NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 304

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORENDIC ACID

(CAS NO. 115-28-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of 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 (NCTR), 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 CHLORENDIC ACID

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(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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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 for use in June 1983 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 quintet 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).

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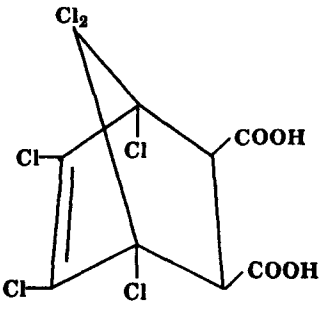

CHLORENDIC ACID
CAS No. 115-28-6

$C_9H_4O_4Cl_6$ **Molecular weight 388.9**

1,4,5,6,7,7-hexachloro-5-norbornene-2,3-dicarboxylic acid

ABSTRACT

Chlorendic acid is a chemical intermediate used in the preparation of fire-retardant polyester resins and plasticizers. Toxicology and carcinogenesis studies of chlorendic acid (greater than 98% pure) were conducted by administering the chemical in feed to groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice at concentrations of 0, 620, or 1,250 ppm for 103 weeks. The estimated mean daily consumption of chlorendic acid was 27 and 56 mg/kg body weight for low dose and high dose male rats and 39 and 66 mg/kg for low dose and high dose female rats. In mice, the estimated daily consumption was 89 and 185 mg/kg for low dose and high dose males and 100 and 207 mg/kg for low dose and high dose females. These concentrations were selected because higher levels in the 14-day and 13-week studies caused decreased mean body weights, more deaths, and increased incidences of liver lesions (rats: centrilobular cytomegaly, mitotic alterations, bile duct hyperplasia; mice: centrilobular cytomegaly, mitotic alterations, coagulative necrosis) relative to control groups.

Survival and feed consumption of dosed male and female rats and mice in the 2-year studies were similar to those of controls. Mean body weights of high dose male and female rats and mice were lower than those of controls. Mean body weights of high dose female rats were 16%-24% lower than those of controls during the second half of the study.

In the 2-year chlorendic acid feed studies, incidences of nonneoplastic lesions of the liver in dosed male rats (cystic degeneration) and dosed female rats (granulomatous inflammation, pigmentation, and bile duct hyperplasia) were increased. The incidences of neoplastic nodules of the liver were significantly increased in dosed male rats (control, 2/50; low dose, 21/50; high dose, 23/50) and high dose female rats (1/50; 3/49; 11/50). The incidence of hepatocellular carcinomas was also increased in high dose female rats (0/50; 3/49; 5/50). In mice, the incidences of nonneoplastic lesions of the liver were increased in dosed males (coagulative necrosis) and high dose females (mitotic alterations). The incidences of hepatocellular adenomas (5/50; 9/49; 10/50), hepatocellular carcinomas (9/50; 17/49; 20/50), and hepatocellular adenomas or carcinomas (combined) (13/50; 23/49; 27/50) were increased in dosed male mice. Hepatocellular carcinomas metastasized to the lung in 2/50 control, 4/49 low dose, and 7/50 high dose male mice. Hepatocellular adenomas or carcinomas (combined) were not significantly increased in female mice (3/50; 7/49; 7/50).

The incidences of acinar cell hyperplasia (0/49; 4/50; 4/50) and acinar cell adenomas (0/49; 4/50; 6/50) of the pancreas were increased in dosed male rats relative to those of controls. Pancreatic acinar cell adenoma is an uncommon neoplasm in untreated control F344/N rats in NTP studies (3/1,667).

In dosed male rats, incidences of alveolar/bronchiolar adenomas of the lung (0/50; 3/50; 5/50) were increased. The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in dosed female mice were also increased (1/50; 5/50; 6/50). Preputial gland carcinomas occurred at a greater incidence in low dose male rats (1/50; 8/50; 4/50) than in controls. An adenoma and a squamous cell papilloma were observed in two low dose male rats. The incidences of sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) of the salivary gland (1/50; 2/49; 4/50) were increased in dosed male rats. The incidences in the dosed groups were not significantly different from that in the controls, but these tumors are uncommon in F344/N rats receiving no treatment (3/1,689).

Chlorendic acid was not mutagenic in strains TA100, TA98, TA1535, or TA1537 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver activation when tested according to the preincubation protocol. Chlorendic acid was mutagenic in the L5178Y/TK$^{+/-}$ mouse lymphoma cell forward assay (in the absence of activation) at a dose resulting in toxicity.

An audit of the experimental data was conducted for the 2-year studies of chlorendic acid. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenicity** of chlorendic acid for male F344/N rats as shown by increased incidences of neoplastic nodules of the liver and acinar cell adenomas of the pancreas. Increased incidences of alveolar/bronchiolar adenomas and preputial gland carcinomas may also have been related to the administration of chlorendic acid. There was *clear evidence of carcinogenicity* of chlorendic acid for female F344/N rats as shown by increased incidences of neoplastic nodules and of carcinomas of the liver. There was *clear evidence of carcinogenicity* of chlorendic acid for male B6C3F$_1$ mice as shown by increased incidences of hepatocellular adenomas and of hepatocellular carcinomas. There was *no evidence of carcinogenicity* of chlorendic acid for female B6C3F$_1$ mice given chlorendic acid in the diet at concentrations of 620 or 1,250 ppm for 103 weeks.

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*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 14.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorendic Acid is based on the 13-week studies that began in August 1979 and ended in November 1979 and on the 2-year studies that began in June 1980 and ended in June 1982 at Hazleton Laboratories America, Inc.

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The members of the Peer Review Panel who evaluated the draft Technical Report on chlorendic acid on August 14, 1985, 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 CHLORENDIC ACID

On August 14, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of chlorendic acid received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Purchase, a principal reviewer, agreed with the conclusions proposed for male mice (clear evidence of carcinogenicity) and female mice (no evidence of carcinogenicity) but suggested that the conclusion proposed for male and female rats (clear evidence of carcinogenicity) be changed to some evidence of carcinogenicity, since male rats had only benign tumors in the liver and pancreas whereas malignant tumors in the liver were decreased in incidence. In female rats, he suggested that the increased incidence of liver carcinomas was offset by the top dose being greater than the maximum tolerated dose. Dr. J. French, NTP, stated that the conclusions in male and female rats were supported by high incidences of neoplastic nodules of the liver, especially in males, and a significant increase in carcinomas in females. Dr. Purchase said that use of life table analysis for lung adenomas in female mice was not appropriate, since these neoplasms are not life threatening. He thought that the genetic toxicology data were too brief for the general reader.

As a second principal reviewer, Dr. Kotelchuck agreed with the conclusions proposed for male and female rats and male mice but thought that the conclusion for female mice should be equivocal evidence of carcinogenicity because the increase in alveolar/bronchiolar adenomas or carcinomas (combined) was marginal. He said that the statistical trend tests and pairwise comparisons for these tumors were statistically significant, and although the concurrent control incidences were relatively low, the high-dose incidence was about 75% greater than the historical control average incidence.

As a third principal reviewer, Dr. Kociba agreed with the conclusions for male and female mice and female rats but supported Dr. Purchase's rationale for changing the conclusion in male rats to some evidence of carcinogenicity or, preferably, some evidence of benign tumor induction. He noted that both doses selected for the 2-year studies in mice induced necrosis of the liver. Dr. Swenberg commented on the increased emphasis to report metastases of liver tumors to the lungs in mice and urged that this reporting procedure be more standardized.

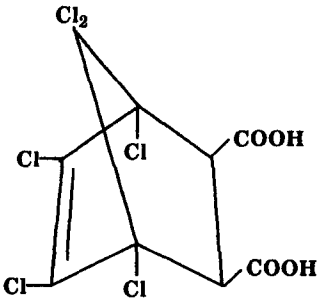
In further discussion on the strength of evidence for liver tumors in rats, Dr. Perera stated that substantially increased incidences of benign neoplasms support the conclusions as written. Dr. Hooper added that, although the increases in benign liver tumors in female rats were less striking than in males, the significant increases in carcinomas strengthened support for the stated conclusions. Dr. Hook commented that the definitions for the levels of evidence are working guidelines and the Panel should attempt to use these definitions.

Dr. Purchase moved that the conclusions as written for male mice, clear evidence of carcinogenicity, and for female mice, no evidence of carcinogenicity, be accepted. Dr. Swenberg seconded the motion, and it was approved unanimously with nine affirmative votes. Dr. Kotelchuck moved that the conclusion as written for female rats, clear evidence of carcinogenicity, be accepted. Dr. Hooper seconded the motion, and it was approved by eight affirmative votes to one negative vote (Dr. Purchase). Dr. Purchase moved that the conclusion for male rats be changed to some evidence of carcinogenicity. Dr. Kociba seconded the motion, and it was defeated by seven negative votes (Dr. Crowley, Dr. Hooper, Dr. Jones, Dr. Kotelchuck, Dr. Perera, Dr. Swenberg, and Dr. Turnbull) to two affirmative votes (Dr. Kociba and Dr. Purchase). Dr. Hooper then moved that the conclusion as written for male rats, clear evidence of carcinogenicity, be accepted. Dr. Kotelchuck seconded the motion, and it was approved by seven affirmative votes to two negative votes (Dr. Kociba and Dr. Purchase).

I. INTRODUCTION

Chemical Identification
Uses, Production, and Exposure
Chemical Disposition
General Toxicology
Cellular and Genetic Toxicology
Carcinogenicity
Study Rationale

I. INTRODUCTION



CHLORENDIC ACID
CAS No. 115-28-6

$C_9H_4O_4Cl_6$ **Molecular weight 388.9**

1,4,5,6,7,7-hexachloro-5-norbornene-2,3-dicarboxylic acid

Chemical Identification

Chlorendic acid is a hexachloronorbornene compound structurally related to the chlorinated cyclodiene insecticides (heptachlor, chlordane, endosulfan, endrin, and dieldrin) (Murphy, 1980). It is a fine, white, nondusting crystal that is poorly soluble in water and nonpolar organic solvents (benzene, carbon tetrachloride, *n*-hexane) and is readily soluble in more polar organic solvents (methanol, ethanol, and acetone). The acid form loses water in a heated open system; and at temperatures above 200° C, the chemical tends to discolor and forms an anhydride that melts at 230°-235° C. The octanol/water partition coefficient depends on the pH of the aqueous phase. At pH 7 (neutral), the compound will be predominantly in the ionized form, whereas at an acidic pH, partitioning will be largely of the neutral molecule. Chlorendic acid is very resistant to hydrolytic dechlorination, readily forms salts of a variety of metals, forms esters by heating with or without azeotropic solvent (e.g., chlorobenzene), and readily forms alkyl type polyester resins by reaction with glycols and other polyols (Kirk-Othmer, 1981; USEPA, 1983). Chlorendic acid is classified as a reactive flame retardant; it is chemically incorporated into the polyester and does not migrate or leach out.

Uses, Production, and Exposure

Chlorendic acid and chlorendic anhydride are the principal chemicals used as reactive flame retardants (Kirk-Othmer, 1981). Chlorendic acid and chlorendic anhydride are used primarily as chemical intermediates in the manufacture of corrosion-resistant polyester resins, as intermediates in the manufacture of polymer systems used in oil-modified paints and coatings, and as hardening agents for epoxy resins used in printed circuit boards (USEPA, 1983).

In 1981, manufacture of chlorendic anhydride in the United States was estimated at approximately 7 million pounds (3.2×10^6 kg) and imports at approximately 140,000 pounds (6.3×10^4 kg). Chlorendic anhydride is manufactured by reacting hexachlorocyclopentadiene with maleic anhydride in a Diels-Alder condensation; chlorendic acid results from hydrolysis of the anhydride (USEPA, 1983).

Chlorendic anhydride is manufactured in an essentially closed system. Although this procedure would seem to minimize human exposure, there are no published data on the level of occupational exposure to chlorendic anhydride or chlorendic acid. Since both are produced from hexachlorocyclopentadiene, the Resource Conservation and Recovery Act (RCRA) guidelines

(U.S. Code of Federal Regulations) cover the resulting waste streams. Chlorendic acid and anhydride wastes are therefore controlled.

Chlorendic acid may be released via hydrolytic degradation of polyesters in the environment (soil and water) after disposal. Chlorendic acid is an oxidation product of heptachlor and its metabolites (Cochrane and Forbes, 1974) and endosulfan (Martens, 1972); it could therefore appear in the environment from sources other than direct fugitive emission.

Chlorendic acid has been reported to be present in the leachate of a landfill (New York State Department of Health, 1985). Exposure of workers to chlorendic acid along with other industrial chemicals was investigated in an epidemiologic study (M. Zavon, personal communication to NTP, December 16, 1985).

Chemical Disposition

After oral or intravenous administration of ^{14}C-chlorendic acid (3 mg/kg) to 200-g male F344/N rats, the parent compound was rapidly absorbed, distributed, and metabolized (Decad and Fields, 1982; Appendix O). The major site for deposition of chlorendic acid-derived radioactivity by either route of administration was the liver; more than 50% of the total dose was found in the liver within 15 minutes. Twice as much radioactivity remained in the liver 24 hours after oral administration of chlorendic acid than after intravenous injection. Approximately 75% of the single oral or intravenous dose was excreted as acid-labile conjugates in the feces after biliary excretion within the first 24 hours. Another 25% of the radioactivity was excreted in the feces as the parent compound, and only 3%-6% of the radioactivity was excreted in the urine.

General Toxicology

No published reports were found on the toxicity of chlorendic acid other than the reported oral LD_{50} value in rats (strain, age, and sex unspecified)--1,770 mg/kg of body weight (NIOSH, 1982); this value is greater than those for the structurally related hexachlorinated norbornene insecticides (chlordane, LD_{50} = 335 mg/kg; dieldrin, LD_{50} = 46 mg/kg; heptachlor, LD_{50} = 100 mg/kg) (Murphy, 1980). The rapid absorption, metabolism, and excretion of chlorendic acid after oral administration (Decad and Fields, 1982) suggest that it may have different toxic effects than the hexachlorinated norbornene insecticides, which are metabolized slowly and retained longer (Murphy, 1980).

Cellular and Genetic Toxicology

Chlorendic acid was not mutagenic in strains TA100, TA98, TA1535, or TA1537 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 when tested according to the preincubation protocol (Appendix G). Chlorendic acid was mutagenic in the L5178Y/TK$^{+/-}$ mouse lymphoma assay in the absence of S9; it was not tested in the presence of S9. The NTP is currently testing chlorendic acid for cytogenetic effects in Chinese hamster ovary cells in vitro. No additional literature references were found on the genetic toxicology of this compound. Chlordane, endosulfan, endrin, and heptachlor were not mutagenic in Salmonella in NTP tests (Haworth et al., 1983).

Carcinogenicity

No published reports were found on the carcinogenicity of chlorendic acid. A series of National Cancer Institute carcinogenesis tests on hexachloronorbornene compounds has been completed (NCI, 1977a,b, 1978a,b). These chemicals were mixed individually in feed and supplied to male and female Osborne-Mendel rats and B6C3F$_1$ mice (10 or 20 matched animals per control group, 50 animals per low or high dose group). Pooled controls (at least 50 animals of the same strain, age and sex) from concurrent tests of other chemicals tested under the same experimental conditions were used for statistical purposes. Animals were fed the study compound for at least 80 weeks and then observed for an additional number of weeks (rats, 24-29 weeks;

mice, 10 weeks) before necropsy and histologic examination. The results indicate that several of these compounds cause hepatocellular carcinomas in male $B6C3F_1$ mice and some cause hepatocellular carcinomas in female $B6C3F_1$ mice (Table 1). Follicular cell adenomas of the thyroid gland were associated with chemical administration in male and female Osborne-Mendel rats but not in male or female $B6C3F_1$ mice.

Study Rationale

Chlorendic acid was studied by the NTP Carcinogenesis Program after being nominated by the National Cancer Institute following a review of flame retardants because of the large production, structure-activity considerations, and the potential for human exposure. The dietary route was chosen to obtain systemic exposure to chlorendic acid.

TABLE 1. RESULTS OF NCI FEED STUDIES ON HEXACHLORINATED NORBORNENE STRUCTURAL ANALOGS OF CHLORENDIC ACID

Chemical	Report No.	Organ Site	Osborne-Mendel Rats (a) Male	Osborne-Mendel Rats (a) Female	$B6C3F_1$ Mice (a) Male	$B6C3F_1$ Mice (a) Female
Aldrin	NCI TR 21 (1978a)	(b) Liver	No effect	No effect	3/20, 16/49, 25/45	No effect
Chlordane	NCI TR 8 (1977a)	(b) Liver	No effect	No effect	2/18, 16/48, 43/49	0/19, 3/47, 34/49
		(c) Thyroid gland	0/6, 1/34, 6/31	0/10, 4/43, 6/32	No effect	No effect
Dieldrin	NCI TR 21 (1978a)	(b) Liver	No effect	No effect	3/18, 12/50, 16/45	No effect
Endrin	NCI TR 12 (1979)	(b) Liver	No effect	No effect	No effect	No effect
Endosulfan	NCI TR 62 (1978b)		Inadequate study	Inadequate study	Inadequate study	Inadequate study
Heptachlor	NCI TR 9 (1977b)	(b) Liver	No effect	No effect	5/19, 11/46, 34/47	2/10, 3/47, 30/42
		(c) Thyroid gland	No effect	1/9, 3/43, 14/38	No effect	No effect

(a) Incidence--control, low dose, high dose
(b) Hepatocellular carcinomas
(c) Follicular cell adenomas of the thyroid gland

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORENDIC ACID

Chlorendic acid was obtained in two lots (lot no. 6287 and lot no. 6745) from Hooker Chemical Co. (Niagara Falls, New York). Lot no. 6287 was used for the 14-day studies and 13-week studies, and lot no. 6745 was used for the 2-year studies.

Purity and identity determinations were conducted on both lots (Appendix H). Chemical identity was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of both lots was determined to be approximately 99% by elemental analysis, water analysis, titration of the two carboxyl groups, thin-layer chromatography, and gas chromatography.

Stability studies monitored by gas chromatography indicated that chlorendic acid was stable on storage for 2 weeks at temperatures up to 60° C (Appendix H). During the study, the chlorendic acid study material was stored at 5° C. Periodic characterization of chlorendic acid by infrared spectroscopy and titration detected no deterioration over the course of the studies (Appendix H).

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

Studies performed at the analytical laboratory demonstrated that homogeneous chlorendic acid formulated diets could be prepared. Stability studies of a 1,000-ppm diet blend demonstrated that the chlorendic acid was stable in feed for 7 days when stored at room temperature (Appendix I). There was an indication that the chlorendic acid was binding with feed ingredients during storage, making it difficult to extract from feed for analysis even when strongly polar extractant solvents were used. Formulated diets were prepared by adding a dry premix (approximately equal amounts of feed and chlorendic acid) to the feed (Table 2). The mixture was then blended for 10-15 minutes. In the 13-week studies, the formulated diets were stored at 5° C for no more than 2 weeks. In the 2-year studies, the formulated diets were stored at 14° C for no longer than 1 week.

TABLE 2. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF CHLORENDIC ACID

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Appropriate amount of chemical mixed for 5 min with 5 kg feed in Hobart® mixing bowl; then mixed with 5 additional kg feed in a Patterson-Kelly® V-blender for 10 additional min	Appropriate amount of chemical mixed with a small amount of feed in a Waring® blender for 1-2 min; then ground with a mortar and pestle. This premix mixed with 5 kg feed in a Hobart® mixing bowl for 5 min; then with 5 more kg feed in a Patterson-Kelly® V-blender for 12 min	Chemical and a small amount of feed mixed in a Waring® blender for 2 min; then mixed with 5 kg feed in a Hobart® mixing bowl for 1 min/kg. This mixture added to the required amount of feed in a Patterson-Kelly® Twin-Shell blender (with intensifier bar) and mixed for 1 min/kg
Maximum Storage Time		
1 wk	2 wk	1 wk
Storage Conditions		
Room temperature in air-tight containers	Air-tight containers at 5° C	14° C

Analyses for chlorendic acid in feed mixtures were performed to confirm that correct concentrations were formulated (Appendix J). The method of analysis involved a methanolic extraction, preparation of the dimethyl derivative of chlorendic acid, and gas chromatography as a quantitation step. Because 3/28 samples analyzed were not within ±10% of the target concentration, it is estimated that approximately 89% of the mixes were formulated within specifications during the 2-year studies (Table 3; Appendix K, Table K2).

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for approximately 2 weeks before the studies began. Animals were 6-7 weeks old when placed on study. Groups of four or five males and five females were fed diets containing 0, 3,100, 6,200, 12,500, 25,000, or 50,000 ppm chlorendic acid for 14 days. Rats and mice were observed daily and were weighed on days 0, 7, and 14. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 4.

THIRTEEN-WEEK STUDIES

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

Four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 3 weeks, and assigned to dosed and control groups according to a table of random numbers. Diets containing 0, 620, 1,250, 2,500, 5,000, or 10,000 ppm chlorendic acid were fed to groups of 10 rats of each sex. Diets containing 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm chlorendic acid were fed to groups of 10 mice of each sex.

Animals were housed five per cage. Formulated diets, control diets, and water were available ad libitum. Further experimental details are summarized in Table 4.

