr>
<tr>
<td>12 months</td>
<td>6/8</td>
<td>PVM</td>
</tr>
<tr>
<td></td>
<td>1/10</td>
<td>Sendai</td>
</tr>
<tr>
<td>18 months</td>
<td>2/10</td>
<td>PVM</td>
</tr>
<tr>
<td></td>
<td>2/10</td>
<td>Sendai</td>
</tr>
<tr>
<td>24 months</td>
<td>6/10</td>
<td>PVM</td>
</tr>
<tr>
<td></td>
<td>2/10</td>
<td>Reo 3</td>
</tr>
<tr>
<td></td>
<td>1/10</td>
<td>Sendai</td>
</tr>
<tr>
<td></td>
<td>1/10</td>
<td>MHV</td>
</tr>
</tbody>
</table>

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.
8-Hydroxyquinoline, NTP TR 276
APPENDIX L

FEED AND COMPOUND CONSUMPTION
BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES
OF 8-HYDROXYQUINOLINE
### TABLE L1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Week</th>
<th>Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(grams)</td>
<td>(grams)</td>
<td>(grams)</td>
</tr>
<tr>
<td></td>
<td>Feed/</td>
<td>Body</td>
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</tr>
<tr>
<td></td>
<td>Day (a)</td>
<td>Weight</td>
<td>Day (a)</td>
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<tr>
<td>11</td>
<td>18.1</td>
<td>329</td>
<td>17.9</td>
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<td>353</td>
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<td>380</td>
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<td>395</td>
<td>22.9</td>
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<td>462</td>
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<td>19.9</td>
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<td>20.7</td>
<td>476</td>
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<td>21.9</td>
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<td>20.1</td>
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<td>71</td>
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<td>477</td>
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<td>463</td>
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<td>472</td>
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<td>87</td>
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<td>450</td>
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</tr>
<tr>
<td>Mean</td>
<td>21.7</td>
<td>425</td>
<td>20.2</td>
</tr>
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</table>

(a) Grams of feed consumed per animal per day
(b) Grams of feed per day for the dosed group divided by the same value for the controls
(c) Milligrams of compound consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) \times 100
### TABLE 1. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Week</th>
<th>Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Grams/Day (a)</td>
<td>Body Weight (grams)</td>
<td>Grams/Day (a)</td>
</tr>
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<td>164</td>
<td>14.4</td>
</tr>
<tr>
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<td>187</td>
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</tr>
<tr>
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<td>16.9</td>
<td>203</td>
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</tr>
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<td>18.1</td>
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<td>297</td>
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<td>307</td>
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<td>316</td>
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<td>72</td>
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<td>324</td>
<td>16.0</td>
</tr>
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<td>76</td>
<td>16.7</td>
<td>328</td>
<td>15.0</td>
</tr>
<tr>
<td>80</td>
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<td>334</td>
<td>15.4</td>
</tr>
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<td>84</td>
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<td>339</td>
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<td>88</td>
<td>17.4</td>
<td>340</td>
<td>14.4</td>
</tr>
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<td>92</td>
<td>17.4</td>
<td>347</td>
<td>13.3</td>
</tr>
<tr>
<td>96</td>
<td>18.3</td>
<td>344</td>
<td>16.4</td>
</tr>
<tr>
<td>100</td>
<td>16.9</td>
<td>336</td>
<td>16.9</td>
</tr>
</tbody>
</table>

Mean 17.0 274 15.2 265 0.9 89 13.4 249 0.8 166
SD (d) 1.2 1.6 0.1 18 0.9 0.1 29
CV (e) 7.1 10.5 11.1 20.2 6.7 12.5 17.8