Animals were checked twice daily; 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. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 4.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 620, or 1,250 ppm chlorendic acid were fed to groups of 50 male and 50 female rats and 50 male and 50 female mice for 103 weeks.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the NTP

TABLE 3. SUMMARY OF RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

	Concentration of Chlorendic Acid in Feed for Target Concentration	
	620 ppm	1,250 ppm
Mean (ppm)	621	1,226
Standard deviation	49.8	78.5
Coefficient of variation (percent)	8.0	6.4
Range (ppm)	555-710	1,095-1,380
Number of samples	14	14

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF CHLORENDIC ACID

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
Rats--5 of each sex; mice--4 or 5 of each sex	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
0, 3,100, 6,200, 12,500, 25,000, or 50,000 ppm chlorendic acid in the diet	Rats--0, 620, 1,250, 2,500, 5,000, or 10,000 ppm chlorendic acid in the diet; mice--0, 1,250, 2,500, 5,000, 10,000 or 20,000 ppm chlorendic acid in the diet	0, 620, or 1,250 ppm chlorendic acid in the diet
Date of First Dose		
5/16/79	Rats--8/6-8/7/79; mice--8/8/79	Rats--6/16/80; mice--6/5/80
Date of Last Dose		
5/30/79	Data not available	Rats--6/7/82; mice--5/24/82
Duration of Dosing		
14 d	13 wk	103 wk
Type and Frequency of Observation		
Weighed at initiation, after 1 wk, and at termination. Observed daily; observed weekly for clinical signs	Observed 2 × d; body weight, feed consumption, and clinical signs recorded 1 × wk	Body weight and feed consumption measured 1 × wk for 91 d and 1 × mo thereafter; observed 2 × d
Necropsy and Histologic Examination		
Necropsy performed on all animals	Necropsy performed on all animals. The following tissues were examined microscopically for control and high dose animals: gross lesions and tissue masses, blood smear, mandibular or mesenteric lymph nodes, salivary glands, sternum including marrow, thyroid gland, parathyroids, small intestine, colon, liver, gallbladder (mice), prostate/testes or ovaries/uterus, lungs and mainstem bronchi, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, and mammary gland	The following tissues were examined histologically for all animals: gross lesions, skin, mandibular lymph nodes, mammary gland, salivary glands, sternum including bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, pancreas, small intestine, colon, mesenteric lymph nodes, liver, spleen, kidneys, adrenal glands, urinary bladder, prostate/testes or ovaries/uterus, brain, pituitary gland, tissue masses or suspected tumors, and regional lymph nodes
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	Same as 14-d studies	Same as 14-d studies
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory		
Hazleton Laboratories America, Inc. (Vienna, VA)	Hazleton Laboratories America, Inc. (Vienna, VA)	Hazleton Laboratories America, Inc. (Vienna, VA)
Method of Animal Identification		
Ear clipping	Ear clipping	Ear tag
Time Held Before Study		
2 wk	21 d	Rats--25 d; mice--14 d

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF CHLORENDIC ACID (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Age When Placed on Study Rats--7 wk; mice--6 wk	7 wk	8 wk
Age When Killed Rats--9 wk; mice--8 wk	20 wk	112 wk
Necropsy Dates 5/31/79	Rats--11/7-11/8/79; mice--11/6-11/8/79	Rats--6/14-6/17/82; mice--6/4-6/9/82
Method of Animal Distribution Stratified by body weight and assigned to groups such that average cage weights were approximately equal	According to a table of random numbers	Distributed to weight classes and then assigned to study and control groups according to a table of random numbers
Feed Purina Rodent Laboratory Chow 5001® (Ralston Purina, St. Louis, MO); available ad libitum	Same as 14-d studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardeners, PA); available ad libitum
Bedding Heat-treated hardwood chips (Sani-Chips, P. J. Murphy Forest Products, Moonachie, NJ)	Same as 14-d studies	Heat-treated hardwood chips (P. J. Murphy Forest Products, Moonachie, NJ)
Water Available ad libitum	Automatic watering system; available ad libitum	Automatic watering system (Hazleton Systems, Inc., Aberdeen, MD); available ad libitum
Cages Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
Cage Filters DuPont Reemay® nonwoven fiber sheets (National Paper Co., Baltimore, MD)	Same as 14-d studies	Same as 14-d studies
Animals per Cage 5	5	Rats and female mice--5; male mice--5, then 1
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--74° ± 2° F; humidity--45% ± 5%; fluorescent light 12 h/d; 10-15 room air changes/h	Temp--75° ± 3° F; humidity--50% ± 10%; fluorescent light 12 h/d; 10-12 room air changes/h	Temp--72.2°-75.0° F; humidity--40.4%-57.1%; fluorescent light 12 h/d; 10-12 room air changes/h

Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 5 weeks of age, and mice, at 6 weeks. The rats were quarantined at the study facility for 25 days, and the mice, for 14 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were 57 days old and the mice were 55 days old when placed on study. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix L).

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 B6C3F$_1$ study 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 electophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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 B6C3F$_1$ 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 concurrent controls were included in each study.

Animal Maintenance

Rats and female mice were housed five per cage. Male mice were initially housed five per cage but were later housed individually. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 4.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was 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 4.

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. For subsequent evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

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) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: 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 include 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 a necropsy was 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 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. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analysis--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 studies, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case,

the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analysis--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: weeks 0-52, weeks 53-78, weeks 79-92, 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 a necropsy was 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 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.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

Three male and two female rats that received the 50,000-ppm diet died on day 15 (Table 5). Rats of each sex that received 25,000 or 50,000 ppm appeared hunched and thin. Rats of each sex that received 12,500, 25,000, or 50,000 ppm and females that received 6,200 ppm lost weight during the studies. Males that received 6,200 ppm gained no weight. Females that received 3,100 gained notably less weight than did the controls. No compound-related gross observations were reported, and histologic examinations were not performed.

A maximum concentration of 10,000 ppm was selected for the 13-week studies because of chlorendic acid-related deaths in both sexes at 50,000 ppm and body weight losses in both sexes at 12,500, 25,000, and 50,000 ppm.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF CHLORENDIC ACID

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	200	227	+27	--
3,100	5/5	196	230	+34	101.3
6,200	5/5	198	198	0	87.2
12,500	5/5	198	184	-14	81.1
25,000	5/5	197	137	-60	70.4
50,000	(c) 2/5	200	119	-81	52.4
FEMALE					
0	5/5	146	162	+16	--
3,100	5/5	147	153	+6	94.4
6,200	5/5	148	141	-7	87.0
12,500	5/5	145	129	-16	79.6
25,000	5/5	145	104	-41	64.2
50,000	(c) 3/5	145	93	-52	57.4

(a) Number surviving/number in group
(b) Mean body weight change of the group
(c) Day of death: all 15

THIRTEEN-WEEK STUDIES

All the rats survived to the end of the studies (Table 6). The final mean body weights of male rats that received 2,500 ppm or more chlorendic acid were more than 10% lower than that of the controls. The final mean body weights of female rats that received 1,250 ppm or more chlorendic acid were at least 10% lower than that of the controls. Feed consumption by the 5,000- and 10,000-ppm groups during the first 7 weeks was lower than that of the controls; thereafter, the feed consumption by the 10,000-ppm group was greater than that of the controls. Feed consumption by other groups of dosed rats was generally comparable to that of the controls. There was no evidence of a compound-related effect on physical appearance (except that the high dose group was reported to be thin), behavior, or organs or tissues receiving gross pathologic examination.

Hepatocytomegaly, mitotic alteration of the liver, and bile duct hyperplasia were observed at increased incidences in rats that received 5,000 or 10,000 ppm (Table 7). The degree of severity of bile duct hyperplasia at the two highest concentrations was greater in female rats than in male rats. Mitotic alterations included an increase in both mitotic figures per field and abnormal mitotic figures.

Dose Selection Rationale: A maximum concentration of 1,250 ppm was selected for the 2-year studies because of reductions in mean body weights relative to controls at concentrations of 2,500 ppm and greater in the 13-week studies. The hepatic lesions occurring at 5,000 ppm and 10,000 ppm were not considered to be life threatening but still considered significantly toxic.

TABLE 6. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF CHLORENDIC ACID

Conc. (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	150 ± 4	332 ± 6	+182 ± 4	--	12.1	10.7
620	10/10	164 ± 3	328 ± 4	+164 ± 3	99	11.7	11.4
1,250	10/10	155 ± 4	303 ± 5	+148 ± 2	91	10.8	11.1
2,500	10/10	160 ± 3	297 ± 5	+137 ± 4	89	10.5	10.7
5,000	10/10	154 ± 3	251 ± 5	+97 ± 5	76	9.0	10.8
10,000	10/10	159 ± 2	193 ± 7	+34 ± 5	58	6.4	14.8
FEMALE							
0	10/10	116 ± 3	198 ± 4	+82 ± 2	--	7.6	9.0
620	10/10	113 ± 2	182 ± 2	+69 ± 1	92	6.4	6.7
1,250	10/10	113 ± 2	172 ± 2	+59 ± 1	87	6.5	7.5
2,500	10/10	113 ± 1	162 ± 3	+49 ± 3	82	6.3	6.3
5,000	10/10	117 ± 2	161 ± 2	+44 ± 1	81	6.1	8.8
10,000	10/10	102 ± 5	146 ± 3	+44 ± 5	74	5.3	12.3

(a) Number surviving/number in group
(b) Initial group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams per animal per day

TABLE 7. NUMBERS OF RATS WITH LIVER LESIONS IN THE THIRTEEN-WEEK FEED STUDIES OF CHLORENDIC ACID

Concentration (ppm)	Lesion		
	Cytomegaly	Mitotic Alteration	Bile Duct Hyperplasia
MALE			
0	0	0	2
620	0	0	0
1,250	0	0	0
2,500	0	0	0
5,000	10	10	5
10,000	10	10	9
FEMALE			
0	0	0	1
620	0	0	0
1,250	0	0	0
2,500	0	1	1
5,000	6	7	10
10,000	10	10	10

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial weight of the high dose male rats was 4% lower than that of the controls, and the mean body weights of this group were 5%-10% lower throughout the study (Table 8 and Figure 1). Mean body weights of high dose female rats were 10% lower than those of the controls after week 11 and 20% lower after week 57. Mean body weights of low dose female rats were approximately 5% lower than those of the controls by week 10 and 10% lower by week 45.

The average daily feed consumption per rat by low dose and high dose rats was 96% and 94% that of the controls for males and 122% and 96% for females (Appendix M, Tables M1 and M2). The average amount of chlorendic acid consumed per day was estimated to be 27 mg/kg and 56 mg/kg for low dose and high dose male rats and 39 mg/kg and 66 mg/kg for low dose and high dose female rats.

There was no evidence of a compound-related effect on physical appearance or behavior.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

Weeks on Study	Control Av. Wt. (grams)	Control No. of Survivors	620 ppm Av. Wt. (grams)	620 ppm Wt. (percent of controls)	620 ppm No. of Survivors	1,250 ppm Av. Wt. (grams)	1,250 ppm Wt. (percent of controls)	1,250 ppm No. of Survivors
MALE								
0	173	50	171	99	50	166	96	50
1	199	50	194	97	50	191	96	50
2	222	50	214	96	50	210	95	50
3	239	50	231	97	50	227	95	50
4	252	50	246	98	50	239	95	50
5	269	50	259	96	50	254	94	50
6	284	50	268	94	50	266	94	50
7	296	50	283	96	50	276	93	50
8	305	50	292	96	50	285	93	50
9	318	50	304	96	50	294	92	50
10	323	50	306	95	50	297	92	50
11	342	50	320	94	50	311	91	50
12	346	50	332	96	50	306	88	50
13	355	50	332	94	50	319	90	50
17	379	50	359	95	50	345	91	50
21	396	50	368	93	50	352	89	50
25	401	50	380	95	50	364	91	50
29	412	49	391	95	50	369	90	50
33	429	49	402	94	50	381	89	50
37	440	49	414	94	50	390	89	50
41	443	49	417	94	50	395	89	50
45	446	49	421	94	50	401	90	49
49	453	49	430	95	50	406	90	49
53	434	49	410	94	50	392	90	49
57	447	49	421	94	50	398	89	49
61	444	48	420	95	50	398	90	49
65	445	47	424	95	50	402	90	48
69	449	47	422	94	50	406	90	48
73	447	47	425	95	50	402	90	47
77	445	44	430	97	49	408	92	45
81	435	41	428	98	49	399	92	44
85	437	39	420	96	48	398	91	39
89	437	38	426	97	45	397	91	35
93	427	34	417	98	43	392	92	31
97	417	31	413	99	37	397	95	28
101	403	27	409	101	34	390	97	25
104	406	23	400	99	32	384	95	25
FEMALE								
0	135	50	133	99	50	132	98	50
1	143	50	143	100	50	140	98	50
2	153	50	151	99	50	147	96	50
3	159	50	158	99	50	152	96	50
4	166	50	164	99	50	157	95	50
5	174	50	172	99	50	164	94	50
6	179	50	176	98	50	168	94	50
7	183	50	180	98	50	172	94	50
8	187	50	183	98	50	174	93	50
9	192	50	187	97	50	178	93	50
10	195	49	186	95	50	177	91	50
11	203	49	194	96	50	183	90	50
12	203	49	193	95	50	181	89	50
13	206	49	197	96	50	185	90	50
17	219	49	207	95	50	194	89	50
21	226	49	212	94	50	199	88	50
25	229	49	214	93	50	202	88	50
29	234	49	217	93	50	204	87	50
33	241	49	220	91	50	205	85	50
37	250	49	228	91	50	211	84	50
41	256	49	233	91	50	214	84	50
45	264	49	236	89	50	219	83	50
49	271	49	243	90	50	221	82	50
53	271	49	245	90	50	221	82	50
57	286	49	253	88	50	227	79	50
61	298	48	260	87	50	232	78	50
65	305	48	272	89	48	237	78	49
69	319	48	281	88	48	247	77	49
73	325	48	283	87	48	251	77	48
77	329	48	289	88	48	250	76	48
81	330	48	286	87	48	253	77	45
85	335	46	294	88	46	259	77	44
89	344	42	300	87	45	267	78	40
93	350	40	302	86	43	271	77	40
97	351	38	302	86	42	274	78	39
101	346	35	306	88	37	273	79	37
104	346	31	303	88	36	290	84	34

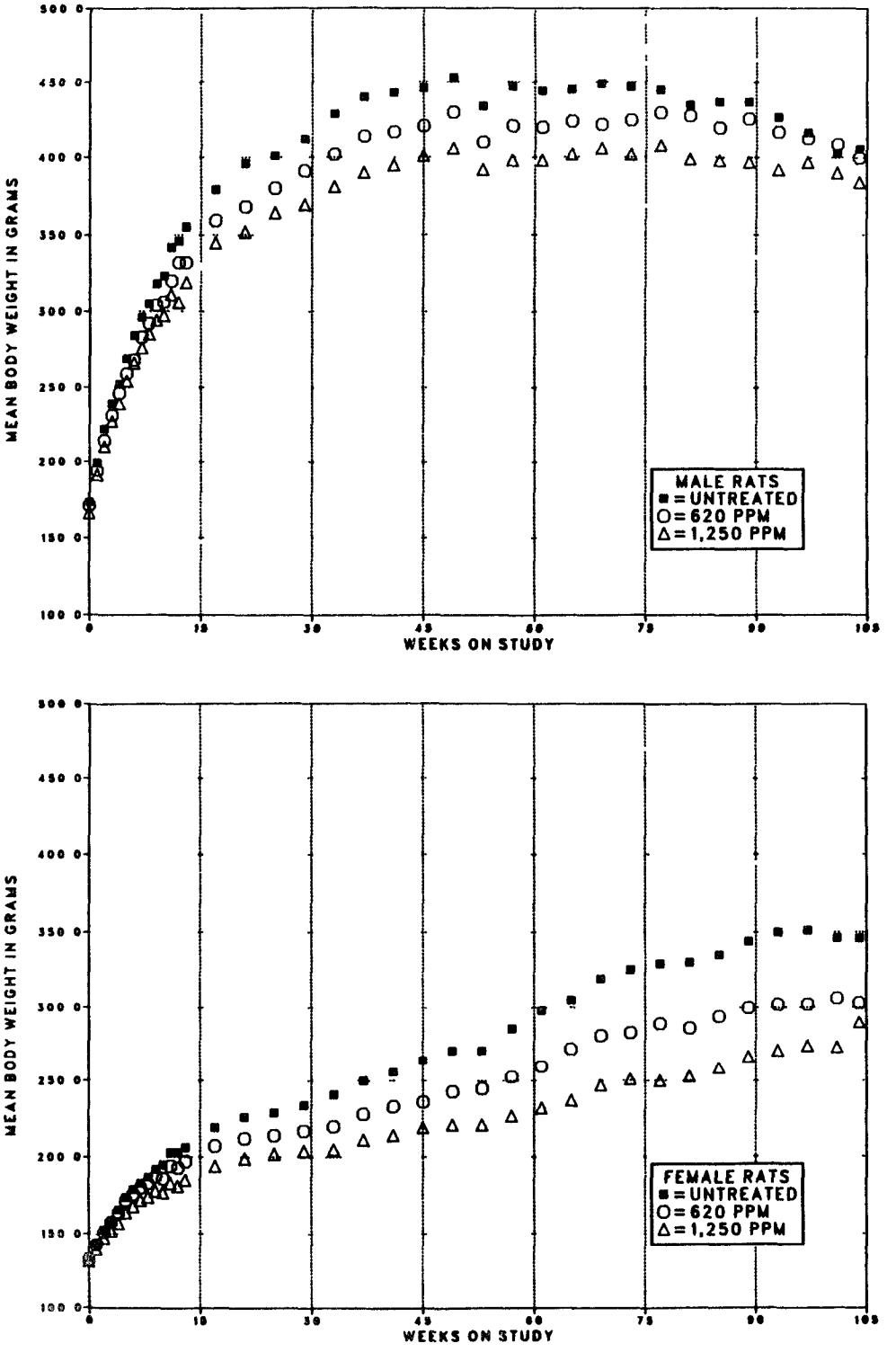


FIGURE 1. GROWTH CURVES FOR RATS FED DIETS CONTAINING CHLORENDIC ACID FOR TWO YEARS

Survival

Estimates of the probabilities for survival of male and female rats fed diets containing chlorendic acid at the concentrations used in these studies and those of controls are shown in Table 9 and in the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the liver, pancreas, lung, preputial gland, uterus, salivary gland, urinary system, mammary gland, adrenal gland, testis, and pituitary gland. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives 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) contains 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). Historical incidences of tumors in control animals are listed in Appendix F.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	26	18	25
Killed at termination	24	30	25
Died during termination period	0	2	0
Survival P values (c)	1.000	0.099	0.944
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	14	15
Accidentally killed	1	0	0
Killed at termination	31	34	34
Died during termination period	0	2	1
Survival P values (c)	0.643	0.496	0.718

(a) Terminal-kill period: week 104
(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 pairwise comparisons with the controls are in the dosed columns.

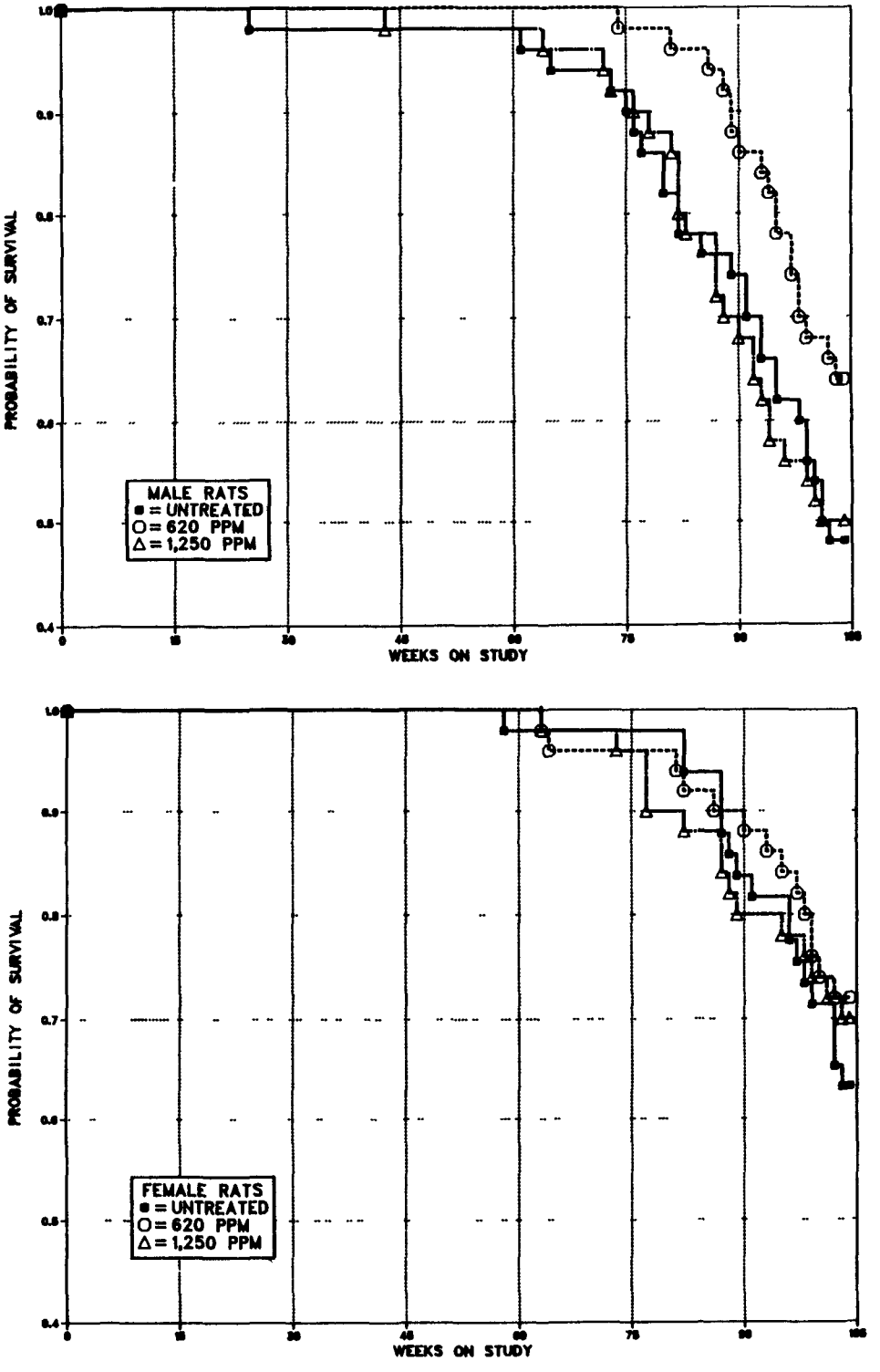


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING CHLORENDIC ACID FOR TWO YEARS

Liver: Cystic degeneration, focal cellular change, granulomatous inflammation, pigmentation, and bile duct hyperplasia were observed at increased incidences in dosed male or female rats (Table 10). These increases generally occurred in only one sex. Microscopically, cystic degeneration appeared as multiple focal cystic complexes filled with a finely granular eosinophilic material. The dividing septa were not lined by endothelium or other recognizable cell types. Hepatocytes, either single or multiple, were often trapped within the cystic lesion. Small spindle cells resembling fibroblasts were sometimes present in the interstices between individual cystic spaces.

Neoplastic nodules in male and female rats and hepatocellular carcinomas in female rats occurred with significant positive trends (Table 11). The incidences of neoplastic nodules in dosed males and high dose females, and of hepatocellular carcinomas in high dose females, were significantly greater than those in the controls.

Hepatocellular carcinomas present in female rats appeared as large solid nodules with marked compression of the adjacent hepatic parenchyma. Hepatocytes were usually arranged in distorted cords, often resulting in a multinodular pattern within the tumor. The cords were usually one or two cell layers thick in solid areas. The cords were several layers thick in tumors with trabecular patterns and ended abruptly in dilated sinusoids. Hepatocytes in these tumors were markedly enlarged, containing abundant eosinophilic cytoplasm and a central round or oval vesicular nucleus with one to four nucleoli. Nuclei were pleomorphic and multiple in some cells. Mitosis was uncommon.