(a) Grams of feed consumed per animal per day
(b) Grams of feed per day for the dosed group divided by the same value for the controls
(c) Milligrams of compound consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100
### TABLE L3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Week</th>
<th>Control</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grams Body</td>
<td>Grams Body</td>
<td>Grams Body</td>
</tr>
<tr>
<td></td>
<td>Feed/ Weight</td>
<td>Feed/ Weight</td>
<td>Feed/ Weight</td>
</tr>
<tr>
<td></td>
<td>Day (a) (grams)</td>
<td>Day (a) (grams)</td>
<td>Day (a) (grams)</td>
</tr>
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<td>7.4 29 7.4 29 1.0 384 5.6 29 0.7 576</td>
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<td></td>
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<tr>
<td>12</td>
<td>5.9 34 5.9 33 1.0 266 5.0 33 0.9 455</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
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<tr>
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- **Mean**: 7.2 41 5.8 41 0.8 217 5.2 40 0.7 396
- **SD (d)**: 1.1 0.5 0.1 45 0.4 0.1 68
- **CV (e)**: 15.3 8.6 12.5 20.7 7.7 14.3 17.2

(a) Grams of feed consumed per animal per day
(b) Grams of feed per day for the dosed group divided by the same value for the controls
(c) Milligrams of compound consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) \times 100
<table>
<thead>
<tr>
<th>Week</th>
<th>Control Grams Body Weight (grams)</th>
<th>Low Dose Grams Body Weight (grams)</th>
<th>Low Dose Control (b) Day (grams)</th>
<th>High Dose Grams Body Weight (grams)</th>
<th>High Dose Control (b) Day (grams)</th>
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<tbody>
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<td>8.0 22</td>
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<td>8.0 26</td>
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<td>6.3 32</td>
<td>0.8 589</td>
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<td>1.0 654</td>
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<td>0.9 266</td>
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<td>0.8 575</td>
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<td>0.8 238</td>
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<td>0.6 514</td>
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<tr>
<td>88</td>
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<td>0.7 275</td>
<td>7.3 41</td>
<td>0.6 533</td>
</tr>
<tr>
<td>92</td>
<td>12.6 49</td>
<td>8.6 46</td>
<td>0.7 280</td>
<td>7.1 41</td>
<td>0.6 523</td>
</tr>
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<td>11.0 44</td>
<td>0.8 375</td>
<td>8.0 40</td>
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<td>100</td>
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<td>6.9 39</td>
<td>0.5 527</td>
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<td>Mean</td>
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<td>0.9 349</td>
<td>7.0 35</td>
<td>0.7 619</td>
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<td>SD (d)</td>
<td>1.6 0.9</td>
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<td>8.7 1.1</td>
<td>0.1 1.0</td>
<td>0.6 1.1</td>
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<tr>
<td>CV (e)</td>
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<td>11.1 13.2</td>
<td>23.2 14.3</td>
<td>10.0 17.1</td>
<td>619</td>
</tr>
</tbody>
</table>

(a) Grams of feed consumed per animal per day
(b) Grams of feed per day for the dosed group divided by the same value for the controls
(c) Milligrams of compound consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100
APPENDIX M

GENETIC TOXICOLOGY OF 8-HYDROXYQUINOLINE
TABLE M1. INDUCTION OF UNSCHEDULED DNA SYNTHESIS IN RAT HEPATOCYTES BY 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Compound (a)</th>
<th>Dose (µg/ml)</th>
<th>Net Grains per Nucleus ± Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO (percent)</td>
<td>1</td>
<td>-4.99 ± 0.23</td>
</tr>
<tr>
<td>2-Acetylaminofluorene (µg/ml)</td>
<td>10</td>
<td>18.87 ± 0.42</td>
</tr>
<tr>
<td>8-Hydroxyquinoline (µg/ml)</td>
<td>2.5</td>
<td>-3.19 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-3.43 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>-3.42 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>25 Toxic</td>
<td></td>
</tr>
</tbody>
</table>

(a) Unscheduled DNA synthesis was determined essentially by the method of Williams (1977). Hepatocytes from male F344/N rats were isolated according to the procedure of Williams et al. (1977); inoculated into Williams Medium E supplemented with 2mM glutamine, 50 µg/ml gentamicin, and 10% fetal bovine serum; and allowed to attach for 2 hours. After incubation, the cells were washed, and serum-free medium was added. Three cultures were used per dose of compound (and for controls), and cultures were exposed simultaneously to the test compound and to tritiated thymidine (10µCi/ml for 18 h. After exposure, cultures were washed, swelled in a hypotonic solution, fixed, and washed with water. The coverslips were mounted to slides, dipped in Kodak NTB-2 emulsion, and exposed at 20°C for 6 days. Cells were stained with methyl-free Pyronin. The grains over 60 morphologically unaltered cells were counted, and the highest count from two nuclear-sized areas over the most heavily labeled cytoplasmic areas adjacent to the nucleus was subtracted from the nuclear count to obtain the net grains per nucleus.