TABLE 10. NUMBERS OF RATS WITH LIVER LESIONS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

	Concentration (ppm)					
	Male			Female		
Lesion	0	620	1,250	0	620	1,250
Number examined	50	50	50	50	49	50
Cystic degeneration	13	32	31	1	1	1
Granulomatous inflammation	1	1	1	10	21	20
Pigmentation	1	1	1	1	3	8
Focal cellular change	15	32	20	30	23	28
Bile duct hyperplasia	31	42	41	3	17	40
Neoplastic nodule	2	21	23	1	3	11
Hepatocellular carcinoma	3	5	1	0	3	5

TABLE 11. ANALYSIS OF LIVER TUMORS IN RATS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID (a)

	Control	620 ppm (b)	1,250 ppm (b)
MALE			
Neoplastic Nodule			
Overall Rates	2/50 (4%)	21/50 (42%)	23/50 (46%)
Adjusted Rates	8.3%	61.6%	78.6%
Terminal Rates	2/24 (8%)	19/32 (59%)	19/25 (76%)
Week of First Observation	104	97	83
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma			
Overall Rates	3/50 (6%)	5/50 (10%)	1/50 (2%)
Adjusted Rates	9.5%	15.6%	4.0%
Terminal Rates	1/24 (4%)	5/32 (16%)	1/25 (4%)
Week of First Observation	77	104	104
Life Table Tests	P=0.244N	P=0.498	P=0.304N
Incidental Tumor Tests	P=0.277N	P=0.371	P=0.356N
Neoplastic Nodule or Hepatocellular Carcinoma (c)			
Overall Rates	5/50 (10%)	22/50 (44%)	23/50 (46%)
Adjusted Rates	17.3%	64.6%	78.6%
Terminal Rates	3/24 (13%)	20/32 (63%)	19/25 (76%)
Week of First Observation	77	97	83
Life Table Tests	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
FEMALE			
Neoplastic Nodule			
Overall Rates	1/50 (2%)	3/49 (6%)	11/50 (22%)
Adjusted Rates	3.2%	8.3%	31.4%
Terminal Rates	1/31 (3%)	3/36 (8%)	11/35 (31%)
Week of First Observation	104	104	104
Life Table Tests	P=0.001	P=0.359	P=0.004
Incidental Tumor Tests	P=0.001	P=0.359	P=0.004
Hepatocellular Carcinoma			
Overall Rates	0/50 (0%)	3/49 (6%)	5/50 (10%)
Adjusted Rates	0.0%	7.8%	14.3%
Terminal Rates	0/31 (0%)	2/36 (6%)	5/35 (14%)
Week of First Observation		95	104
Life Table Tests	P=0.028	P=0.146	P=0.044
Incidental Tumor Tests	P=0.023	P=0.133	P=0.044
Neoplastic Nodule or Hepatocellular Carcinoma (d)			
Overall Rates	1/50 (2%)	5/49 (10%)	16/50 (32%)
Adjusted Rates	3.2%	13.2%	45.7%
Terminal Rates	1/31 (3%)	4/36 (11%)	16/35 (46%)
Week of First Observation	104	95	104
Life Table Tests	P<0.001	P=0.138	P<0.001
Incidental Tumor Tests	P<0.001	P=0.130	P<0.001

(a) The statistical analyses used are discussed 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 Appendix M.
(c) Historical incidence in NTP studies (mean ± SD): 73/1,719 (4.2% ± 3.5%)
(d) Historical incidence in NTP studies (mean ± SD): 48/1,766 (2.7% ± 3.0%)

Pancreatic Acinus: Focal hyperplasia of the pancreatic acinus was observed in dosed male rats (control, 0/49; low dose, 4/50; high dose, 4/50). Acinar cell adenomas in male rats occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the controls (Table 12). Acinar cell adenomas were observed in 1/49 low dose and 1/50 high dose female rats.

Microscopically, acinar cell adenomas were large round nodules that often replaced all or a substantial portion of an entire pancreatic lobe. Although these neoplasms were not encapsulated, compression of adjacent pancreatic tissue occurred. Ducts and islets of Langerhans were not present within the nodules. Neoplastic cells were arranged in irregularly shaped acini and tubules with little intervening stroma. These neoplastic cells were larger than normal pancreatic acinar cells with basally located nuclei and abundant apical eosinophilic granular cytoplasm. Mitotic figures were rare. Cells with pyknotic nuclei and cytolysis were seen occasionally. The distinction between adenomas and focal acinar cell hyperplasia was not always clear. These hyperplastic lesions were smaller, with little evidence of compression and, together with adenomas, may represent a spectrum of the same lesion. The criteria used to classify the proliferative exocrine pancreatic lesions have been published (Boorman and Eustis, 1984).

Lung: Alveolar/bronchiolar adenomas in male rats occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the controls (Table 13). The incidences of alveolar/bronchiolar adenomas in female rats were as follows: control, 1/50; low dose, 1/49; high dose, 1/50.

Preputial Gland: The incidence of carcinomas in low dose male rats was significantly greater than those in the controls (Table 14). One adenoma and one squamous cell papilloma were also seen in the low dose group.

TABLE 12. ANALYSIS OF PANCREATIC TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Acinar Cell Adenoma (a)			
Overall Rates	0/49 (0%)	4/50 (8%)	6/50 (12%)
Adjusted Rates	0.0%	11.3%	24.0%
Terminal Rates	0/24 (0%)	3/32 (9%)	6/25 (24%)
Week of First Observation		88	104
Life Table Tests	P=0.011	P=0.104	P=0.018
Incidental Tumor Tests	P=0.014	P=0.082	P=0.018

(a) Historical incidence of acinar cell neoplasms in NTP studies (mean ± SD): 3/1,667 (0.2% ± 0.6%)

TABLE 13. ANALYSIS OF LUNG LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Alveolar Epithelial Hyperplasia			
Overall Rates	1/50 (2%)	1/50 (2%)	1/50 (2%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	0/50 (0%)	3/50 (6%)	5/50 (10%)
Adjusted Rates	0.0%	9.4%	18.5%
Terminal Rates	0/24 (0%)	3/32 (9%)	3/25 (12%)
Week of First Observation		104	100
Life Table Tests	P=0.019	P=0.175	P=0.036
Incidental Tumor Tests	P=0.014	P=0.175	P=0.021
Alveolar/Bronchiolar Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)
Alveolar/Bronchiolar Adenoma or Carcinoma (a)			
Overall Rates	0/50 (0%)	4/50 (8%)	5/50 (10%)
Adjusted Rates	0.0%	12.5%	18.5%
Terminal Rates	0/24 (0%)	4/32 (13%)	3/25 (12%)
Week of First Observation		104	100
Life Table Tests	P=0.025	P=0.104	P=0.036
Incidental Tumor Tests	P=0.019	P=0.104	P=0.021

(a) Historical incidence in NTP studies (mean ± SD): 35/1,723 (2% ± 2%)

TABLE 14. ANALYSIS OF PREPUTIAL GLAND TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Carcinoma			
Overall Rates	1/50 (2%)	8/50 (16%)	4/50 (8%)
Adjusted Rates	4.2%	22.7%	13.2%
Terminal Rates	1/24 (4%)	6/32 (19%)	2/25 (8%)
Week of First Observation	104	81	82
Life Table Tests	P=0.194	P=0.047	P=0.189
Incidental Tumor Tests	P=0.198	P=0.035	P=0.185
Adenoma, Carcinoma, or Squamous Cell Papilloma (a)			
Overall Rates	1/50 (2%)	10/50 (20%)	4/50 (8%)
Adjusted Rates	4.2%	27.8%	13.2%
Terminal Rates	1/24 (4%)	7/32 (22%)	2/25 (8%)
Week of First Observation	104	81	82
Life Table Tests	P=0.210	P=0.018	P=0.189
Incidental Tumor Tests	P=0.201	P=0.012	P=0.185

(a) Historical incidence in NTP studies (mean ± SD): 105/1,727 (6% ± 5%)

Uterus/Endometrium: Uterine cysts were observed at increased incidence in high dose female rats (control, 5/50; low dose, 8/49; high dose, 12/50). The incidence of endometrial stromal polyps in low dose female rats was significantly greater than that in the controls by the incidental tumor test (Table 15).

Salivary Gland: Sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) of the salivary gland were observed in 1/50 control, 2/49 low dose, and 4/50 high dose male rats. The salivary gland neoplasms were composed of round, stellate, or spindle cells. The small neoplasms clearly arose in the interstitial tissue of the salivary gland. The large destructive masses appeared to arise from or invade the salivary gland or adjacent tissue. Most tumors contained entrapped remnants of salivary acini or ducts that had undergone dedifferentiation and squamous metaplasia. Most tumors had areas that morphologically resembled fibrosarcomas and were composed of stellate to fusiform spindle cells; the nuclei were elongated to oval, and hyperchromatic nucleoli varied from two to three in number and were prominent. Multinucleated cells were present in some masses. Mitotic figures were common. The amount of cytoplasm varied, and cytoplasmic boundaries were sometimes difficult to distinguish from stroma. Many of these tumors contained poorly formed neovascularized areas. Necrosis of tumor tissue, hemorrhage, and inflammation were common findings. One tumor in this group contained cells that resembled a neurofibrosarcoma. This mass was composed of interwoven bundles and whorls of elongated, fusiform cells. Often the nuclei of the bundles were parallel to each other in a regimented or palisaded pattern. Other areas showed a looser texture with irregularly arranged cells of plumper fusiform outline and more extracellular space. Mitotic figures were numerous throughout the mass. The incidences in the dosed groups were not significantly different from those in the controls.

Urinary System: Lymphoid hyperplasia was observed in the kidneys of male rats, and calculi (microscopically confirmed) were observed at increased incidence in low dose female rats (Table 16). The incidences of nephropathy in dosed female rats were notably lower than that in the controls. A transitional cell carcinoma was observed in the kidney of 1/50 low dose male rats, and a transitional cell papilloma was observed in the urinary bladder of 1/50 high dose male rats.

Mammary Gland: The incidence of fibroadenomas in high dose female rats was significantly lower than that in the controls (Table 17).

Adrenal Gland (Medulla): Pheochromocytomas and pheochromocytomas or malignant pheochromocytomas (combined) occurred in male rats with significant negative trends, and the incidences in the dosed groups were significantly lower than those in the controls (Table 18).

TABLE 15. ANALYSIS OF UTERINE TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Endometrial Stromal Polyp (a)			
Overall Rates	6/50 (12%)	15/49 (31%)	10/50 (20%)
Adjusted Rates	17.8%	39.1%	27.5%
Terminal Rates	5/31 (16%)	13/36 (36%)	9/35 (26%)
Week of First Observation	58	86	88
Life Table Tests	P=0.271	P=0.051	P=0.276
Incidental Tumor Tests	P=0.274	P=0.040	P=0.315

(a) Historical incidence in NTP studies (mean ± SD): 383/1,750 (22% ± 8%)

TABLE 16. NUMBERS OF RATS WITH LESIONS OF THE URINARY SYSTEM IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

Site/Lesion	Male			Female		
	Control	620 ppm	1,250 ppm	Control	620 ppm	1,250 ppm
Number examined	50	50	50	50	49	50
Kidney						
Lymphoid hyperplasia	8	19	15	4	1	1
Nephropathy	35	40	32	24	5	1
Calculi	0	0	0	0	12	1
Transitional cell carcinoma	0	1	0	0	0	0
Urinary bladder						
Transitional cell papilloma	0	0	1	0	0	0

TABLE 17. ANALYSIS OF MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Fibroadenoma (a)			
Overall Rates	22/50 (44%)	16/50 (32%)	4/50 (8%)
Adjusted Rates	58.5%	38.5%	11.4%
Terminal Rates	16/31 (52%)	11/36 (31%)	4/35 (11%)
Week of First Observation	87	82	104
Life Table Tests	P<0.001N	P=0.081N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.162N	P<0.001N

(a) Historical incidence in NTP studies (mean ± SD): 492/1,772 (28% ± 10%)

TABLE 18. ANALYSIS OF ADRENAL GLAND (MEDULLA) TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Pheochromocytoma			
Overall Rates	25/50 (50%)	17/50 (34%)	15/50 (30%)
Adjusted Rates	72.6%	46.2%	52.6%
Terminal Rates	15/24 (63%)	13/32 (41%)	12/25 (48%)
Week of First Observation	76	88	78
Life Table Tests	P=0.022N	P=0.010N	P=0.034N
Incidental Tumor Tests	P=0.032N	P=0.017N	P=0.048N
Pheochromocytoma, Malignant			
Overall Rates	3/50 (6%)	0/50 (0%)	0/50 (0%)
Pheochromocytoma or Pheochromocytoma, Malignant (a)			
Overall Rates	26/50 (52%)	17/50 (34%)	15/50 (30%)
Adjusted Rates	75.7%	46.2%	52.6%
Terminal Rates	16/24 (67%)	13/32 (41%)	12/25 (48%)
Week of First Observation	76	88	78
Life Table Tests	P=0.013N	P=0.005N	P=0.021N
Incidental Tumor Tests	P=0.019N	P=0.009N	P=0.029N

(a) Historical incidence in NTP studies (mean ± SD): 358/1,702 (21% ± 10%)

Testis: Interstitial cell tumors in male rats occurred with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the controls (Table 19).

Pituitary Gland: Adenomas and adenomas or carcinomas (combined) in female rats occurred with significant negative trends, and the incidences in the high dose group were significantly lower (by life table analysis) than those in the controls (Table 20).

TABLE 19. ANALYSIS OF TESTICULAR LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Interstitial Cell Hyperplasia			
Overall Rates	4/49 (8%)	10/50 (20%)	8/50 (16%)
Interstitial Cell Tumor (a)			
Overall Rates	41/49 (84%)	35/50 (70%)	22/50 (44%)
Adjusted Rates	97.5%	80.9%	61.5%
Terminal Rates	23/24 (96%)	24/32 (75%)	12/25 (48%)
Week of First Observation	73	81	64
Life Table Tests	P<0.001N	P=0.008N	P=0.002N
Incidental Tumor Tests	P<0.001N	P=0.013N	P<0.001N

(a) Historical incidence in NTP studies (mean ± SD): 1,511/1,703 (89% ± 8%)

TABLE 20. ANALYSIS OF PITUITARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Adenoma			
Overall Rates	31/50 (62%)	34/50 (68%)	23/50 (46%)
Adjusted Rates	83.3%	76.9%	55.7%
Terminal Rates	25/31 (81%)	26/36 (72%)	17/35 (49%)
Week of First Observation	82	64	82
Life Table Tests	P=0.027N	P=0.498N	P=0.035N
Incidental Tumor Tests	P=0.060N	P=0.476	P=0.083N
Carcinoma			
Overall Rates	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	33/50 (66%)	37/50 (74%)	24/50 (48%)
Adjusted Rates	86.4%	80.3%	58.2%
Terminal Rates	26/31 (84%)	27/36 (75%)	18/35 (51%)
Week of First Observation	82	64	82
Life Table Tests	P=0.018N	P=0.553N	P=0.022N
Incidental Tumor Tests	P=0.044N	P=0.384	P=0.057N

(a) Historical incidence in NTP studies (mean ± SD): 805/1,704 (47% ± 11%)

FOURTEEN-DAY STUDIES

Four male mice that received the 50,000-ppm diet died on day 7 (Table 21). Mice that received 50,000 ppm chlorendic acid appeared hunched and thin. Male and female mice that received 50,000 ppm lost weight during the studies; mice that received 6,200 ppm or more gained less weight than did the controls. No compound-related gross lesions were observed at necropsy, and histologic examinations were not performed.

A maximum concentration of 20,000 ppm was selected for the 13-week studies because of chlorendic acid-related deaths in males at 50,000 ppm and marked reduction in body weight gains in both sexes at 25,000 ppm and 50,000 ppm in the 14-day studies.

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF CHLORENDIC ACID

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	24	29	+5	--
3,100	4/4	24	29	+5	100.0
6,200	5/5	25	28	+3	96.6
12,500	5/5	23	27	+4	93.1
25,000	5/5	24	25	+1	86.2
50,000	(c) 1/5	25	22	−3	75.9
FEMALE					
0	5/5	17	21	+ 4	--
3,100	5/5	17	21	+ 4	100.0
6,200	5/5	17	19	+ 2	90.5
12,500	5/5	17	20	+ 3	95.2
25,000	5/5	17	19	+ 2	90.5
50,000	5/5	17	16	− 1	76.2

(a) Number surviving/number in group
(b) Mean body weight change of the group
(c) Day of death: all 7

THIRTEEN-WEEK STUDIES

All the mice survived to the end of the studies (Table 22). The final mean body weights of all groups of dosed mice were at least 7% lower than those of the controls. Feed consumption was not notably affected by the incorporation of chlorendic acid in feed. Except for the decrease in relative body weight gain, there was no evidence of a compound-related effect on physical appearance, behavior, or development of gross lesions. Compound-related changes were observed microscopically in the liver of male and female mice and included centrilobular cytomegaly, mitotic alteration, and coagulative necrosis (Table 23).

Dose Selection Rationale: A maximum concentration of 1,250 ppm was selected for the 2-year studies because potentially life-threatening hepatic effects (necrosis) occurred in males at 10,000 and 20,000 ppm and a marked reduction in body weight gain relative to controls was seen in males at 2,500 ppm or more and in females at 10,000 ppm or more in the 13-week studies. Female mice received chlorendic acid at the same concentrations as did the males in the 2-year studies in order to simplify study performance, although female mice appeared to be less susceptible to the effects of chlorendic acid administration than were male mice during the 13-week studies.

TABLE 22. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF CHLORENDIC ACID

Conc. (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	28.0 ± 0.7	36.7 ± 1.1	+8.7 ± 0.8	--	3.6	2.7
1,250	10/10	27.2 ± 0.3	32.9 ± 0.4	+5.7 ± 0.5	89.6	3.3	2.9
2,500	10/10	26.4 ± 0.6	31.2 ± 0.5	+4.8 ± 0.5	85.0	3.2	3.0
5,000	10/10	27.5 ± 0.6	33.2 ± 0.7	+5.7 ± 0.3	90.5	3.8	3.4
10,000	10/10	26.7 ± 0.6	31.5 ± 0.8	+4.8 ± 0.3	85.8	4.1	3.5
20,000	10/10	26.8 ± 0.8	29.9 ± 0.9	+3.1 ± 0.7	81.5	4.1	3.8
FEMALE							
0	10/10	21.3 ± 0.4	28.7 ± 0.9	+7.4 ± 0.6	--	3.8	3.4
1,250	10/10	20.3 ± 0.4	26.4 ± 0.8	+6.1 ± 0.4	92.0	3.7	3.1
2,500	10/10	21.1 ± 0.4	26.7 ± 0.7	+5.6 ± 0.4	93.0	4.0	3.6
5,000	10/10	21.4 ± 0.6	26.0 ± 0.6	+4.6 ± 0.2	90.6	3.6	3.8
10,000	10/10	21.2 ± 0.3	25.3 ± 0.4	+4.1 ± 0.2	88.2	3.9	3.9
20,000	10/10	21.0 ± 0.4	23.6 ± 0.4	+2.6 ± 0.3	82.2	3.7	3.8

(a) Number surviving/number in group
(b) Initial group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams per animal per day

TABLE 23. NUMBERS OF MICE WITH LIVER LESIONS IN THE THIRTEEN-WEEK FEED STUDIES OF CHLORENDIC ACID

Concentration (ppm)	Lesion (a)		
	Centrilobular Cytomegaly	Mitotic Alteration	Coagulative Necrosis
MALE			
0	0	0	0
1,250	0	0	2
2,500	0	0	0
5,000	0	0	1
10,000	0	0	5
20,000	10	7	8
FEMALE			
0	0	1	0
1,250	0	0	0
2,500	0	0	0
5,000	0	0	0
10,000	0	3	1
20,000	8	7	1

(a) These lesions were not graded for severity.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

From week 11 to the end of the studies, mean body weights of high dose male mice were 5%-10% lower than those of the controls (Table 24 and Figure 3). Mean body weights of low dose male mice varied from 2% above to 9% below those of the controls throughout the study. Mean body weights of high dose female mice were variable but remained 5%-10% lower than those of the controls throughout most of the study. Mean body weights of low dose female mice varied from 2% above to 7% below those of the controls throughout most of the study. The average daily feed consumption by low dose and high dose male mice was 107% and 109% that of the controls and by low dose and high dose female mice, 102% that of the controls (Appendix M, Tables M3 and M4). The average amount of chlorendic acid consumed per day was estimated to be 89 mg/kg and 185 mg/kg for low dose and high dose male mice and 100 mg/kg and 207 mg/kg for low dose and high dose female mice, based on group feed consumption data.

There was no evidence of a compound-related effect on physical appearance or behavior.

TABLE 24. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

Weeks on Study	Control Av. Wt. (grams)	Control No. of Survivors	620 ppm Av. Wt. (grams)	620 ppm Wt. (percent of controls)	620 ppm No. of Survivors	1,250 ppm Av. Wt. (grams)	1,250 ppm Wt. (percent of controls)	1,250 ppm No. of Survivors
MALE								
0	24 9	50	24 8	100	50	25 0	100	50
1	26 3	50	26 7	102	50	25 3	96	50
2	27 8	50	27 2	98	50	26 8	96	50
3	28 3	50	27 1	96	50	26 7	94	50
4	29 1	50	27 6	95	50	28 0	96	50
5	29 7	50	28 5	96	50	28 4	96	50
6	30 2	50	29 3	97	50	29 3	97	50
7	31 3	50	30 2	96	50	30 3	97	50
8	30 6	50	31 0	101	50	30 8	101	50
9	31 6	50	30 4	96	50	30 5	97	50
10	32 2	50	30 4	94	50	30 6	95	50
11	32 4	50	31 8	98	50	31 4	97	50
12	33 0	50	31 7	96	50	31 4	95	50
13	32 9	50	31 9	97	50	31 3	95	50
17	35 0	50	33 2	95	50	33 1	95	49
21	36 6	50	34 3	94	49	33 9	93	49
25	35 7	49	34 0	95	48	33 2	93	49
29	36 7	48	34 3	93	48	34 3	93	49
33	37 2	47	34 4	92	46	33 8	91	46
37	38 9	46	35 5	91	45	36 1	93	46
41	38 9	46	36 4	94	45	35 3	91	46
45	40 9	46	37 6	92	45	37 3	91	45
49	40 0	46	37 4	94	45	36 0	90	44
53	41 2	45	38 0	92	43	37 1	90	44
57	41 0	45	39 0	95	43	37 0	90	44
61	41 0	45	40 2	98	42	38 0	93	43
65	41 2	45	40 5	98	42	38 5	93	43
69	41 6	44	40 0	96	41	38 1	92	41
73	41 0	42	39 2	96	41	37 2	91	41
77	40 8	42	39 5	97	39	37 7	92	39
81	40 4	42	38 4	95	37	36 7	91	39
85	40 1	41	38 3	96	35	37 4	93	35
89	40 0	41	38 0	95	32	37 0	93	34
93	39 0	41	38 0	97	32	37 0	95	33
97	39 4	40	37 6	95	30	37 1	94	32
101	40 0	38	38 0	95	29	38 0	95	30
103	40 0	38	37 0	93	29	36 0	90	29
104	40 0	37	36 3	91	28	36 7	92	29
FEMALE								
0	19 0	50	18 8	99	50	18 5	97	50
1	20 4	50	19 0	93	50	19 3	95	50
2	21 0	50	19 6	93	50	20 6	98	50
3	22 1	50	21 3	96	50	19 8	90	50
4	22 7	50	21 6	95	50	21 2	93	49
5	23 6	50	22 5	95	50	22 4	95	49
6	24 0	50	23 2	97	50	23 2	97	49
7	24 8	50	24 7	100	50	24 9	100	49
8	24 0	50	24 2	101	50	23 7	99	49
9	24 8	50	24 4	98	50	23 6	95	49
10	24 9	50	25 2	101	50	24 3	98	49
11	25 8	50	25 5	99	50	25 1	97	49
12	27 2	50	26 0	96	50	25 3	93	49
13	26 9	50	26 0	97	50	25 2	94	49
17	28 5	50	28 5	100	49	27 2	95	49
21	30 4	50	29 6	97	49	28 2	93	49
25	31 8	50	30 1	95	49	32 7	103	49
29	32 7	50	30 8	94	48	29 6	91	49
33	33 1	50	31 9	96	47	30 4	92	49
37	35 5	50	34 6	97	47	32 1	90	49
41	36 2	50	35 2	97	47	32 8	91	49
45	38 8	49	36 9	95	47	34 9	90	49
49	37 4	49	36 5	98	47	35 3	94	49
53	38 3	49	36 8	96	47	34 3	90	49
57	39 0	49	38 0	97	47	37 0	95	49
61	38 9	49	38 6	99	47	36 9	95	49
65	38 7	49	38 4	99	47	36 9	95	47
69	39 0	49	39 1	100	47	36 7	94	47
73	38 3	49	37 4	98	46	35 3	92	47
77	37 6	47	38 2	102	45	36 3	97	46
81	37 8	46	36 6	97	43	34 4	91	46
85	37 2	45	36 3	98	42	35 0	94	44
89	38 0	44	37 0	97	41	35 0	92	40
93	39 0	41	37 0	95	41	35 0	90	38
97	39 3	40	37 8	96	40	35 3	90	37
101	39 0	39	38 0	97	40	36 0	92	37
103	38 0	39	36 0	95	39	34 0	89	35
104	37 6	39	35 8	95	39	34 3	91	35

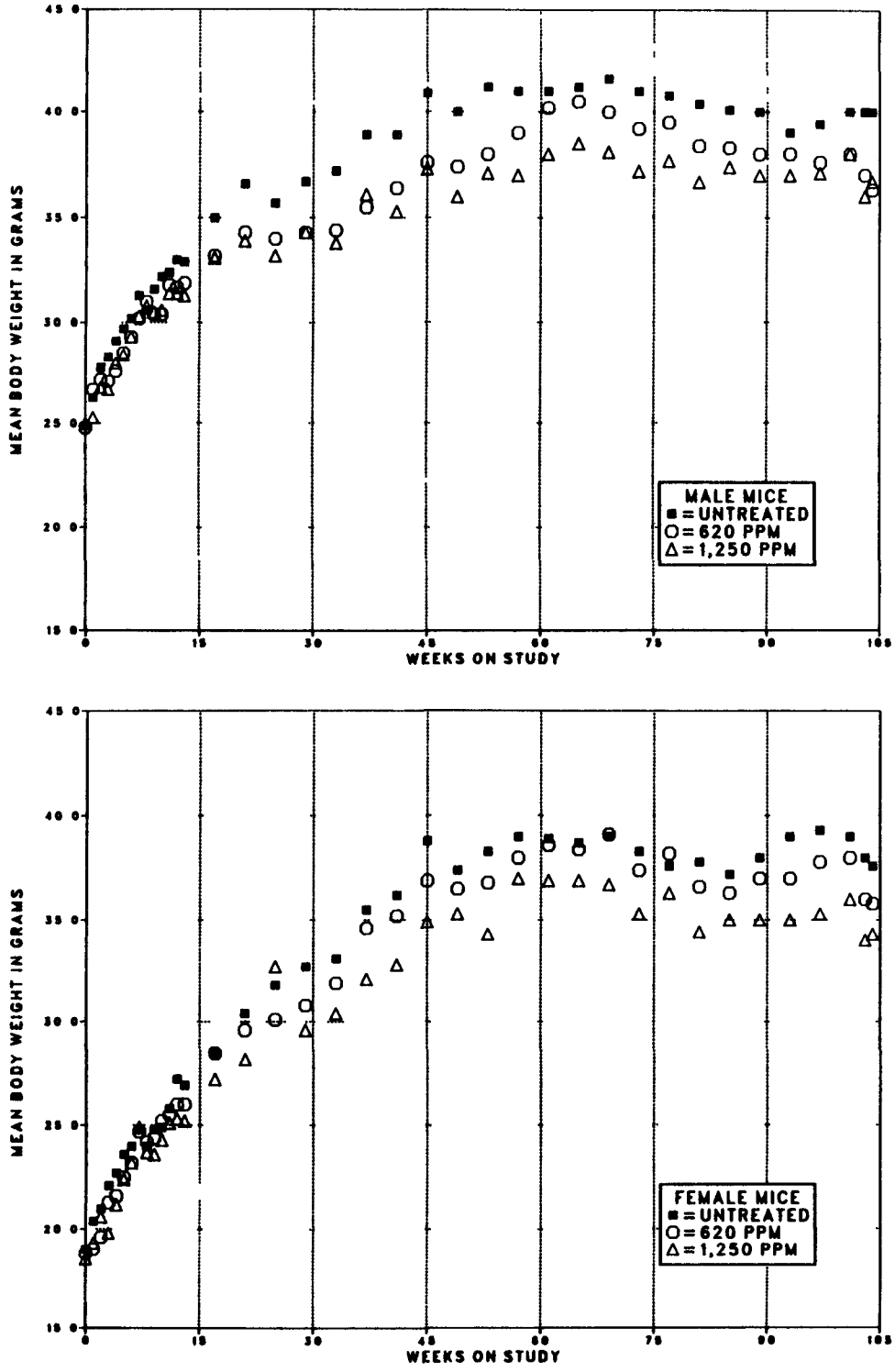


FIGURE 3. GROWTH CURVES FOR MICE FED DIETS CONTAINING CHLORENDIC ACID FOR TWO YEARS

Survival

Estimates of the probabilities for survival of male and female mice fed diets containing chlorendic acid at the concentrations used in these studies and those of controls are shown in Table 25 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, lung, thyroid gland, pituitary gland, and forestomach. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives 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) contains 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). Historical incidences of tumors in control animals are listed in Appendix F.

TABLE 25. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	20	21
Accidentally killed	0	2	0
Killed at termination	36	26	29
Died during termination period	1	2	0
Survival P values (c)	0.132	0.170	0.146
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	10	15
Accidentally killed	0	1	0
Killed at termination	39	39	34
Died during termination period	0	0	1
Survival P values (c)	0.395	0.906	0.464

(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 results of the life table pairwise comparisons with the controls are in the dosed columns.

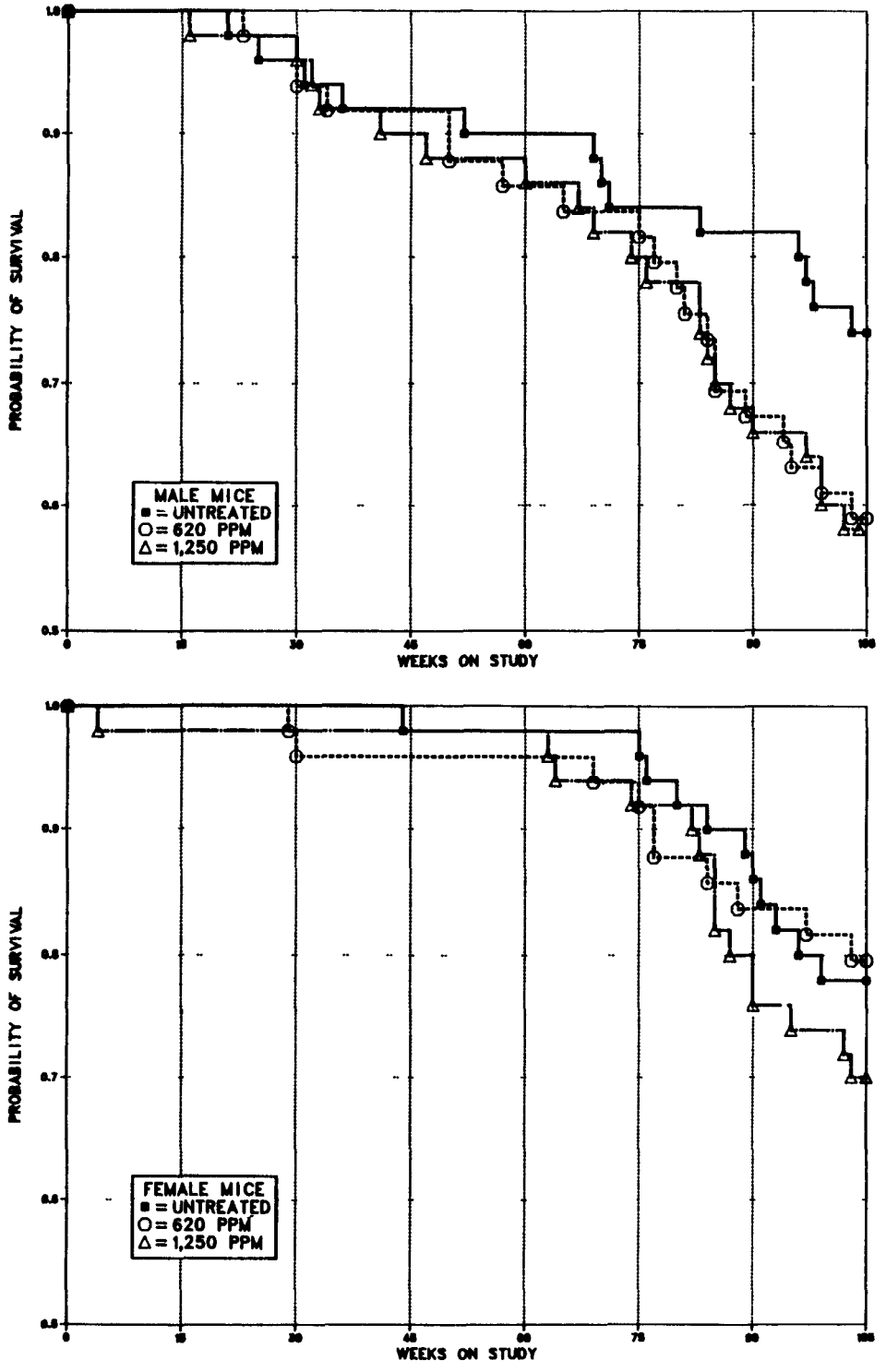


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING CHLORENDIC ACID FOR TWO YEARS

Liver: Necrosis was observed at increased incidences in dosed male mice, and mitotic alteration was observed in high dose female mice (Table 26).

Hepatocellular adenomas, hepatocellular carcinomas, and hepatocellular adenomas or carcinomas (combined) in male mice occurred with significant positive trends (Table 27). The incidences of hepatocellular adenomas in high dose males and of hepatocellular carcinomas and hepatocellular carcinomas or adenomas (combined) in dosed males were significantly greater than those in the controls. Metastases to the lung were seen in 2/50 control, 4/49 low dose, and 7/50 high dose male mice. The following incidences of hepatocellular adenomas or carcinomas (combined) were observed in female mice: control, 3/50; low dose, 7/49; high dose, 7/50.

Hepatocellular adenomas observed in these studies had well-defined borders that compressed adjacent parenchyma. Neoplastic cells were generally basophilic and varied in size from smaller than to equal to normal hepatocytes. Occasional neoplastic cells were observed that were large and eosinophilic. Neoplasms were usually solid, consisted of closely packed cells, and were usually devoid of sinusoids. Infrequently, fatty changes or vacuolation of the cytoplasm was prominent. Occasionally, a trabecular pattern was observed consisting of neoplastic cells one to two cell layers thick with sinusoids separating the cords. In solid tumors, the neoplastic cells varied greatly in size and nuclear morphology. Dilation of the sinusoids with blood, thrombi, and associated necrosis of neoplastic cells were frequent. Trabecular patterns consisted of cords of neoplastic cells several layers thick and often ended abruptly in a sinusoid. Infrequently, a glandular pattern of the tumor architecture was observed.

Hepatocellular carcinomas varied from solid to trabecular to mixed type patterns. In the solid neoplasms, the neoplastic cells varied greatly in size and nuclear morphology. Dilation of the sinusoids with blood, thrombi, and associated necrosis of neoplastic cells were frequent. Trabecular patterns consisted of cords of neoplastic cells several layers thick and often ended abruptly in a sinusoid. Infrequently, a glandular pattern of the tumor architecture was observed, as seen in the adenomas.

TABLE 26. NUMBERS OF MICE WITH LIVER LESIONS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

	Concentration (ppm)					
	Male			Female		
Lesion	0	620	1,250	0	620	1,250
Number examined	50	49	50	50	49	50
Necrosis	3	12	11	1	3	3
Mitotic alteration	0	0	0	0	0	7
Focal cellular change	3	4	6	1	1	5
Hepatocellular adenoma	5	9	10	2	2	3
Hepatocellular carcinoma	9	17	20	1	5	4

TABLE 27. ANALYSIS OF LIVER TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (a)

	Control	620 ppm (b)	1,250 ppm (b)
Hepatocellular Adenoma			
Overall Rates	5/50 (10%)	9/49 (18%)	10/50 (20%)
Adjusted Rates	13.5%	30.1%	33.3%
Terminal Rates	5/37 (14%)	8/28 (29%)	9/29 (31%)
Week of First Observation	105	30	102
Life Table Tests	P=0.038	P=0.077	P=0.047
Incidental Tumor Tests	P=0.041	P=0.081	P=0.050
Hepatocellular Carcinoma			
Overall Rates	9/50 (18%)	17/49 (35%)	20/50 (40%)
Adjusted Rates	22.1%	46.5%	51.8%
Terminal Rates	6/37 (16%)	9/28 (32%)	11/29 (38%)
Week of First Observation	70	75	60
Life Table Tests	P=0.004	P=0.018	P=0.005
Incidental Tumor Tests	P=0.023	P=0.084	P=0.038
Hepatocellular Adenoma or Carcinoma (c)			
Overall Rates	13/50 (26%)	23/49 (47%)	27/50 (54%)
Adjusted Rates	32.2%	61.4%	70.6%
Terminal Rates	10/37 (27%)	14/28 (50%)	18/29 (62%)
Week of First Observation	70	30	60
Life Table Tests	P<0.001	P=0.006	P<0.001
Incidental Tumor Tests	P=0.003	P=0.028	P=0.005

(a) The statistical analyses used are discussed 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 Appendix M.
(c) Historical incidence in NTP studies (mean ± SD): 540/1,784 (30% ± 8%)

Lung: Alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas or carcinomas (combined) in female mice occurred with significant positive trends (Table 28). The following incidences of alveolar/bronchiolar adenomas or carcinomas (combined) were observed in male mice: control, 15/50; low dose, 4/49; high dose, 9/50 (historical incidence in NTP studies: 296/1,780, 17% ± 8.2%). The incidence in the low dose group was significantly lower ($P<0.025$) than that in the controls.

Thyroid Gland: Follicular cell adenomas in male mice occurred with a significant positive trend; the incidence in the high dose group was not significantly greater than that in the controls (Table 29). There were no follicular cell lesions reported in female mice.

TABLE 28. ANALYSIS OF LUNG LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Alveolar Epithelial Hyperplasia			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adjusted Rates	0.0%	10.3%	10.5%
Terminal Rates	0/39 (0%)	4/39 (10%)	3/35 (9%)
Week of First Observation		104	74
Life Table Tests	P=0.047	P=0.063	P=0.054
Incidental Tumor Tests	P=0.050	P=0.063	P=0.066
Alveolar/Bronchiolar Carcinoma			
Overall Rates	1/50 (2%)	2/50 (4%)	2/50 (4%)
Alveolar/Bronchiolar Adenoma or Carcinoma (a)			
Overall Rates	1/50 (2%)	5/50 (10%)	6/50 (12%)
Adjusted Rates	2.6%	12.8%	16.1%
Terminal Rates	1/39 (3%)	5/39 (13%)	5/35 (14%)
Week of First Observation	104	104	74
Life Table Tests	P=0.034	P=0.103	P=0.045
Incidental Tumor Tests	P=0.037	P=0.103	P=0.053

(a) Historical incidence in NTP studies (mean ± SD): 122/1,777 (7% ± 4%)

TABLE 29. ANALYSIS OF THYROID GLAND LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Follicular Cell Hyperplasia			
Overall Rates	2/50 (4%)	1/47 (2%)	1/50 (2%)
Follicular Cell Adenoma (a)			
Overall Rates	0/50 (0%)	0/47 (0%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	9.1%
Terminal Rates	0/37 (0%)	0/28 (0%)	2/29 (7%)
Week of First Observation			67
Life Table Tests	P=0.030	(b)	P=0.093
Incidental Tumor Tests	P=0.039	(b)	P=0.120

(a) Historical incidence in NTP studies of follicular cell adenoma or carcinoma (combined) (mean ± SD): 28/1,680 (2% ± 2%)
(b) No P value is reported because no tumors were observed in the 620-ppm and control groups.

Pituitary Gland: Adenomas in female mice occurred with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the controls (Table 30).

Forestomach: Squamous cell papillomas in female mice occurred with a significant negative trend (control, 3/50; low dose, 0/48; high dose, 0/50); the incidences in the dosed groups were not significantly lower than that in the controls.

TABLE 30. ANALYSIS OF PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Hyperplasia			
Overall Rates	4/48 (8%)	2/47 (4%)	0/50 (0%)
Adenoma			
Overall Rates	12/48 (25%)	4/47 (9%)	3/50 (6%)
Adjusted Rates	30.8%	10.2%	8.6%
Terminal Rates	12/39 (31%)	3/37 (8%)	3/35 (9%)
Week of First Observation	104	77	104
Life Table Tests	P=0.009N	P=0.035N	P=0.019N
Incidental Tumor Tests	P=0.008N	P=0.028N	P=0.019N
Adenoma or Carcinoma (a)			
Overall Rates	13/48 (27%)	4/47 (9%)	3/50 (6%)
Adjusted Rates	32.4%	10.2%	8.6%
Terminal Rates	12/39 (31%)	3/37 (8%)	3/35 (9%)
Week of First Observation	91	77	104
Life Table Tests	P=0.005N	P=0.022N	P=0.012N
Incidental Tumor Tests	P=0.003N	P=0.021N	P=0.009N

(a) Historical incidence in NTP studies (mean ± SD): 122/1,777 (7% ± 4%)

IV. DISCUSSION AND CONCLUSIONS

Thirteen-Week Studies
Two-Year Studies
Mutagenicity

IV. DISCUSSION AND CONCLUSIONS

Chlorendic acid, a principal chemical intermediate used in the preparation of fire-retardant polyester resins and plasticizers, has been studied in 14-day, 13-week, and 2-year toxicology and carcinogenesis studies. The main findings of these studies indicate that feeding chlorendic acid in the diet results in both nonneoplastic and neoplastic lesions of the liver in male and female F344/N rats and male B6C3F$_1$ mice. In male rats, administration of chlorendic acid in feed is also associated with an uncommon pancreatic acinar cell lesion and possibly with the occurrence of alveolar/bronchiolar adenomas and preputial gland carcinomas.

Thirteen-Week Studies

Thirteen-week studies were conducted by offering feed containing chlorendic acid to male and female F344/N rats (0, 620, 1,250, 2,500, 5,000, or 10,000 ppm) and B6C3F$_1$ mice (0, 1,250, 2,500, 5,000, or 10,000 ppm). Results included decreases in body weights when compared with those of controls (see Tables 6 and 22) and increased incidences of deaths and lesions of the liver when compared with those of controls (see Tables 7 and 23). The liver was the only affected organ identified in these 90-day studies.

The occurrence of liver lesions in rats (centrilobular cytomegaly, mitotic alterations, and bile duct hyperplasia) was dose related (see Table 7). Mitotic alterations included an increase in both normal and abnormal mitotic figures. The incidence and number of mitotic alterations in male rats were slightly greater than those in female rats at the two highest concentrations. The incidence and degree of severity of bile duct hyperplasia were greater in female rats than in male rats at the two highest concentrations. In mice, mitotic alterations were not seen as often as in the rats and did not occur at levels corresponding to those in rats (see Table 23). Cytomegaly of minimal severity was consistently seen in male and female rats at the two highest doses and in male and female mice at the highest dose. The hepatic lesions in male mice were primarily coagulative necrosis. The effect was greater in male mice than in female mice.

Chemical disposition studies (Decad and Fields, 1982; Appendix O) in male F344 rats demonstrated that the liver is the major site of deposition of chlorendic acid after a single gavage administration. The 13-week feed studies, considered in conjunction with the evidence for disposition and metabolism for chlorendic acid, indicate the liver is a major site for chemical accumulation and toxic injury at the concentrations used. The degree of severity of the hepatic lesions observed in these studies was proportional to the amount of chlorendic acid consumed.

Feed consumption (group means) by the two highest dose groups was lower than that by the controls during the first 7 weeks of the study in both male and female rats but was similar to that of the controls during the last 6 weeks, except at the highest dose at which food consumption exceeded that of the controls (see Table 6). There were no differences in feed consumption values for male and female mice over the course of the study relative to those of controls (see Table 22).

Two-Year Studies

Two-year toxicology and carcinogenesis studies were conducted by offering feed containing chlorendic acid to male and female F344/N rats and B6C3F$_1$ mice at 0, 620, or 1,250 ppm for 103 weeks. These concentrations were based on a decrease in mean body weights and on liver lesions observed in the 13-week studies. Higher concentrations of chlorendic acid were not chosen because adverse effects on survival and the health of the animals would be anticipated over the course of the 2-year studies.

In rats, these dietary levels resulted in an estimated average daily consumption of chlorendic acid of 27 and 56 mg/kg for low dose and high dose males and 39 and 66 mg/kg for low dose and high dose females. The estimated consumption was 89 and 188 mg/kg for male mice and 100 and 207 mg/kg for female mice. These exposures to chlorendic acid did not affect survival in either rats or mice (see Tables 9 and 25; Figures 2 and 4). The relatively lower survival of control and high dose male rats compared with that of the low dose group or with historical rates cannot be explained on the basis of available information. The apparent dose-related decrease in mean

body weights in dosed female rats was not reflected by lower survival in this group. Mean body weights of male rats and male and female mice varied from 2% above the control values to 11% below (see Tables 8 and 24; Figures 1 and 3).

In the 2-year chlorendic acid feed studies, hepatic lesions were observed in dosed male rats (cystic degeneration) and female rats (granulomatous inflammation, pigmentation, and bile duct hyperplasia) (see Table 10). The incidences of neoplastic nodules of the liver in dosed male rats and high dose female rats and of hepatocellular carcinomas in high dose female rats were greater than those in controls (see Table 11). These results contrast with those of NCI feed studies of other hexachlorinated norbornene analogs (see Table 1) in which no liver effects were observed in male and female Osborne-Mendel rats.