TABLE M2. TRANSFORMATION OF BALB/c-3T3 CELLS BY 8-HYDROXYQUINOLINE

<table>
<thead>
<tr>
<th>Compound (a)</th>
<th>Dose (µg/ml)</th>
<th>No. of Dishes With Foci</th>
<th>Total No. of Foci</th>
<th>No. of Foci/Dish</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO (percent)</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>3-Methylcholanthrene (µg/ml)</td>
<td>5</td>
<td>14</td>
<td>22</td>
<td>1.1</td>
</tr>
<tr>
<td>8-Hydroxyquinoline (µg/ml)</td>
<td>0.031</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.063</td>
<td>1</td>
<td>2</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>0.125</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.250</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.500</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(a) The protocol was based on that of Kakunaga (1973). Twenty-four hours before treatment, 60-mm dishes were inoculated with 104 cells/dish and incubated. Test compound was then added, and the cells were incubated for 72 h. Cells were then washed, fresh medium was added, and incubation continued for approximately 4 weeks with feeding twice a week. Cell monolayers were then fixed with methanol, stained with Giemsa, and examined by eye and by microscope to determine the number of foci of transformed cells.

(b) Before the transformation experiment, the cytotoxicity of the compound was determined by incubating 200 cells/60-mm dish for 24 h, adding various doses of test compound, and incubating for 72 h. The cells were then washed, fresh medium was added, and incubation continued for an additional 3-5 days. The surviving colonies were fixed, stained, and counted. The relative survival obtained after treatment with 8-hydroxyquinoline was: 108% (0.006 µg/ml), 93% (0.031 µg/ml), 82% (0.063 µg/ml), 44% (0.125 µg/ml), and 4% (0.26 µg/ml).
APPENDIX N

DATA AUDIT SUMMARY
APPENDIX N. DATA AUDIT SUMMARY

The experimental data and tables of the draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of 8-Hydroxyquinoline were examined for completeness, consistency, and accuracy and for compliance with Good Laboratory Practice during the period November 28-December 2, 1983. The following persons were involved in the audit: National Toxicology Program—Ms. C. Davies, Dr. S. Eustis, Dr. J. French, Ms. A. Grant, Dr. B. Gupta, Dr. C. Lingeman, Dr. B. Schwetz, Dr. C. Whitmire, and Dr. M. Wolfe; Dynamac Corporation—Dr. H. Appleton, Mr. D. Dippel, Mr. C. Lunchick, Mr. J. Plautz, Dr. R. Schueler, and Ms. C. Synier.

The full report of the audit of these studies on 8-hydroxyquinoline is on file at the National Toxicology Program, NIEHS. The audit consisted of (a) review of records for the in-life portion of the studies, including clinical observations and body weight data for 10% of the animals and all environmental and mortality records, (b) review of all chemistry data, and (c) review of pathology data, including all individual animal pathology records (IADRs), 100% slide/block match for all animals, and wet tissues for 10% of the animals in each group.

There were no discrepancies or omissions that were considered of sufficient importance to affect the interpretation of the studies. Examples of discrepancies of lesser importance are as follows: Although environmental conditions were not considered adequately controlled compared with current standards, adverse effects observed during the course of the studies could not be related to any significant deviations in temperature or humidity. Another minor discrepancy was a lack of correlation between some of the grossly observed lesions and microscopic descriptions of the same lesions. For example, some of the fight wounds in male mice and some of the joint arthritides reported in mice grossly were not always described microscopically. Because these are common observations that are unrelated to the test chemical, the level of attention given to these lesions was not always as great as for lesions that were more likely related to chemical exposure.

In summary, there were no findings that were considered to have significantly influenced the final interpretation of these studies. Minor problems not mentioned here were likewise not considered to have affected the outcome of the studies.