The pathologic diagnosis of neoplastic nodules and hepatocellular carcinomas in male F344/N rats was complicated in those animals with severe leukemic infiltrates. The incidence of leukemia in dosed rats in the current study (male: control, 24/50; low dose, 22/50; high dose, 28/50; female: control, 13/50; low dose, 15/50; high dose, 16/50) did not decrease, although this phenomenon occurred in previous studies that had increases in liver neoplasia (Haseman, 1983). Grossly, livers with hepatocellular neoplasms had multiple red or yellow foci and/or yellow foci and/or one or more tan to brown focal nodules either within the parenchyma or raised above the surface. The size of these nodules ranged from a few millimeters to several centimeters. Animals with an entire nodular liver surface usually had mononuclear cell leukemia. Neoplastic nodules were less difficult to diagnose than were the hepatocellular carcinomas. In all animals with both hepatocellular carcinomas and mononuclear cell leukemia, there was degeneration and atrophy of the centrilobular hepatocytes and hypertrophy of intervening hepatocytes which resulted in a multinodular liver. These effects were usually observed as multiple lesions and were the type most commonly seen in dosed animals. The lesions in dosed animals varied from hyperplastic to neoplastic. Hepatocellular carcinomas present in female rats appeared as large, solid nodules with marked compression of adjacent hepatic parenchyma, frequently raised from the liver surface.

In the 2-year chlorendic acid feed studies, incidences of nonneoplastic lesions of the liver increased in dosed male mice (coagulative necrosis) and high dose female mice (mitotic alteration) (see Table 26). In dosed male mice, coagulative necrosis occurred both within normal hepatic parenchyma and liver neoplasms. Since necrosis was identified as a liver lesion in the 13-week studies and again as a component associated with hepatocellular neoplasms in the 2-year studies, it is unclear if the lesion in the 2-year studies is a direct effect of chlorendic acid feeding or is a secondary effect of neoplasia.

In male mice, the incidences of hepatocellular adenomas and of hepatocellular carcinomas occurred with positive trends. The incidences of hepatocellular adenomas in high dose male mice and of hepatocellular carcinomas in dosed male mice were greater than those in controls. Metastasis to the lungs occurred in male mice in a dose-related manner (control, 2/50; low dose, 4/49; high dose, 7/50; Appendix B, Table B3). The biologic significance of the association between hepatocellular neoplasms in male mice and the feeding of chlorendic acid was strengthened by this metastasis. In dosed female mice, the incidences of hepatocellular adenomas or carcinomas (combined) were somewhat increased but not significantly different from that in the controls (control, 3/50; low dose, 7/49; high dose, 7/50; Appendix E, Table E4).

Gross observations in mice showed that hepatocellular neoplasms were nodular or multinodular consolidations of one or more liver lobes. These tumors were rounded or nodular and cystic, soft to firm masses varying between 0.5 and 4.5 cm at the greatest diameter. Hepatocellular carcinomas varied from solid to trabecular to mixed type patterns. In these studies, most of the hepatocellular carcinomas were large masses with prominent trabecular patterns.

Previous studies of other hexachlorinated norbornene analogs indicate that several of these compounds cause hepatocellular carcinomas in

male B6C3F$_1$ mice and some cause hepatocellular carcinomas in female B6C3F$_1$ mice (NCI, 1977a,b, 1978a,b; see Table 1). The absence of significant effects of chlorendic acid on female B6C3F$_1$ mice in this study may be due to either insufficient exposure concentrations or sex differences in chemical disposition and metabolism and hence, susceptibility. In the chlorendic acid 13-week studies, no great differences in responses were seen between the sexes, and no information is available on chlorendic acid chemical disposition and metabolism in female rats or mice.

Acinar cell adenomas of the pancreas occurred in male rats with a dose-related positive trend (see Table 12). The incidence in high dose male rats was greater than that in controls. These neoplasms were not detected by gross observation. The biologic importance of this lesion is supported by an increase in acinar cell hyperplasia in both dose groups. Acinar cell adenoma of the pancreas is an uncommon neoplasm in NTP historical untreated control male F344/N rats.

Alveolar/bronchiolar adenomas occurred with positive trends in male rats (see Table 13), and the incidences in the high dose male rats were greater than those in the controls. In female mice, the incidence of alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas or carcinomas (combined) occurred with positive trends (see Table 28). In male rats and female mice, this marginal trend in the incidence of alveolar/bronchiolar adenomas or carcinomas (combined) is not supported by an increase in alveolar/bronchiolar hyperplasia. In male rats, the incidence of alveolar/bronchiolar adenomas may have been related to the administration of chlorendic acid. In female mice, the incidences of alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas or carcinomas (combined) in the concurrent controls were low compared with the historical control average (Appendix F, Table F15), and hence the biologic significance of the association of these lesions with administration of chlorendic acid is unclear.

Preputial gland carcinomas occurred with a greater incidence in low dose male rats than in the controls (see Table 14). Two other male rats in the low dose group had either an adenoma or squamous cell papilloma, making the group incidence outside the range of preputial gland neoplasms (0/50 to 8/50) seen in untreated male F344/N rats in NTP studies. This effect may be related to the administration of chlorendic acid. No tumors were found in the clitoral gland of female rats in this study.

Sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) of the salivary gland occurred in male rats at incidences of 1/50 (control), 2/49 (low dose), and 4/50 (high dose). Although the incidence in the high dose group is not statistically significant, these neoplasms are uncommon (3/1,689 in NTP untreated controls). These tumors were morphologically similar to those found in the salivary glands of rats administered methylene chloride (inhalation) (Burek et al., 1984). Fibrosarcomas also occurred in subcutaneous tissue at sites distinct from the salivary gland.

Uterine cysts were observed at an increased incidence in high dose female rats. The incidence of endometrial stromal polyps was marginally greater in low dose female rats than in the controls (see Table 15). There was no dose-response relationship. The incidence of this relatively common lesion in untreated controls has ranged from 4/50 to 18/49. Since an increase was not observed in the high dose group and the low dose incidence falls within this historical range, it is unlikely that this lesion is associated with the feeding of chlorendic acid to F344/N female rats.

Follicular cell adenomas of the thyroid gland occurred in male B6C3F$_1$ mice with a positive trend (see Table 29). There were no significant differences between either dosed group and controls. The marginal trend in the absence of a dose-related increase in epithelial hyperplasia and an incidence that falls within the range of untreated control incidences do not support an association of this lesion with administration of chlorendic acid. In previous studies with hexachlorinated norborenes (see Table 1), follicular cell adenomas were associated with chemical administration in male and female Osborne-Mendel rats but not in male or female B6C3F$_1$ mice.

Pheochromocytomas of the adrenal gland and interstitial cell tumors of the testis occurred with significant negative trends in male F344/N rats (see Tables 18 and 19). Mammary gland fibroadenomas in female F344/N rats (see Table 17) and pituitary gland adenomas and adenomas or carcinomas (combined) in female B6C3F$_1$ mice (see Table 30) all occurred with negative trends. These are common, age-related lesions in these strains. Haseman (1983) showed an association between decreased incidence of these tumors and decreased body weight gain in F344 rats. An effect on body weight gain was also seen in this study.

Mutagenicity

Chlorendic acid was not mutagenic in strains TA100, TA98, TA1535, or TA1537 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 when tested according to the preincubation protocol (Appendix G). Chlorendic acid was mutagenic in the L5178Y/TK$^{+/-}$ mouse lymphoma cell forward assay in the absence of activation and was not tested in the presence of activation. There was no mutagenic response in the absence of severe toxicity. The toxicity curve was sharp, going from relative total growth of 74% at 1,600 µg/ml to 5% at 1,700 µg/ml. The increase in mutant count and mutant frequency was observed only at the higher dose; this response was replicated in another experiment. When the only mutagenic response occurs at toxic doses, the question arises of whether the mutagenicity is indirect and not due to the direct interaction of the chemical with DNA. This assay, as performed, does not answer this question. Chlordane, endosulfan, endrin, and heptachlor did not cause mutations in NTP Salmonella mutagenicity tests (Haworth et al., 1983).

Conclusions: Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenicity** of chlorendic acid for male F344/N rats as shown by increased incidences of neoplastic nodules of the liver and acinar cell adenomas of the pancreas. Increased incidences of alveolar/bronchiolar adenomas and preputial gland carcinomas may also have been related to the administration of chlorendic acid. There was *clear evidence of carcinogenicity* of chlorendic acid for female F344/N rats as shown by increased incidences of neoplastic nodules and of carcinomas of the liver. There was *clear evidence of carcinogenicity* of chlorendic acid for male B6C3F$_1$ mice as shown by increased incidences of hepatocellular adenomas and of hepatocellular carcinomas. There was *no evidence of carcinogenicity* of chlorendic acid for female B6C3F$_1$ mice given chlorendic acid in the diet at concentrations of 620 or 1,250 ppm for 103 weeks.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 14.

V. REFERENCES

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Fibrous histiocytoma, malignant		1 (2%)	
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Squamous cell carcinoma			1 (2%)
Basal cell carcinoma	1 (2%)	2 (4%)	1 (2%)
Keratoacanthoma	4 (8%)	†4 (8%)	3 (6%)
*Subcutaneous tissue	(50)	(50)	(50)
Sebaceous adenocarcinoma			1 (2%)
Sarcoma, NOS			1 (2%)
Fibroma	4 (8%)	†4 (8%)	3 (6%)
Fibrosarcoma		1 (2%)	3 (6%)
Fibrous histiocytoma, malignant		1 (2%)	
Neurofibrosarcoma	1 (2%)		
*Skeletal muscle	(50)	(50)	(50)
Fibrous histiocytoma, malignant	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		3 (6%)	5 (10%)
Alveolar/bronchiolar carcinoma		1 (2%)	
C-cell carcinoma, metastatic	1 (2%)		
Paraganglioma, metastatic	1 (2%)		
Fibrosarcoma, metastatic			3 (6%)
Carcinosarcoma, metastatic			1 (2%)
Mesothelioma, metastatic		1 (2%)	
Neurofibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undiffer type			2 (4%)
Malignant lymphoma, histiocytic type		1 (2%)	
Leukemia, mononuclear cell	24 (48%)	22 (44%)	28 (56%)
#Spleen	(50)	(50)	(49)
Mesothelioma, metastatic	1 (2%)		
#Mandibular lymph node	(50)	(50)	(50)
Carcinosarcoma, invasive			1 (2%)
Neurofibrosarcoma, invasive		1 (2%)	
#Cervical lymph node	(50)	(50)	(50)
C-cell carcinoma, metastatic			1 (2%)
#Renal lymph node	(50)	(50)	(50)
Neurofibrosarcoma, metastatic			1 (2%)
#Thymus	(41)	(39)	(36)
Thymoma, benign	1 (2%)		
Thymoma, malignant		1 (3%)	
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Spleen	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)		1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Lymph node	(50)	(50)	(50)
Hemangiosarcoma, metastatic			1 (2%)
*Vertebra	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
*Hard palate	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Salivary gland	(50)	(49)	(50)
Fibrosarcoma	1 (2%)	1 (2%)	4 (8%)
Carcinosarcoma, invasive			1 (2%)
Neurofibrosarcoma		1 (2%)	
#Liver	(50)	(50)	(50)
Neoplastic nodule	2 (4%)	21 (42%)	23 (46%)
Hepatocellular carcinoma	3 (6%)	5 (10%)	1 (2%)
#Pancreas	(49)	(50)	(50)
Acinar cell adenoma		4 (8%)	6 (12%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Transitional cell carcinoma		1 (2%)	
#Urinary bladder	(49)	(50)	(50)
Transitional cell papilloma			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	1 (2%)	1 (2%)
#Anterior pituitary	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	
Adenoma, NOS	15 (30%)	21 (42%)	18 (36%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma	2 (4%)		2 (4%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	25 (50%)	17 (34%)	15 (30%)
Pheochromocytoma, malignant	3 (6%)		
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	10 (20%)	7 (14%)	12 (24%)
C-cell carcinoma	5 (10%)	3 (6%)	3 (6%)
#Parathyroid	(48)	(49)	(48)
Adenoma, NOS		1 (2%)	1 (2%)
#Pancreatic islets	(49)	(50)	(50)
Islet cell adenoma	2 (4%)	5 (10%)	6 (12%)
Islet cell carcinoma	4 (8%)	1 (2%)	3 (6%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	8 (16%)	4 (8%)
Squamous cell papilloma		1 (2%)	
Adenoma, NOS		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Testis	(49)	(50)	(50)
Interstitial cell tumor	41 (84%)	35 (70%)	22 (44%)
*Scrotum	(50)	(50)	(50)
Mesothelioma, invasive	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Carcinoma, NOS, invasive		1 (2%)	1 (2%)
#Cerebrum	(50)	(50)	(50)
Astrocytoma			1 (2%)
#Brain	(50)	(50)	(50)
Granular cell tumor, NOS		1 (2%)	
*Pineal body	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		1 (2%)
Carcinosarcoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Mandible	(50)	(50)	(50)
Ameloblastic odontoma	1 (2%)		
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Paraganglioma, malignant	1 (2%)		
Fibrosarcoma			1 (2%)
Neurofibrosarcoma			1 (2%)
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
Mesothelioma, malignant	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	12	10
Moribund sacrifice	17	8	15
Terminal sacrifice	24	30	25

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	50	50	50
Total primary tumors	163	183	178
Total animals with benign tumors	46	49	40
Total benign tumors	109	109	95
Total animals with malignant tumors	38	37	43
Total malignant tumors	51	52	60
Total animals with secondary tumors##	3	3	8
Total secondary tumors	4	4	10
Total animals with tumors uncertain--benign or malignant	3	22	23
Total uncertain tumors	3	22	23

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ
† Multiple occurrence of morphology in the same organ; tissue is counted once only.

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)		1 (2%)
Fibrosarcoma	2 (4%)	1 (2%)	
Fibrous histiocytoma, malignant	1 (2%)		
Fibrous histiocytoma, metastatic	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Carcinoma, NOS, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	1 (2%)
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undiffer type			2 (4%)
Leukemia, mononuclear cell	13 (26%)	15 (30%)	16 (32%)
#Mandibular lymph node	(50)	(50)	(50)
Carcinoma, NOS, metastatic			1 (2%)
Fibrosarcoma, invasive	1 (2%)		
#Mesenteric lymph node	(50)	(50)	(50)
Malignant lymphoma, undiffer type	1 (2%)		
CIRCULATORY SYSTEM			
#Brain stem	(50)	(50)	(50)
Angioma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Myocardium	(50)	(50)	(50)
Neurilemoma	2 (4%)		
#Myocardium/rt. ventr	(50)	(50)	(50)
Neurilemoma			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(50)	(50)
Sarcoma, NOS		2 (4%)	
Fibrosarcoma			1 (2%)
#Liver	(50)	(49)	(50)
Neoplastic nodule	1 (2%)	3 (6%)	11 (22%)
Hepatocellular carcinoma		3 (6%)	5 (10%)
Fibrous histiocytoma, metastatic	1 (2%)		
#Pancreas	(49)	(49)	(50)
Acinar cell adenoma		1 (2%)	1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	2 (4%)	2 (4%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Anterior pituitary	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	3 (6%)	1 (2%)
Adenoma, NOS	29 (58%)	32 (64%)	21 (42%)
#Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma	2 (4%)	3 (6%)	2 (4%)
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma	1 (2%)		2 (4%)
C-cell adenoma	7 (14%)	10 (20%)	13 (26%)
C-cell carcinoma	2 (4%)	7 (14%)	2 (4%)
#Parathyroid	(45)	(47)	(47)
Adenoma, NOS	1 (2%)	1 (2%)	1 (2%)
#Pancreatic islets	(49)	(49)	(50)
Islet cell carcinoma	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	3 (6%)	3 (6%)
Adenocarcinoma, NOS	1 (2%)	5 (10%)	4 (8%)
Fibroadenoma	22 (44%)	16 (32%)	4 (8%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	4 (8%)	5 (10%)	6 (12%)
Adenoma, NOS			1 (2%)
#Uterus	(50)	(49)	(50)
Leiomyosarcoma	1 (2%)		
Endometrial stromal polyp	5 (10%)	15 (31%)	10 (20%)
Endometrial stromal sarcoma		1 (2%)	1 (2%)
#Cervix uteri	(50)	(49)	(50)
Endometrial stromal polyp	1 (2%)		
#Ovary	(50)	(49)	(50)
Granulosa cell carcinoma	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)	1 (2%)	
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)	2 (4%)	1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Paraganglioma, malignant	1 (2%)		
*Mesentery	(50)	(50)	(50)
Leiomyosarcoma, metastatic	1 (2%)		

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	10	10	5
Moribund sacrifice	8	6	11
Terminal sacrifice	31	34	34
Accidentally killed, nda	1		
TUMOR SUMMARY			
Total animals with primary tumors**	48	48	48
Total primary tumors	110	130	113
Total animals with benign tumors	42	45	37
Total benign tumors	76	84	63
Total animals with malignant tumors	27	25	29
Total malignant tumors	33	43	39
Total animals with secondary tumors##	6	4	2
Total secondary tumors	7	4	3
Total animals with tumors uncertain--benign or malignant	1	3	11
Total uncertain tumors	1	3	11

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
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 CHLORENDIC ACID: UNTREATED CONTROL

ANIMAL NUMBER	04 8	01 1	04 2	02 1	00 8	04 7	04 6	02 5	04 3	03 8	04 1	04 0	02 3	00 5	02 6	00 1	00 2	01 9	03 1	01 4	03 4	04 5	02 0	01 8	03 0
WEEKS ON STUDY	02 5	06 1	06 5	07 3	07 5	07 6	07 7	08 0	08 0	08 2	08 2	08 5	08 9	09 1	09 1	09 3	09 3	09 5	09 5	09 8	09 9	09 9	10 0	10 1	10 1
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell carcinoma																									
Keratoacanthoma																				X					X
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma					X																				
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell carcinoma, metastatic															X										
Paraganglioma, metastatic		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, metastatic																X									
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	+	–	+	+	–	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma							X														X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS															X										
Adenoma, NOS					X				X				X	X							X	X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma						X									X	X	X	X		X	X	X	X		X
Pheochromocytoma, malignant																	X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Follicular cell carcinoma															X										
C-cell adenoma														X											X
C cell carcinoma															X										
Parathyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Islet cell adenoma													X									X			
Islet cell carcinoma																	X								
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Interstitial cell tumor				X	X	X		X		X	X	X		X	X	X	X	X	X			X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma	X																								
Ameloblastic odontoma												X													
Muscle	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Fibrous histiocytoma, malignant																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Paraganglioma, malignant		X																							
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Mesothelioma, NOS										X															
Mesothelioma, malignant															X										
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X	X		X	X	X	X	X	X			X			X	X	X	X	X		X	X	X
Scrotum, NOS																									
Mesothelioma, invasive															X										

\+ Tissue Examined Microscopically
– Required Tissue Not Examined Microscopically
X Tumor Incidence
N Necropsy, No Autolysis, No Microscopic Examination
S Animal Missexed
No Tissue Information Submitted
C Necropsy, No Histology Due To Protocol
A Autolysis
M Animal Missing
B No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	0024	0033	0044	0066	0097	0099	0100	0122	0133	0155	0166	0177	0222	0227	0288	0299	0321	0333	0353	0366	0377	0399	0444	0449	0550	TOTAL TISSUES TUMORS
WEEKS ON STUDY	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																							X			1
Basal cell carcinoma													X													1
Keratoacanthoma																X	X									4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma				X	X																X					4
Neurofibrosarcoma										X																1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell carcinoma, metastatic																										1
Paraganglioma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, metastatic																										1
Hemangiosarcoma		X																								1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	41
Thymoma, benign																	X									1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																		X								1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																						X	X			2
Hepatocellular carcinoma				X																						3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS				X		X		X			X	X			X		X				X		X	X		17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma								X																	X	2
Pheochromocytoma				X		X	X		X	X	X	X	X	X			X	X	X	X			X	X		25
Pheochromocytoma, malignant			X	X																						3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
C-cell adenoma	X		X		X	X		X	X													X	X			10
C-cell carcinoma				X												X		X			X					5
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										2
Islet cell carcinoma								X								X						X			4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma						X																				1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS											X															1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS														X												1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Ameloblastic odontoma																										1
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	*50
Fibrous histiocytoma, malignant																				X						1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Paraganglioma, malignant																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X			X			X					X		X				X					X			24
Scrotum, NOS																										
Mesothelioma, invasive																										1

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: LOW DOSE

ANIMAL NUMBER	13 37	13 33	11 19	15 50	11 11	12 24	10 08	11 12	11 18	11 13	14 00	12 22	12 26	11 10	12 11	10 08	10 07	11 15	10 01	10 02	10 03	10 04	10 05	10 09	11 14
WEEKS ON STUDY	07 4	08 1	08 6	08 8	08 9	08 9	09 0	09 3	09 4	09 5	09 5	09 7	09 7	09 8	09 8	09 9	10 2	10 3	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma												X													
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
Fibrosarcoma																				X					
Fibrous histiocytoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		X
Alveolar/bronchiolar carcinoma																									
Mesothelioma, metastatic				X																					
Neurofibrosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma, invasive																									
Thymus	+	+	–	+	–	+	+	–	–	–	–	+	+	–	–	–	–	+	+	+	+	+	+	+	+
Thymoma, malignant																			X						
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Neurofibrosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
Neoplastic nodule													X					X		X	X		X		
Hepatocellular carcinoma																			X		X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma				X																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS															X										
Adenoma, NOS	X					X		X		X			X					X	X					X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X					X	X						X			X		X		X	X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma						X																			
C-cell adenoma																							X		
C-cell carcinoma										X															
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma						X										X	X								
Islet cell carcinoma																									X
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X	X	X	X		X	X			X	X			X		X	X	X	X	X	X		X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS		X															X			X			X		
Squamous cell papilloma																X									
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive															X										
Granular cell tumor, NOS																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, malignant				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrous histiocytoma, malignant											X														
Malig. lymphoma, histiocytic type								X																	
Leukemia, mononuclear cell			X		X	X	X					X		X		X	X		X				X		

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

ANIMAL NUMBER	116	117	120	123	125	127	128	129	130	131	132	134	135	136	138	139	141	142	143	144	145	146	147	148	149	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell carcinoma				X									X													2
Keratoacanthoma	X													X									X@			4
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma				X				X						X@												4
Fibrosarcoma																										1
Fibrous histiocytoma, malignant												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												3
Alveolar/bronchiolar carcinoma																	X									1
Mesothelioma, metastatic																										1
Neurofibrosarcoma, metastatic																X										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurofibrosarcoma, invasive																X										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	39
Thymoma, malignant																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma					X					X																2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Fibrosarcoma				X																						1
Neurofibrosarcoma																X										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule			X	X		X	X	X	X	X	X				X		X	X				X	X	X	X	21
Hepatocellular carcinoma			X														X	X								5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma						X																	X	X		4
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS		X	X	X		X	X				X	X	X	X	X		X					X		X		22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X						X					X		X	X			X	X	X		X				17
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
C-cell adenoma	X					X							X							X	X	X				7
C-cell carcinoma			X		X																					3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																									X	1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma	X	X																								5
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X		X	X	X	X		X	X	X		X	X	X		X	X	X				X	X	X	X	35
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS				X		X		X			X															8
Squamous cell papilloma																										1
Adenoma, NOS												X														1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Granular cell tumor, NOS													X													1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrous histiocytoma, malignant																										1
Malig. lymphoma, histiocytic type																										1
Leukemia, mononuclear cell		X				X		X		X	X	X					X	X	X		X		X		X	22

* Animals Necropsied
@ : Multiple occurrence of Morphology

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: HIGH DOSE

ANIMAL NUMBER	221	217	240	223	234	237	212	208	210	243	209	202	222	233	247	241	232	246	231	205	248	228	250	218	238
WEEKS ON STUDY	043	064	072	073	076	078	081	082	082	082	083	087	087	087	088	090	092	092	093	094	094	096	099	100	101
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Basal cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenocarcinoma																									
Sarcoma, NOS																									
Fibroma																									
Fibrosarcoma														X									X		
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	X
Fibrosarcoma, metastatic														X											
Carcinosarcoma, metastatic				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																									
Carcinosarcoma, invasive				X																					
Hemangiosarcoma, metastatic																									
Neurofibrosarcoma, metastatic		X																							
Thymus	+	+	+	+	+	+	–	–	–	+	–	+	–	–	+	+	+	+	+	+	–	–	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																		X							
Carcinosarcoma, invasive				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule											X			X				X				X			
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																			X						
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X			X														X	X
Pineal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma						X														X			X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma														X				X	X						
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																		X							
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X									X		X		X		X	X		X	X		X	X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS								X														X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
Astrocytoma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	+	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS	X																								
Carcinosarcoma				X																					
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma														X											
Neurofibrosarcoma		X																							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, undiffer type													X			X									
Leukemia, mononuclear cell			X	X	X	X		X	X	X	X	X					X	X	X	X	X	X	X		

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

ANIMAL NUMBER	201	203	204	206	207	211	213	214	215	216	219	220	225	226	227	229	230	234	235	236	239	242	244	245	249	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma					X																					1
Basal cell carcinoma		X																								1
Keratoacanthoma	X																		X						X	3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenocarcinoma													X													1
Sarcoma, NOS				X																						1
Fibroma												X												X	X	3
Fibrosarcoma					X																					3
Hemangiosarcoma																									X	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X			X									X		5
Fibrosarcoma, metastatic					X					X																3
Carcinosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma							X																			1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																								X		1
Carcinosarcoma, invasive																										1
Hemangiosarcoma, metastatic							X																			1
Neurofibrosarcoma, metastatic																										1
Thymus	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma							X			X							X										4
Carcinosarcoma, invasive																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X			X			23
Hepatocellular carcinoma																							X			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma	X				X	X			X										X				X			6
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS				X	X		X	X	X	X	X						X		X	X	X		X	X	X	19
Pineal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS												X														1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma									X												X					2
Pheochromocytoma		X	X			X	X	X		X						X	X	X		X	X			X		15
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma	X		X					X			X	X				X		X		X				X	12
C-cell carcinoma							X										X						X			3
Parathyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																		X								1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma			X						X				X	X				X								6
Islet cell carcinoma	X																						X		X	3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X		X							X	X	X	X	X	X	X			X					22
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS									X				X													4
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive												X														1
Astrocytoma								X																		1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Carcinosarcoma																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
Neurofibrosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig lymphoma, undiffer type																										2
Leukemia, mononuclear cell	X	X	X							X	X	X	X		X	X	X		X						X	28

*Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: UNTREATED CONTROL

ANIMAL NUMBER	075	052	056	085	054	070	071	060	063	059	055	096	093	090	100	066	078	086	092	051	053	057	058	061	062
WEEKS ON STUDY	009	058	082	082	087	087	087	088	089	091	096	096	097	098	099	102	102	102	103	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma										X															
Fibrous histiocytoma, malignant																									
Fibrous histiocytoma, metastatic																									
Hemangiosarcoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, invasive																									
Malig. lymphoma, undiffer type								X																	
Thymus	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma												X													
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																			X						
Fibrous histiocytoma, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS												X												X	
Adenoma, NOS			X		X	X	X									X	X			X	X	X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X																			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																	X								
C-cell adenoma												X	X											X	X
C cell carcinoma																									
Parathyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																				X					
Fibroadenoma					X	X			X	X					X				X		X	X		X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS				X															X	X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																X									
Endometrial stromal polyp		X																					X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive												X												X	
Angioma																	X								
SPECIAL SENSE ORGANS																									
Zymbal gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS		X																							
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Paraganglioma, malignant																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma, metastatic																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, metastatic		X																							
Leukemia, mononuclear cell			X				X			X	X		X	X						X				X	

+ Tissue Examined Microscopically
− Required Tissue Not Examined Microscopically
X Tumor Incidence
N Necropsy, No Autolysis, No Microscopic Examination
S Animal Missexed
B No Necropsy Performed
C Necropsy, No Histology Due To Protocol
A Autolysis
M Animal Missing

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	0064	0065	0067	0068	0069	0072	0073	0074	0076	0077	0079	0080	0081	0082	0083	0084	0087	0088	0089	0091	0094	0095	0097	0098	0099	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																					X					1
Fibrosarcoma						X																				2
Fibrous histiocytoma, malignant												X														1
Fibrous histiocytoma, metastatic												X														1
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, invasive						X																				1
Malig. lymphoma, undiffer type																										1
Thymus	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma														X												2
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Fibrous histiocytoma, metastatic												X														1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										2
Adenoma, NOS	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	31
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																	X									2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
C-cell adenoma	X					X																		X		7
C-cell carcinoma					X																				X	2
Parathyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS																							X			1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma									X																X	2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																			X							1
Adenocarcinoma, NOS																										1
Fibroadenoma	X		X	X	X			X		X	X	X				X				X			X		X	22
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																						X				4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Endometrial stromal polyp	X					X								X		X										6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell carcinoma									X																	1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										2
Angioma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Paraganglioma, malignant							X																			1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, metastatic																										1
Leukemia, mononuclear cell		X			X								X				X			X						13

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: LOW DOSE

ANIMAL NUMBER	185	151	199	182	200	161	170	166	197	172	179	196	178	180	152	153	154	155	156	157	158	159	160	162	163
WEEKS ON STUDY	063	064	081	082	086	090	093	095	097	098	099	099	100	102	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Fibrosarcoma, metastatic																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X								
Liver	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																							X		
Hepatocellular carcinoma								X															X		
Bile duct	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																							X		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS											X		X												
Adenoma, NOS		X	X	X			X	X	X	X				X		X		X	X	X	X	X		X	X
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma							X								X		X			X			X		
C-cell carcinoma													X			X				X				X	
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS													X												
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS								X					X							X					
Fibroadenoma				X	X				X				X	X			X	X	X	X					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS															X					X					
Uterus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp					X						X					X		X	X				X		
Endometrial stromal sarcoma																									
Ovary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive											X		X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X			X			X	X		X	X											X		

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	164	165	167	168	169	171	173	174	175	177	178	181	183	184	186	187	188	189	190	191	192	193	194	195	198	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma													X													1
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS	X																									2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule							X									X										3
Hepatocellular carcinoma																								X		3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																	X									3
Adenoma, NOS	X			X	X				X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	34
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma												X						X								3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma					X					X				X		X									X	10
C-cell carcinoma		X							X											X						7
Parathyroid	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS											X				X					X						3
Adenocarcinoma, NOS									X										X							5
Fibroadenoma	X		X				X			X	X				X										X	16
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS															X		X		X							5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp		X		X		X								X			X		X		X	X	X			15
Endometrial stromal sarcoma																									X	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell carcinoma																	X									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																	X									3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X							X					X	X	X		X							X	X	15

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: HIGH DOSE

ANIMAL NUMBER	26202	28220	26060	29898	29999	27777	27979	28787	28811	29911	25454	25353	27878	25551	27711	25112	25252	25656	25757	25858	25959	26161	26363	26464	26565
WEEKS ON STUDY	06303	07303	07707	07707	07707	08282	08707	08707	08808	08909	09505	09908	09909	10101	10303	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic					X																				
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic					X																				
Thymus	+	+	−	−	+	+	+	+	−	−	+	+	−	+	+	+	+	+	−	+	−	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																							X		
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																X	X				X	X			X
Hepatocellular carcinoma																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																						X			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS						X		X	X		X	X			X			X		X		X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma									X																
C cell adenoma														X				X	X				X		
C cell carcinoma																				X					
Parathyroid	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X	X								
Adenocarcinoma, NOS	X											X										X			
Fibroadenoma																									X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS													X												
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp									X									X	X				X		
Endometrial stromal sarcoma																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig lymphoma, undiffer type							X			X															
Leukemia, mononuclear cell		X	X	X							X	X		X			X	X		X	X			

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	266	267	268	269	270	272	273	274	275	276	280	283	284	285	286	288	289	290	292	293	294	295	296	297	300	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Thymus	+	+	−	+	+	−	+	+	−	+	−	−	−	−	+	−	+	+	+	+	+	+	+	−	+	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma									X																	1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule		X						X								X					X		X	X		11
Hepatocellular carcinoma	X				X														X	X						5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																	X									1
Adenoma, NOS			X	X	X			X		X	X			X		X			X	X	X	X		X	X	23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																		X			X					2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																	X									2
C cell adenoma				X				X					X	X			X			X	X	X		X		13
C cell carcinoma						X																				2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																		X								3
Adenocarcinoma, NOS										X																4
Fibroadenoma							X			X										X						4
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS	X					X			X		X													X		6
Adenoma, NOS		X																								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp	X		X				X		X									X							X	10
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																	X									1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig lymphoma, undiffer type																										2
Leukemia, mononuclear cell	X			X			X										X			X				X		16

*Animals Necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS	1 (2%)		
Squamous cell papilloma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		2 (4%)	
Fibroma	2 (4%)	1 (2%)	1 (2%)
Fibrosarcoma	6 (12%)	7 (14%)	7 (14%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Hepatocellular carcinoma, metastatic	2 (4%)	4 (8%)	7 (14%)
Alveolar/bronchiolar adenoma	11 (22%)	2 (4%)	7 (14%)
Alveolar/bronchiolar carcinoma	5 (10%)	2 (4%)	3 (6%)
Sarcoma, NOS, metastatic		1 (2%)	
Fibrosarcoma, metastatic	1 (2%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, histiocytic type	1 (2%)	2 (4%)	2 (4%)
Malignant lymphoma, mixed type	3 (6%)		1 (2%)
#Spleen	(50)	(49)	(50)
Malignant lymphoma, histiocytic type			1 (2%)
#Lumbar lymph node	(49)	(47)	(50)
Fibrosarcoma, metastatic	1 (2%)		
#Liver	(50)	(49)	(50)
Malignant lymphoma, histiocytic type		1 (2%)	
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Spleen	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)	
#Mesenteric lymph node	(49)	(47)	(50)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Hepatocellular adenoma	5 (10%)	9 (18%)	10 (20%)
Hepatocellular carcinoma	9 (18%)	17 (35%)	20 (40%)
#Glandular stomach	(50)	(48)	(49)
Carcinoma in situ, NOS			1 (2%)
#Forestomach	(50)	(48)	(49)
Squamous cell papilloma	1 (2%)		
#Duodenum	(50)	(47)	(50)
Adenomatous polyp, NOS			1 (2%)
#Jejunum	(50)	(47)	(50)
Adenomatous polyp, NOS	1 (2%)		
*Rectum	(50)	(50)	(50)
Mucinous cystadenocarcinoma			2 (4%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
*Anus	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Adenocarcinoma in adenomatous polyp	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Tubular cell adenocarcinoma	1 (2%)		
Fibrosarcoma, metastatic		1 (2%)	
#Urinary bladder	(49)	(48)	(50)
Transitional cell carcinoma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(47)	(48)
Adenoma, NOS	1 (2%)		
#Adrenal	(49)	(47)	(49)
Hepatocellular carcinoma, metastatic			1 (2%)
Cortical adenoma	2 (4%)		
#Adrenal/capsule	(49)	(47)	(49)
Adenoma, NOS			1 (2%)
#Thyroid	(50)	(47)	(50)
Follicular cell adenoma			3 (6%)
REPRODUCTIVE SYSTEM			
#Testis	(49)	(48)	(49)
Interstitial cell tumor			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Papillary adenoma	3 (6%)		
Papillary cystadenoma, NOS	2 (4%)	2 (4%)	
MUSCULOSKELETAL SYSTEM			
*Muscle of neck	(50)	(50)	(50)
Fibrosarcoma, invasive		1 (2%)	
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrosarcoma, metastatic	2 (4%)	1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	14	11
Moribund sacrifice	5	8	10
Terminal sacrifice	36	26	29
Accidentally killed, NOS		2	
TUMOR SUMMARY			
Total animals with primary tumors**	35	31	39
Total primary tumors	59	47	62
Total animals with benign tumors	21	11	22
Total benign tumors	31	14	24
Total animals with malignant tumors	23	27	27
Total malignant tumors	28	33	38
Total animals with secondary tumors##	5	8	8
Total secondary tumors	6	10	8

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
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 CHLORENDIC ACID

	Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma		4 (8%)	4 (8%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	2 (4%)
Osteosarcoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undiffer type	2 (4%)		1 (2%)
Malignant lymphoma, lymphocytic type	4 (8%)	1 (2%)	2 (4%)
Malignant lymphoma, histiocytic type	2 (4%)	2 (4%)	4 (8%)
Malignant lymphoma, mixed type	6 (12%)	12 (24%)	5 (10%)
#Spleen	(50)	(48)	(50)
Malignant lymphoma, undiffer type	1 (2%)		
Malignant lymphoma, histiocytic type	1 (2%)		
Malignant lymphoma, mixed type			1 (2%)
#Cervical lymph node	(50)	(50)	(49)
Carcinoma, NOS, metastatic			1 (2%)
CIRCULATORY SYSTEM			
*Skin	(50)	(50)	(50)
Hemangiosarcoma, invasive			1 (2%)
#Spleen	(50)	(48)	(50)
Hemangiosarcoma		1 (2%)	2 (4%)
#Liver	(50)	(49)	(50)
Hemangiosarcoma, metastatic			1 (2%)
*Mesentery	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Uterus	(50)	(48)	(50)
Hemangiosarcoma, invasive			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Hepatocellular adenoma	2 (4%)	2 (4%)	3 (6%)
Hepatocellular carcinoma	1 (2%)	5 (10%)	4 (8%)
#Forestomach	(50)	(48)	(50)
Squamous cell papilloma	3 (6%)		
#Cecum	(50)	(49)	(49)
Leiomyoma		1 (2%)	
URINARY SYSTEM			
None			

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary	(48)	(47)	(50)
Carcinoma, NOS	1 (2%)		
#Anterior pituitary	(48)	(47)	(50)
Adenoma, NOS	12 (25%)	4 (9%)	3 (6%)
#Adrenal/capsule	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	1 (2%)		
#Pancreatic islets	(50)	(49)	(50)
Islet cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS		1 (2%)	1 (2%)
Papillary cystadenoma, NOS		1 (2%)	
#Uterus	(50)	(48)	(50)
Leiomyosarcoma	1 (2%)		
Endometrial stromal polyp	2 (4%)	1 (2%)	3 (6%)
#Ovary	(49)	(47)	(48)
Cystadenoma, NOS		1 (2%)	
Papillary cystadenoma, NOS	1 (2%)		
Teratoma, NOS			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS, invasive			1 (2%)
Papillary adenoma	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Fibrosarcoma		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrosarcoma, invasive		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	8	9	12
Moribund sacrifice	3	1	4
Terminal sacrifice	39	39	34
Accidentally killed, NOS		1	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	29	32	31
Total primary tumors	44	41	39
Total animals with benign tumors	20	14	14
Total benign tumors	24	15	14
Total animals with malignant tumors	19	23	22
Total malignant tumors	20	26	24
Total animals with secondary tumors##		2	4
Total secondary tumors		2	6
Total animals with tumors uncertain--benign or malignant			1
Total uncertain tumors			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
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 CHLORENDIC ACID: UNTREATED CONTROL

ANIMAL NUMBER	021	027	026	030	039	024	022	033	012	010	014	017	013	001	002	003	004	005	006	007	008	009	011	015	016
WEEKS ON STUDY	021	025	031	036	052	069	070	071	083	096	097	098	103	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma															X										
Fibrosarcoma						X			X									X							
Hemangiosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic							X																		
Alveolar/bronchiolar adenoma														X										X	
Alveolar/bronchiolar carcinoma																					X				
Fibrosarcoma, metastatic									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic									X																
Hemangiosarcoma													X												
Thymus	+	–	+	+	–	–	–	–	–	–	–	–	+	–	+	–	–	–	+	–	–	+	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X				
Hepatocellular carcinoma							X	X					X					X		X	X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Adenocarcinoma in adenomatous polyp											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									X
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Adenoma, NOS																	X								
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	–	+	+	–	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
Papillary cystadenoma, NOS																				X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic						X												X							
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																									

+	Tissue Examined Microscopically		No Tissue Information Submitted
–	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Missexed	B	No Necropsy Performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	018	019	020	023	025	028	029	031	032	034	035	036	037	038	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS											X															1
Squamous cell papilloma																									X	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																								X		2
Fibrosarcoma													X			X				X						6
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																	X									2
Alveolar/bronchiolar adenoma		X					X		X			X			X	X					X		X		X	11
Alveolar/bronchiolar carcinoma										X	X							X							X	5
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
Hemangiosarcoma																										1
Thymus	−	−	+	+	+	+	−	+	+	+	−	−	+	−	+	+	+	+	+	−	−	−	−	+	+	23
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X				X				X					X						5
Hepatocellular carcinoma			X														X	X								9
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS				X																						1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rectum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	*50
Squamous cell papilloma																									X	1
Adenoca in adenomatous polyp																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma							X									X										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	43
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma													X					X						X		3
Papillary cystadenoma, NOS				X																						2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, metastatic																										2
Malig lymphoma, histiocytic type														X												1
Malignant lymphoma, mixed type					X										X		X									3

* Animals Necropsied

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

ANIMAL NUMBER	110	118	122	125	124	137	144	140	127	142	135	138	147	107	104	129	116	150	139	114	148	119	108	101	102
WEEKS ON STUDY	020	023	030	030	034	050	050	057	065	075	077	080	081	084	085	085	087	089	094	095	099	103	104	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																					X				
Fibroma																									
Fibrosarcoma									X		X	X									X	X	X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X		X									
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar carcinoma																									
Sarcoma, NOS, metastatic																									
Fibrosarcoma, metastatic											X												X		
Trachea	+	A	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Lymph nodes	+	A	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	–	+	–	–	–	–	–	+	–	+	+	+	–	+	+	–	–	–	+	–	+	+
CIRCULATORY SYSTEM																									
Heart	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	A	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X																						
Hepatocellular carcinoma										X			X	X		X		X	X	X		X	X		X
Malig. lymphoma, histiocytic type														X											
Bile duct	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	N	+
Pancreas	+	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	A	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic																						X			
Urinary bladder	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	A	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	A	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	A	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	A	–	–	+	–	+	+	–	+	+	–	–	–	–	+	+	+	–	+	+	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary cystadenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, invasive																						X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic																						X			
Malig. lymphoma, lymphocytic type													X												
Malig. lymphoma, histiocytic type																									

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

ANIMAL NUMBER	103	105	106	109	111	112	113	115	117	120	121	123	126	128	130	131	132	133	134	136	141	143	145	146	149	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																							X	X		2
Fibroma																										1
Fibrosarcoma											X															7
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic		X								X																4
Alveolar/bronchiolar adenoma							X																			2
Alveolar/bronchiolar carcinoma	X																								X	2
Sarcoma, NOS, metastatic																								X		1
Fibrosarcoma, metastatic																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	−	+	−	+	+	+	−	+	+	+	+	+	−	−	+	−	−	−	+	+	−	+	−	+	+	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma			X		X		X			X						X					X		X		X	9
Hepatocellular carcinoma		X	X					X	X	X			X										X			17
Malig. lymphoma, histiocytic type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	−	−	+	+	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	X	N	N	*50
Papillary cystadenoma, NOS																										2
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, metastatic																										1
Malig. lymphoma, lymphocytic type																										1
Malig. lymphoma, histiocytic type	X															X										2

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: HIGH DOSE

ANIMAL NUMBER	23 37	23 36	23 39	23 34	20 06	21 19	20 08	23 33	22 27	22 20	20 09	20 07	21 16	21 10	23 22	21 12	22 29	22 22	24 45	24 48	23 38	20 01	20 02	20 03	20 04
WEEKS ON STUDY	01 16	03 00	03 32	03 33	04 41	04 47	06 00	06 67	06 69	07 74	07 76	08 33	08 33	08 44	08 85	08 87	09 00	09 07	09 99	09 99	10 22	10 44	10 44	10 44	10 44
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X						
Fibrosarcoma						X							X				X	X		X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X						X					
Alveolar/bronchiolar adenoma					X									X				X					X		
Alveolar/bronchiolar carcinoma																	X	X							
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig lymphoma, histiocytic type																					X				
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	+	+	−	+	+	−	−	+	−	−	−	+	+	−	+	−	−	−	−	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X			X	X
Hepatocellular carcinoma							X		X			X		X	X	X	X			X	X			X	X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma in situ, NOS																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																			X						
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	N	N	N	N	N	N	N	+	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mucinous cystadenocarcinoma								X			X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma								X																	
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Hepatocellular carcinoma, metastatic															X										
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma								X																	
Parathyroid	−	+	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																							X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig lymphoma, histiocytic type																			X						
Malignant lymphoma, mixed type												X													

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

ANIMAL NUMBER	20 05	21 11	21 13	21 14	21 15	21 17	21 18	22 21	22 23	22 24	22 25	22 26	22 28	23 30	23 31	23 35	24 40	24 41	24 42	24 43	24 44	24 46	24 47	24 49	25 50	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma	X						X																			7
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic	X					X												X		X					X	7
Alveolar/bronchiolar adenoma											X					X				X						7
Alveolar/bronchiolar carcinoma															X											3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig lymphoma, histiocytic type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	–	+	+	+	–	–	–	+	–	+	+	+	+	–	+	+	–	–	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X		X				X	X			X	X											X		10
Hepatocellular carcinoma	X		X			X	X											X	X	X					X	20
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma in situ, NOS																				X						1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Rectum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mucinous cystadenocarcinoma																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS															X											1
Hepatocellular carcinoma, metastatic																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma					X														X							3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig lymphoma, histiocytic type																								X		2
Malignant lymphoma, mixed type																										1

*Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: UNTREATED CONTROL

ANIMAL NUMBER	06663	08834	08417	09763	06386	08967	09090	09095	09711	08899	05101	05202	05303	05404	05505	05606	05707	05808	05909	06000	06161	06262	06464	06565
WEEKS ON STUDY	04404	07505	07606	08800	08804	08909	09001	09303	09806	09909	10205	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, undiffer type																								
Malig. lymphoma, histiocytic type																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	−	−	+	−	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X					
Hepatocellular carcinoma																								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X		X										
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	−	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS							X																	
Adenoma, NOS												X				X				X	X	X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								
Pheochromocytoma																								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	+	+	−	+	+	−	−	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																								
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																								
Endometrial stromal polyp																				X				
Ovary	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS											X													
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																								
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, undiffer type																								
Malig. lymphoma, lymphocytic type			X		X													X						
Malig. lymphoma, histiocytic type																			X					
Malignant lymphoma, mixed type											X	X		X										

\+ : Tissue Examined Microscopically
− : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	0068	0069	0070	0072	0073	0074	0075	0076	0077	0078	0079	0080	0081	0082	0085	0087	0088	0091	0092	0093	0094	0096	0098	0099	0100	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig. lymphoma, undiffer type																				X						1
Malig. lymphoma, histiocytic type																									X	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	−	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									2
Hepatocellular carcinoma													X													1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma						X																				3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																										1
Adenoma, NOS		X		X						X						X	X								X	12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																								X		1
Pheochromocytoma																				X						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma														X												1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma													X													1
Endometrial stromal polyp														X												2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma				X																						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, undiffer type																X					X					2
Malig. lymphoma, lymphocytic type																			X							4
Malig. lymphoma, histiocytic type										X																2
Malignant lymphoma, mixed type	X			X							X															6

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: LOW DOSE

ANIMAL NUMBER	17 11	16 11	18 13	17 18	19 16	19 12	19 15	19 19	19 11	16 14	15 18	15 11	15 12	15 13	15 14	15 15	15 16	15 17	15 19	16 10	16 12	16 13	16 15	16 16	16 17
WEEKS ON STUDY	01 05	02 09	03 00	08 09	07 05	07 07	07 07	08 04	08 08	09 07	10 03	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic						X																			
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	+	–	+	–	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma										X															
Bile duct	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																			X						
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS						X										X									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	–	–	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS						X																			
Papillary cystadenoma, NOS																									
Uterus	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp										X															
Ovary	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, invasive					X																				
Malig. lymphoma, lymphocytic type											X														
Malig. lymphoma, histiocytic type				X					X																
Malignant lymphoma, mixed type												X		X									X	X	X

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

ANIMAL NUMBER	168	169	170	172	173	174	175	176	177	179	180	181	182	184	185	186	187	188	189	190	193	194	197	198	200	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma	X											X			X											4
Alveolar/bronchiolar carcinoma															X										X	2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	−	+	+	−	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma							X		X																	2
Hepatocellular carcinoma		X									X		X							X						5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS	X							X																		4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	−	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	−	+	36
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																									X	1
Adenocarcinoma, NOS																										1
Papillary cystadenoma, NOS														X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endometrial stromal polyp																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, invasive																										1
Malig. lymphoma, lymphocytic type																										1
Malig. lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type			X			X							X			X			X	X					X	12

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID: HIGH DOSE

ANIMAL NUMBER	27901	28101	29601	28301	29501	25801	26301	28801	29801	28201	27801	28001	25601	25301	25201	25101	25401	25501	25701	25901	26001	26101	26201	26401	26501
WEEKS ON STUDY	00404	00633	00644	00744	00882	00883	00885	00885	00885	00887	00900	00900	00905	01002	01003	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS						X																			
Hemangiosarcoma, invasive																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																		X			
Alveolar/bronchiolar carcinoma																			X						
Osteosarcoma, metastatic					X																				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Malignant lymphoma, mixed type																	X								
Lymph nodes	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic						X																			
Thymus	+	+	+	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	+	−	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma										X	X							X							
Hemangiosarcoma, metastatic												X													
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	+	−	−	−	+	+	−	+	+	+	+	−	−	+	−	+	−	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp		X						X	X																
Hemangiosarcoma, invasive																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Teratoma, NOS								X																	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, invasive						X																			
Papillary adenoma																									
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, undiffer type														X											
Malig. lymphoma, lymphocytic type																								X	
Malig. lymphoma, histiocytic type				X			X						X												
Malignant lymphoma, mixed type											X					X									

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

ANIMAL NUMBER	266	267	268	269	270	271	272	273	274	275	276	277	284	285	286	287	289	290	291	297	292	293	294	299	300	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Carcinoma, NOS																										1
Hemangiosarcoma, invasive			X																							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X														X					4
Alveolar/bronchiolar carcinoma				X																						2
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													2
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic																										1
Thymus	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X		X									X													3
Hepatocellular carcinoma										X																4
Hemangiosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS								X	X																	3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																										3
Hemangiosarcoma, invasive			X																							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
Teratoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, invasive																										1
Papillary adenoma																	X									1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma			X																							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, undiffer type																										1
Malig. lymphoma, lymphocytic type											X															2
Malig. lymphoma, histiocytic type																	X									4
Malignant lymphoma, mixed type	X																					X	X			5

* Animals Necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, suppurative	2 (4%)		
Necrosis, focal	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhagic cyst		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
RESPIRATORY SYSTEM			
#Trachea	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
#Bronchial mucosa	(50)	(50)	(50)
Hyperplasia, focal		1 (2%)	
#Lung	(50)	(50)	(50)
Congestion, NOS		2 (4%)	1 (2%)
Edema, NOS		1 (2%)	1 (2%)
Hemorrhage		3 (6%)	1 (2%)
Pneumonia, aspiration	1 (2%)		
Inflammation, suppurative	1 (2%)		
Inflammation, chronic	3 (6%)	5 (10%)	6 (12%)
Inflammation, chronic focal		5 (10%)	4 (8%)
Inflammation, granulomatous focal	3 (6%)	1 (2%)	1 (2%)
Alveolar macrophages	1 (2%)		1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)	5 (10%)	2 (4%)
#Bone marrow	(49)	(50)	(50)
Atrophy, NOS	1 (2%)		
Myelofibrosis	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, hematopoietic		1 (2%)	3 (6%)
#Spleen	(50)	(50)	(49)
Congestion, NOS	2 (4%)		
Fibrosis			1 (2%)
Fibrosis, focal		1 (2%)	
Infarct, acute		1 (2%)	
Infarct, healed		1 (2%)	
Hemosiderosis		2 (4%)	2 (4%)
Atrophy, NOS		1 (2%)	
Hyperplasia, reticulum cell	1 (2%)		
Hematopoiesis	1 (2%)	1 (2%)	1 (2%)
#Splenic capsule	(50)	(50)	(49)
Fibrosis, focal		1 (2%)	
#Splenic follicles	(50)	(50)	(49)
Necrosis, NOS	1 (2%)		1 (2%)
#Mandibular lymph node	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, suppurative	2 (4%)		
Abscess, NOS	1 (2%)		
Necrosis, NOS	2 (4%)		
Pigmentation, NOS		1 (2%)	
Erythrophagocytosis		2 (4%)	
Hyperplasia, plasma cell	12 (24%)	16 (32%)	8 (16%)
Hyperplasia, lymphoid	2 (4%)	5 (10%)	6 (12%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mediastinal lymph node	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Hemorrhage	1 (2%)	4 (8%)	3 (6%)
Pigmentation, NOS	7 (14%)	4 (8%)	7 (14%)
Erythrophagocytosis	4 (8%)	5 (10%)	6 (12%)
Hyperplasia, plasma cell	1 (2%)		1 (2%)
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Hepatic lymph node	(50)	(50)	(50)
Hemorrhage			1 (2%)
#Pancreatic lymph node	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Necrosis, NOS	1 (2%)		
Pigmentation, NOS	3 (6%)	5 (10%)	
Hyperplasia, reticulum cell		1 (2%)	
Hyperplasia, lymphoid		2 (4%)	
#Mesenteric lymph node	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Necrosis, NOS	2 (4%)		
Pigmentation, NOS	16 (32%)	4 (8%)	2 (4%)
Hyperplasia, plasma cell		1 (2%)	
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, lymphoid		3 (6%)	4 (8%)
#Renal lymph node	(50)	(50)	(50)
Hemorrhage			1 (2%)
Necrosis, NOS	1 (2%)		
Pigmentation, NOS	3 (6%)	1 (2%)	1 (2%)
Hemosiderosis			1 (2%)
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid		1 (2%)	
#Brachial lymph node	(50)	(50)	(50)
Hemorrhage	1 (2%)		
#Lung	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)		2 (4%)
Hyperplasia, lymphoid	26 (52%)	28 (56%)	18 (36%)
#Hepatic sinusoid	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)		
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	8 (16%)	19 (38%)	15 (30%)
#Thymus	(41)	(39)	(36)
Abscess, NOS			1 (3%)
#Thymic lymphocytes	(41)	(39)	(36)
Necrosis, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#Mandibular lymph node	(50)	(50)	(50)
Lymphangiectasis	10 (20%)	16 (32%)	10 (20%)
#Mediastinal lymph node	(50)	(50)	(50)
Lymphangiectasis		3 (6%)	
#Mesenteric lymph node	(50)	(50)	(50)
Lymphangiectasis	2 (4%)	2 (4%)	6 (12%)
#Renal lymph node	(50)	(50)	(50)
Lymphangiectasis			1 (2%)
#Lung	(50)	(50)	(50)
Thrombus, organized	1 (2%)		
#Heart	(50)	(50)	(50)
Myxomatosis, cardiac valve	8 (16%)	13 (26%)	8 (16%)
Inflammation, chronic		2 (4%)	1 (2%)
Fibrosis	2 (4%)	2 (4%)	2 (4%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Heart/atrium	(50)	(50)	(50)
Thrombus, organized	1 (2%)	3 (6%)	4 (8%)
Thrombus, canalized	1 (2%)		
Thrombus, fibrin	3 (6%)	3 (6%)	1 (2%)
Fibrosis		1 (2%)	
#Right atrium	(50)	(50)	(50)
Thrombus, fibrin		1 (2%)	
#Left ventricle	(50)	(50)	(50)
Thrombus, fibrin			1 (2%)
#Myocardium	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Fibrosis	32 (64%)	42 (84%)	30 (60%)
*Hepatic artery	(50)	(50)	(50)
Thrombus, fibrin			1 (2%)
Inflammation, chronic			1 (2%)
*Sup. panc-duod. artery	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		
*Mesenteric artery	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Liver	(50)	(50)	(50)
Thrombus, organized	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Thrombus, organized	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hernia, NOS	1 (2%)		1 (2%)
Congestion, NOS			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, NOS		1 (2%)	
Inflammation, suppurative		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Inflammation, granulomatous			1 (2%)
Inflammation, granulomatous focal	1 (2%)	1 (2%)	
Fibrosis, focal			1 (2%)
Cholangiofibrosis	12 (24%)	18 (36%)	15 (30%)
Hepatitis, toxic	12 (24%)	9 (18%)	15 (30%)
Degeneration, cystic	13 (26%)	32 (64%)	31 (62%)
Necrosis, focal	1 (2%)		
Necrosis, coagulative	3 (6%)	4 (8%)	1 (2%)
Infarct, NOS			1 (2%)
Metamorphosis, fatty	1 (2%)	1 (2%)	2 (4%)
Pigmentation, NOS	1 (2%)	1 (2%)	1 (2%)
Focal cellular change	15 (30%)	32 (64%)	20 (40%)
Atrophy, NOS	1 (2%)		
Hyperplasia, NOS	2 (4%)		2 (4%)
Hyperplasia, focal		4 (8%)	1 (2%)
Angiectasis	4 (8%)	3 (6%)	4 (8%)
#Liver/centrilobular	(50)	(50)	(50)
Metamorphosis, fatty	1 (2%)		
#Liver/periportal	(50)	(50)	(50)
Inflammation, chronic	4 (8%)		
#Bile duct	(50)	(50)	(50)
Cyst, NOS		1 (2%)	1 (2%)
Hyperplasia, NOS	31 (62%)	42 (84%)	41 (82%)
#Pancreas	(49)	(50)	(50)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(49)	(50)	(50)
Atrophy, NOS	8 (16%)	7 (14%)	1 (2%)
Atrophy, focal		2 (4%)	2 (4%)
Hyperplasia, focal		4 (8%)	4 (8%)
#Esophagus	(50)	(50)	(49)
Hyperkeratosis		1 (2%)	1 (2%)
#Gastric mucosa	(50)	(50)	(50)
Ulcer, perforated			1 (2%)
Acanthosis		1 (2%)	
#Glandular stomach	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Ulcer, acute	2 (4%)		1 (2%)
Ulcer, chronic	1 (2%)	1 (2%)	
Necrosis, NOS		1 (2%)	
Necrosis, focal	5 (10%)	4 (8%)	1 (2%)
#Gastric submucosa	(50)	(50)	(50)
Edema, NOS	2 (4%)	2 (4%)	1 (2%)
Hemorrhage		2 (4%)	
Inflammation, suppurative		1 (2%)	
Fibrosis	1 (2%)		
#Forestomach	(50)	(50)	(50)
Hemorrhage			1 (2%)
Ulcer, NOS		3 (6%)	1 (2%)
Inflammation, suppurative		2 (4%)	2 (4%)
Ulcer, acute	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Ulcer, chronic	2 (4%)	1 (2%)	
Ulcer, perforated		1 (2%)	
Hyperkeratosis			1 (2%)
Acanthosis	3 (6%)	2 (4%)	1 (2%)
#Colon	(49)	(50)	(50)
Parasitism		3 (6%)	3 (6%)
#Cecum	(49)	(50)	(50)
Edema, NOS	1 (2%)		
Hemorrhage			4 (8%)
Inflammation, suppurative	1 (2%)		
Amyloid, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cast, NOS	3 (6%)		1 (2%)
Cyst, NOS	3 (6%)	1 (2%)	3 (6%)
Congestion, NOS	2 (4%)		2 (4%)
Inflammation, chronic	6 (12%)		6 (12%)
Nephropathy	35 (70%)	40 (80%)	32 (64%)
Nephrosis, NOS	1 (2%)	1 (2%)	
Infarct, acute		1 (2%)	
Pigmentation, NOS	1 (2%)		2 (4%)
#Kidney/tubule	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Cast, NOS	5 (10%)	3 (6%)	4 (8%)
Degeneration, hyaline	1 (2%)		
Pigmentation, NOS	11 (22%)	6 (12%)	10 (20%)
Regeneration, NOS		1 (2%)	
#Urinary bladder	(49)	(50)	(50)
Hemorrhage			1 (2%)
Hyperplasia, epithelial		1 (2%)	1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary	(50)	(50)	(50)
Cyst, NOS	2 (4%)		
Hypertrophy, focal	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)		
Angiectasis		2 (4%)	1 (2%)
#Pituitary intermedia	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
#Anterior pituitary	(50)	(50)	(50)
Cyst, NOS	3 (6%)	2 (4%)	1 (2%)
Fibrosis, focal			1 (2%)
Pigmentation, NOS			1 (2%)
Hypertrophy, focal		3 (6%)	1 (2%)
Hyperplasia, focal	2 (4%)		4 (8%)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
#Adrenal	(50)	(50)	(50)
Congestion, NOS	1 (2%)		
#Adrenal/capsule	(50)	(50)	(50)
Fibrosis, focal		1 (2%)	
#Adrenal cortex	(50)	(50)	(50)
Degeneration, cystic		1 (2%)	
Necrosis, NOS	1 (2%)		
Metamorphosis, fatty	3 (6%)	2 (4%)	2 (4%)
Hypertrophy, focal	1 (2%)	1 (2%)	
Hyperplasia, focal	4 (8%)	1 (2%)	1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Mineralization	1 (2%)		
Hyperplasia, focal	2 (4%)		6 (12%)
#Thyroid	(50)	(50)	(50)
Cystic follicles			1 (2%)
Follicular cyst, NOS		1 (2%)	1 (2%)
Hyperplasia, C-cell	8 (16%)	4 (8%)	5 (10%)
#Parathyroid	(48)	(49)	(48)
Hyperplasia, NOS	19 (40%)	26 (53%)	15 (31%)
Hyperplasia, focal		1 (2%)	
#Pancreatic islets	(49)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, focal			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	1 (2%)	4 (8%)	2 (4%)
Inflammation, suppurative		1 (2%)	
Inflammation, granulomatous focal			1 (2%)
Fibrosis, focal		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	1 (2%)
Cystic ducts		1 (2%)	
Inflammation, chronic			1 (2%)
Inflammation, granulomatous		1 (2%)	
Fibrosis			1 (2%)
#Prostate	(49)	(50)	(50)
Cyst, NOS	2 (4%)		
Edema, NOS		1 (2%)	
Inflammation, suppurative	16 (33%)	8 (16%)	9 (18%)
Abscess, NOS			1 (2%)
Inflammation, acute/chronic	15 (31%)	5 (10%)	10 (20%)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, epithelial	1 (2%)		1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Seminal vesicle	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Inflammation, suppurative	1 (2%)		1 (2%)
Abscess, NOS		1 (2%)	
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Hyperplasia, epithelial	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Testis	(49)	(50)	(50)
Degeneration, NOS		1 (2%)	2 (4%)
Aspermatogenesis	2 (4%)	2 (4%)	1 (2%)
Hypospermatogenesis			1 (2%)
Hyperplasia, interstitial cell	4 (8%)	10 (20%)	8 (16%)
#Testis/tubule	(49)	(50)	(50)
Granuloma, spermatic			1 (2%)
Degeneration, NOS	33 (67%)	21 (42%)	14 (28%)
Aspermatogenesis	17 (35%)	12 (24%)	7 (14%)
*Epididymis	(50)	(50)	(50)
Edema, interstitial	2 (4%)	2 (4%)	4 (8%)
Steatitis	1 (2%)		
Inflammation, chronic			1 (2%)
Granuloma, spermatic	1 (2%)	1 (2%)	1 (2%)
Fibrosis	2 (4%)		1 (2%)
Fibrosis, diffuse	3 (6%)	1 (2%)	
Necrosis, fat	3 (6%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Cerebral ventricle	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
#Cerebrum	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Necrosis, focal		1 (2%)	
Psammoma bodies			2 (4%)
#Brain	(50)	(50)	(50)
Hemorrhage	2 (4%)	1 (2%)	
Gliosis	1 (2%)		
#Cerebellum	(50)	(50)	(50)
Necrosis, focal		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Cataract	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	2 (4%)	2 (4%)	5 (10%)
*Eye/crystalline lens	(50)	(50)	(50)
Synechia, anterior		1 (2%)	
Cataract	3 (6%)	5 (10%)	5 (10%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Steatitis		1 (2%)	
*Epicardium	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
*Mesentery	(50)	(50)	(50)
Necrosis, fat		2 (4%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
Hemorrhage		1 (2%)	
Inflammation, suppurative			1 (2%)
Inflammation, chronic	1 (2%)		
Diaphragm			
Inflammation, pyogranulomatous			1
Degeneration, NOS			1
Adipose tissue			
Fibrosis	2		
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	2 (4%)		
Hyperplasia, epithelial	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Edema, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#Lung/bronchiole	(50)	(49)	(50)
Inflammation, suppurative		1 (2%)	
#Lung	(50)	(49)	(50)
Atelectasis	1 (2%)		
Congestion, NOS	1 (2%)	3 (6%)	1 (2%)
Edema, NOS			3 (6%)
Hemorrhage	1 (2%)		2 (4%)
Pneumonia, aspiration	1 (2%)		
Inflammation, suppurative		1 (2%)	
Pneumonia, chronic murine	1 (2%)		
Inflammation, chronic	2 (4%)	1 (2%)	5 (10%)
Inflammation, chronic focal	1 (2%)	1 (2%)	2 (4%)
Alveolar macrophages	3 (6%)		2 (4%)
Hyperplasia, alveolar epithelium		3 (6%)	1 (2%)
#Lung/alveoli	(50)	(49)	(50)
Inflammation, suppurative		1 (2%)	
Pigmentation, NOS		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Bone marrow	(50)	(50)	(50)
Myelofibrosis	1 (2%)	1 (2%)	
Hyperplasia, hematopoietic			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Spleen	(50)	(49)	(50)
Inflammation, chronic		1 (2%)	
Fibrosis, focal		1 (2%)	
Necrosis, focal		1 (2%)	
Infarct, acute			1 (2%)
Hemosiderosis		1 (2%)	
Hyperplasia, hematopoietic		1 (2%)	
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid	2 (4%)		
Hematopoiesis	2 (4%)	1 (2%)	2 (4%)
#Splenic capsule	(50)	(49)	(50)
Fibrosis		1 (2%)	
#Lymph node	(50)	(50)	(50)
Pigmentation, NOS	1 (2%)		
#Mandibular lymph node	(50)	(50)	(50)
Congestion, NOS	1 (2%)		
Edema, peripheral			1 (2%)
Hemorrhage	1 (2%)	1 (2%)	
Necrosis, NOS		1 (2%)	
Pigmentation, NOS	1 (2%)	5 (10%)	4 (8%)
Erythrophagocytosis	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, plasma cell	6 (12%)	4 (8%)	8 (16%)
Hyperplasia, reticulum cell	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
#Mandibular lymph node (Continued)	(50)	(50)	(50)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	5 (10%)
#Mediastinal lymph node	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Fibrosis	1 (2%)		
Necrosis, NOS		1 (2%)	
Pigmentation, NOS	3 (6%)	9 (18%)	11 (22%)
Atrophy, NOS	1 (2%)		
Erythrophagocytosis	1 (2%)	5 (10%)	2 (4%)
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Pancreatic lymph node	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, granulomatous		1 (2%)	1 (2%)
Pigmentation, NOS		2 (4%)	2 (4%)
Erythrophagocytosis	1 (2%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)		2 (4%)
Hematopoiesis			1 (2%)
#Mesenteric lymph node	(50)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)	1 (2%)
Inflammation, granulomatous			1 (2%)
Pigmentation, NOS	5 (10%)	1 (2%)	
Hyperplasia, plasma cell		1 (2%)	
Hyperplasia, lymphoid	2 (4%)	1 (2%)	4 (8%)
#Renal lymph node	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Pigmentation, NOS	1 (2%)		
#Lung	(50)	(49)	(50)
Leukocytosis, NOS	2 (4%)		
Hyperplasia, lymphoid	26 (52%)	26 (53%)	20 (40%)
#Lung/alveoli	(50)	(49)	(50)
Leukocytosis, NOS			1 (2%)
#Hepatic sinusoid	(50)	(49)	(50)
Leukocytosis, NOS	1 (2%)		1 (2%)
#Kidney	(50)	(49)	(50)
Hyperplasia, lymphoid	4 (8%)	1 (2%)	1 (2%)
#Thymus	(43)	(46)	(33)
Inflammation, chronic		1 (2%)	
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Lymphangiectasis		1 (2%)	
#Mandibular lymph node	(50)	(50)	(50)
Lymphangiectasis	6 (12%)	7 (14%)	17 (34%)
#Mediastinal lymph node	(50)	(50)	(50)
Lymphangiectasis	1 (2%)		
#Pancreatic lymph node	(50)	(50)	(50)
Lymphangiectasis		1 (2%)	2 (4%)
#Mesenteric lymph node	(50)	(50)	(50)
Lymphangiectasis	2 (4%)		1 (2%)
#Heart	(50)	(50)	(50)
Myxomatosis, cardiac valve	7 (14%)	1 (2%)	1 (2%)
Thrombus, fibrin			1 (2%)
Inflammation, chronic			1 (2%)
#Heart/atrium	(50)	(50)	(50)
Thrombus, organized		1 (2%)	
Thrombus, fibrin	1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)
#Myocardium	(50)	(50)	(50)
Fibrosis	29 (58%)	25 (50%)	12 (24%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
*Aortic arch	(50)	(50)	(50)
Inflammation, granulomatous	1 (2%)		
*Mesenteric artery	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Necrosis, fibrinoid	1 (2%)		
#Liver	(50)	(49)	(50)
Lymphangiectasis			1 (2%)
Thrombosis, NOS		1 (2%)	
Thrombus, organized		1 (2%)	1 (2%)
#Hepatic capsule	(50)	(49)	(50)
Thrombosis, NOS	1 (2%)		
#Uterus	(50)	(49)	(50)
Lymphangiectasis		1 (2%)	
DIGESTIVE SYSTEM			
*Lip	(50)	(50)	(50)
Hematoma, NOS	1 (2%)		
#Salivary gland	(49)	(50)	(50)
Edema, NOS			1 (2%)
Edema, interstitial			1 (2%)
#Liver	(50)	(49)	(50)
Hernia, NOS	3 (6%)	4 (8%)	4 (8%)
Congestion, NOS		3 (6%)	
Hemorrhage		4 (8%)	
Inflammation, NOS		1 (2%)	2 (4%)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic		2 (4%)	
Inflammation, chronic focal			1 (2%)
Inflammation, granulomatous	9 (18%)	20 (41%)	19 (38%)
Granuloma, NOS	1 (2%)		
Inflammation, granulomatous focal	1 (2%)	1 (2%)	1 (2%)
Cholangiofibrosis	2 (4%)	5 (10%)	3 (6%)
Hepatitis, toxic	9 (18%)	4 (8%)	9 (18%)
Degeneration, cystic	1 (2%)	1 (2%)	1 (2%)
Necrosis, coagulative	1 (2%)	3 (6%)	1 (2%)
Metamorphosis, fatty	3 (6%)	5 (10%)	
Pigmentation, NOS	1 (2%)	3 (6%)	8 (16%)
Focal cellular change	30 (60%)	23 (47%)	28 (56%)
Hyperplasia, NOS		1 (2%)	1 (2%)
Hyperplasia, focal		1 (2%)	
Angiectasis	3 (6%)		
#Liver/periportal	(50)	(49)	(50)
Inflammation, chronic	6 (12%)		2 (4%)
#Bile duct	(50)	(49)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Hyperplasia, NOS	3 (6%)	17 (35%)	40 (80%)
#Pancreas	(49)	(49)	(50)
Inflammation, chronic	1 (2%)		1 (2%)
Hyperplasia, nodular		1 (2%)	1 (2%)
#Pancreatic acinus	(49)	(49)	(50)
Atrophy, NOS	2 (4%)		
Atrophy, focal	3 (6%)		2 (4%)
Hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
#Pancreas/interstitial tissue	(49)	(49)	(50)
Inflammation, chronic	1 (2%)		
#Esophagus	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Hyperkeratosis	2 (4%)		
#Stomach	(50)	(49)	(50)
Hyperkeratosis		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Gastric mucosa	(50)	(49)	(50)
Ulcer, NOS	1 (2%)		
Necrosis, focal			1 (2%)
#Glandular stomach	(50)	(49)	(50)
Ulcer, acute	2 (4%)		
Ulcer, chronic	1 (2%)		1 (2%)
Necrosis, NOS			1 (2%)
Necrosis, focal	2 (4%)	2 (4%)	3 (6%)
#Gastric submucosa	(50)	(49)	(50)
Distention	2 (4%)		
Edema, NOS		1 (2%)	
Fibrosis		1 (2%)	
#Forestomach	(50)	(49)	(50)
Ulcer, NOS	1 (2%)		
Inflammation, suppurative	2 (4%)		
Ulcer, acute	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
Ulcer, chronic	3 (6%)	1 (2%)	1 (2%)
Hyperkeratosis	1 (2%)		
Acanthosis	1 (2%)	3 (6%)	1 (2%)
#Colon	(50)	(49)	(50)
Parasitism	2 (4%)	2 (4%)	1 (2%)
#Colonic submucosa	(50)	(49)	(50)
Edema, NOS			2 (4%)
#Cecum	(50)	(49)	(50)
Congestion, NOS	1 (2%)	1 (2%)	
Edema, NOS	2 (4%)	1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	
Necrosis, NOS	1 (2%)	1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Calculus, microscopic examination		12 (24%)	1 (2%)
Cyst, NOS		2 (4%)	
Congestion, NOS	1 (2%)	4 (8%)	
Inflammation, chronic	3 (6%)		
Nephropathy	24 (48%)	5 (10%)	1 (2%)
Hyperplasia, epithelial		1 (2%)	
#Kidney/tubule	(50)	(49)	(50)
Cast, NOS	3 (6%)		
Pigmentation, NOS	15 (30%)	6 (12%)	6 (12%)
ENDOCRINE SYSTEM			
#Pituitary	(50)	(50)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Pigmentation, NOS	1 (2%)		
Angiectasis	2 (4%)		1 (2%)
#Anterior pituitary	(50)	(50)	(50)
Cyst, NOS	4 (8%)	8 (16%)	5 (10%)
Hemorrhagic cyst	1 (2%)	2 (4%)	1 (2%)
Necrosis, NOS	1 (2%)		
Pigmentation, NOS	1 (2%)		
Hyperplasia, NOS		1 (2%)	
Hyperplasia, focal	3 (6%)	2 (4%)	1 (2%)
Angiectasis	2 (4%)	1 (2%)	1 (2%)
#Adrenal	(50)	(49)	(50)
Congestion, NOS	1 (2%)		1 (2%)
Degeneration, cystic			1 (2%)
Pigmentation, NOS		1 (2%)	
Cytoplasmic vacuolization	2 (4%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(49)	(50)
Metamorphosis, fatty	3 (6%)	3 (6%)	2 (4%)
Cytoplasmic vacuolization			1 (2%)
Hypertrophy, focal	2 (4%)		1 (2%)
Hyperplasia, focal	1 (2%)	1 (2%)	
Angiectasis	1 (2%)	1 (2%)	3 (6%)
#Adrenal medulla	(50)	(49)	(50)
Necrosis, NOS			1 (2%)
Pigmentation, NOS			1 (2%)
Hyperplasia, focal	1 (2%)	3 (6%)	
Angiectasis	1 (2%)	1 (2%)	
#Thyroid	(50)	(50)	(50)
Follicular cyst, NOS	1 (2%)		
Hyperplasia, C-cell	14 (28%)	9 (18%)	6 (12%)
#Parathyroid	(45)	(47)	(47)
Hyperplasia, NOS	15 (33%)	8 (17%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	2 (4%)		
Galactocele	21 (42%)	6 (12%)	5 (10%)
Inflammation, chronic	9 (18%)		
Hyperplasia, NOS			2 (4%)
*Clitoral gland	(50)	(50)	(50)
Dilatation/ducts	3 (6%)	2 (4%)	
Inflammation, suppurative	3 (6%)		
Abscess, NOS		1 (2%)	
Inflammation, granulomatous focal		1 (2%)	
#Uterus	(50)	(49)	(50)
Hydrometra		5 (10%)	5 (10%)
Cyst, NOS			1 (2%)
Inflammation, acute/chronic			1 (2%)
#Cervix uteri	(50)	(49)	(50)
Cyst, NOS	1 (2%)		
Epidermal inclusion cyst		1 (2%)	
Inflammation, suppurative	1 (2%)		
Amyloid, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)		
Hyperkeratosis	1 (2%)		
#Uterus/endometrium	(50)	(49)	(50)
Cyst, NOS	5 (10%)	8 (16%)	11 (22%)
Edema, NOS			1 (2%)
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal		1 (2%)	
Hyperplasia, cystic		1 (2%)	
#Uterus/myometrium	(50)	(49)	(50)
Edema, NOS			1 (2%)
#Ovary	(50)	(49)	(50)
Cyst, NOS		1 (2%)	
Parovarian cyst	2 (4%)	7 (14%)	5 (10%)
NERVOUS SYSTEM			
#Subdural space	(50)	(50)	(50)
Hemorrhage	1 (2%)		
#Cerebral ventricle	(50)	(50)	(50)
Dilatation, NOS		2 (4%)	
#Lateral ventricle	(50)	(50)	(50)
Dilatation, NOS			1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
NERVOUS SYSTEM (Continued)			
#Brain	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Gliosis	1 (2%)		
Pigmentation, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	3 (6%)	5 (10%)	2 (4%)
*Eye/crystalline lens	(50)	(50)	(50)
Synechia, anterior		1 (2%)	1 (2%)
Cataract	6 (12%)	5 (10%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Hyperostosis			2 (4%)
*Sternum	(50)	(50)	(50)
Hyperostosis	3 (6%)	3 (6%)	5 (10%)
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		
Necrosis, fat	2 (4%)	1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, suppurative	1 (2%)		
Pigmentation, NOS	1 (2%)		
Adipose tissue			
Hemorrhage	1		
Inflammation, acute/chronic		1	
Inflammation, chronic	4	2	1
Inflammation, chronic focal		1	
Fibrosis	1	4	
Necrosis, fat	4	6	1
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Mineralization	1 (2%)		
Cyst, NOS			1 (2%)
Inflammation, acute			1 (2%)
Inflammation, acute focal	1 (2%)	1 (2%)	
Abscess, NOS	2 (4%)		
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal			1 (2%)
Fibrosis	1 (2%)		
Fibrosis, focal	1 (2%)	1 (2%)	
Necrosis, NOS		1 (2%)	1 (2%)
Necrosis, focal	1 (2%)	1 (2%)	
Hypertrophy, NOS		1 (2%)	
Hyperplasia, focal		1 (2%)	
Hyperkeratosis	1 (2%)		1 (2%)
Acanthosis	3 (6%)		1 (2%)
Metaplasia, osseous		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, NOS	4 (8%)		
RESPIRATORY SYSTEM			
#Lung/bronchiole	(50)	(49)	(50)
Hyperplasia, focal			1 (2%)
#Lung	(50)	(49)	(50)
Congestion, NOS	1 (2%)	6 (12%)	2 (4%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	8 (16%)	4 (8%)	2 (4%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, alveolar epithelium	2 (4%)		4 (8%)
#Lung/alveoli	(50)	(49)	(50)
Histiocytosis	3 (6%)		
HEMATOPOIETIC SYSTEM			
#Brain	(50)	(49)	(50)
Leukocytosis, NOS			1 (2%)
*Multiple organs	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)	1 (2%)	
#Bone marrow	(49)	(47)	(50)
Hyperplasia, NOS		3 (6%)	
Hyperplasia, hematopoietic		2 (4%)	1 (2%)
Myelopoiesis			3 (6%)
#Spleen	(50)	(49)	(50)
Hemorrhage			1 (2%)
Pigmentation, NOS		1 (2%)	
Angiectasis	1 (2%)		
Leukemoid reaction		1 (2%)	1 (2%)
Hyperplasia, lymphoid	3 (6%)	3 (6%)	1 (2%)
Hematopoiesis	12 (24%)	19 (39%)	13 (26%)
Myelopoiesis		2 (4%)	
#Splenic follicles	(50)	(49)	(50)
Atrophy, NOS		1 (2%)	
#Submandibular lymph node	(49)	(47)	(50)
Myelopoiesis			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Tracheal lymph node	(49)	(47)	(50)
Hyperplasia, lymphoid			1 (2%)
#Mediastinal lymph node	(49)	(47)	(50)
Hyperplasia, lymphoid			1 (2%)
#Abdominal lymph node	(49)	(47)	(50)
Inflammation, acute			1 (2%)
Fibrosis			1 (2%)
#Hepatic lymph node	(49)	(47)	(50)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
#Pancreatic lymph node	(49)	(47)	(50)
Erythrophagocytosis	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
#Mesenteric lymph node	(49)	(47)	(50)
Congestion, NOS	5 (10%)	2 (4%)	
Hemorrhage		1 (2%)	
Hemorrhagic cyst	1 (2%)		
Pigmentation, NOS	1 (2%)		
Atrophy, NOS	1 (2%)		1 (2%)
Angiectasis	2 (4%)		
Erythrophagocytosis	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, reticulum cell		1 (2%)	
Hyperplasia, lymphoid	2 (4%)	2 (4%)	5 (10%)
Hematopoiesis			2 (4%)
#Renal lymph node	(49)	(47)	(50)
Hyperplasia, focal		1 (2%)	
Hyperplasia, lymphoid			1 (2%)
#Iliac lymph node	(49)	(47)	(50)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	4 (8%)	3 (6%)	2 (4%)
Hematopoiesis			1 (2%)
#Axillary lymph node	(49)	(47)	(50)
Pigmentation, NOS	1 (2%)		
Erythrophagocytosis	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Inguinal lymph node	(49)	(47)	(50)
Hyperplasia, reticulum cell		1 (2%)	
Hyperplasia, lymphoid	1 (2%)		
#Lung	(50)	(49)	(50)
Leukocytosis, NOS	1 (2%)	1 (2%)	
Hyperplasia, lymphoid		2 (4%)	
#Liver	(50)	(49)	(50)
Leukocytosis, NOS		1 (2%)	1 (2%)
Hematopoiesis	1 (2%)	2 (4%)	2 (4%)
Myelopoiesis		1 (2%)	
#Peyer's patch	(50)	(47)	(50)
Hyperplasia, lymphoid		2 (4%)	
#Kidney	(50)	(49)	(50)
Leukocytosis, NOS		1 (2%)	
Hyperplasia, lymphoid	14 (28%)	6 (12%)	10 (20%)
*Epididymis	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis			1 (2%)
#Thymus	(23)	(27)	(29)
Cyst, NOS			1 (3%)
CIRCULATORY SYSTEM			
*Orbital region	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Myocardium	(50)	(49)	(50)
Inflammation, acute focal		1 (2%)	
Inflammation, chronic focal	2 (4%)	1 (2%)	1 (2%)
Degeneration, NOS	1 (2%)	1 (2%)	
Necrosis, focal		1 (2%)	
*Coronary artery	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Liver	(50)	(49)	(50)
Thrombosis, NOS	1 (2%)	1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(46)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic			1 (2%)
Necrosis, focal		1 (2%)	
#Liver	(50)	(49)	(50)
Hernia, NOS	2 (4%)		
Congestion, NOS	1 (2%)		
Hemorrhage	1 (2%)	2 (4%)	3 (6%)
Hematoma, NOS			1 (2%)
Abscess, NOS			2 (4%)
Inflammation, chronic		1 (2%)	
Fibrosis		1 (2%)	
Fibrosis, focal			1 (2%)
Necrosis, NOS	1 (2%)		
Necrosis, focal	2 (4%)	11 (22%)	10 (20%)
Necrosis, coagulative		1 (2%)	
Infarct, NOS		1 (2%)	
Metamorphosis, fatty	1 (2%)	4 (8%)	3 (6%)
Pigmentation, NOS			2 (4%)
Focal cellular change	3 (6%)	4 (8%)	6 (12%)
Hepatocytomegaly		1 (2%)	1 (2%)
Angiectasis			2 (4%)
#Liver/centrilobular	(50)	(49)	(50)
Necrosis, diffuse			1 (2%)
#Bile duct	(50)	(49)	(50)
Dilatation, NOS			1 (2%)
Cyst, NOS			2 (4%)
Inflammation, chronic		2 (4%)	2 (4%)
Hyperplasia, NOS			3 (6%)
#Pancreas	(50)	(47)	(49)
Ectopia		1 (2%)	
Dilatation/ducts			1 (2%)
Hemorrhage			1 (2%)
Fibrosis			1 (2%)
Necrosis, fat	1 (2%)		
Atrophy, focal		1 (2%)	
#Pancreatic acinus	(50)	(47)	(49)
Atrophy, NOS			1 (2%)
#Stomach	(50)	(48)	(49)
Inflammation, chronic focal	1 (2%)		1 (2%)
Hyperkeratosis			3 (6%)
Acanthosis	1 (2%)		2 (4%)
#Glandular stomach	(50)	(48)	(49)
Necrosis, focal			1 (2%)
Hyperplasia, focal		1 (2%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(50)	(48)	(49)
Inflammation, acute focal	1 (2%)		
Abscess, NOS			1 (2%)
Necrosis, focal	1 (2%)		
Hyperplasia, focal			1 (2%)
Hyperkeratosis	3 (6%)	5 (10%)	2 (4%)
Acanthosis	6 (12%)		1 (2%)
*Rectum	(50)	(50)	(50)
Hematoma, NOS		1 (2%)	
*Anus	(50)	(50)	(50)
Acanthosis		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Mineralization	1 (2%)		
Hydronephrosis			3 (6%)
Congestion, NOS	1 (2%)		
Pyelonephritis, acute			1 (2%)
Inflammation, acute			1 (2%)
Abscess, NOS	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	2 (4%)	14 (29%)	6 (12%)
Inflammation, chronic focal	16 (32%)		16 (32%)
Inflammation, chronic diffuse			1 (2%)
Fibrosis			1 (2%)
Fibrosis, multifocal	1 (2%)		
Necrosis, focal	1 (2%)		
Infarct, NOS		3 (6%)	1 (2%)
Infarct, focal	1 (2%)		
Hyperplasia, tubular cell	1 (2%)		
#Kidney/cortex	(50)	(49)	(50)
Cyst, NOS	2 (4%)		
#Kidney/tubule	(50)	(49)	(50)
Mineralization	2 (4%)		
Cast, NOS	1 (2%)		1 (2%)
Inflammation, chronic focal	2 (4%)		
Cytoplasmic vacuolization	30 (60%)	7 (14%)	2 (4%)
Hyperplasia, focal			1 (2%)
#Kidney/pelvis	(50)	(49)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	
Inflammation, chronic		1 (2%)	
*Ureter	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
#Urinary bladder	(49)	(48)	(50)
Distention	1 (2%)		
Congestion, NOS		1 (2%)	
Inflammation, suppurative			1 (2%)
Inflammation, chronic		2 (4%)	1 (2%)
Inflammation, chronic focal		1 (2%)	
Inflammation, chronic diffuse	2 (4%)	1 (2%)	1 (2%)
Fibrosis, diffuse			1 (2%)
Hyperplasia, epithelial	1 (2%)		1 (2%)
*Urethra	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Hyperplasia, epithelial			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary	(48)	(47)	(48)
Congestion, NOS		1 (2%)	
#Anterior pituitary	(48)	(47)	(48)
Hyperplasia, focal			1 (2%)
#Adrenal	(49)	(47)	(49)
Pigmentation, NOS	2 (4%)		
#Adrenal/capsule	(49)	(47)	(49)
Hyperplasia, focal	11 (22%)	1 (2%)	3 (6%)
#Adrenal cortex	(49)	(47)	(49)
Degeneration, NOS	3 (6%)	1 (2%)	
Atrophy, NOS			1 (2%)
Hypertrophy, focal	1 (2%)		
Hyperplasia, focal			1 (2%)
#Adrenal medulla	(49)	(47)	(49)
Hypertrophy, NOS		1 (2%)	1 (2%)
Hypertrophy, diffuse	1 (2%)		
Hyperplasia, focal	1 (2%)		1 (2%)
#Thyroid	(50)	(47)	(50)
Embryonal rest	1 (2%)		2 (4%)
Cystic follicles	3 (6%)		
Hyperplasia, follicular cell	2 (4%)	1 (2%)	1 (2%)
#Pancreatic islets	(50)	(47)	(49)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Ulcer, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal		1 (2%)	
Necrosis, diffuse		1 (2%)	
Acanthosis		1 (2%)	
*Prepuce	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
Inflammation, chronic		2 (4%)	
Necrosis, diffuse		1 (2%)	
Acanthosis		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Cystic ducts	3 (6%)	5 (10%)	3 (6%)
Abscess, NOS	7 (14%)	4 (8%)	1 (2%)
Inflammation, chronic	4 (8%)	3 (6%)	1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperkeratosis	5 (10%)	4 (8%)	2 (4%)
Acanthosis	1 (2%)		
#Prostate	(49)	(49)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, acute		1 (2%)	
Abscess, NOS		3 (6%)	2 (4%)
Inflammation, active chronic			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic focal	2 (4%)		
Inflammation, chronic diffuse			1 (2%)
Granuloma, spermatic			1 (2%)
Necrosis, NOS		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Seminal vesicle	(50)	(50)	(50)
Distention	1 (2%)	1 (2%)	1 (2%)
Cyst, NOS	7 (14%)	6 (12%)	1 (2%)
Inflammation, acute			1 (2%)
Abscess, NOS			3 (6%)
Inflammation, active chronic			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic diffuse	1 (2%)		1 (2%)
Necrosis, focal			1 (2%)
Hyperplasia, epithelial			1 (2%)
#Testis	(49)	(48)	(49)
Mineralization	3 (6%)		3 (6%)
Spermatocele		1 (2%)	
Degeneration, NOS	3 (6%)	1 (2%)	3 (6%)
Hypospermatogenesis		3 (6%)	
Hyperplasia, interstitial cell			1 (2%)
*Epididymis	(50)	(50)	(50)
Steatitis		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
Granuloma, NOS			1 (2%)
Granuloma, spermatic		2 (4%)	2 (4%)
Necrosis, fat		2 (4%)	1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
Necrosis, focal		1 (2%)	
*Eyelid	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Necrosis, focal		1 (2%)	
Hyperplasia, focal	1 (2%)		
Acanthosis		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Abscess, NOS			1 (2%)
Necrosis, fat		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1
Auto/necropsy/histo perf		1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Edema, NOS		1 (2%)	
Hemorrhage		1 (2%)	
Fibrosis, focal	1 (2%)		
Hypertrophy, focal	1 (2%)		
Acanthosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Necrosis, fat	2 (4%)		1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Congestion, NOS	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic		3 (6%)	3 (6%)
Hyperplasia, alveolar epithelium			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	4 (8%)	2 (4%)	2 (4%)
#Bone marrow	(50)	(50)	(49)
Hyperplasia, hematopoietic	1 (2%)		
#Spleen	(50)	(48)	(50)
Pigmentation, NOS	1 (2%)	1 (2%)	
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, lymphoid	6 (12%)	9 (19%)	1 (2%)
Hematopoiesis	14 (28%)	13 (27%)	15 (30%)
#Mandibular lymph node	(50)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Bronchial lymph node	(50)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)
#Mediastinal lymph node	(50)	(50)	(49)
Pigmentation, NOS	1 (2%)		
Hyperplasia, lymphoid	2 (4%)		2 (4%)
Hematopoiesis	1 (2%)		
#Mesenteric lymph node	(50)	(50)	(49)
Hemorrhage	1 (2%)		1 (2%)
Hyperplasia, lymphoid	6 (12%)		4 (8%)
Hematopoiesis	1 (2%)		
#Renal lymph node	(50)	(50)	(49)
Hyperplasia, lymphoid	3 (6%)		4 (8%)
#Iliac lymph node	(50)	(50)	(49)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	4 (8%)
#Lung	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)		
Hyperplasia, lymphoid	2 (4%)	7 (14%)	9 (18%)
#Heart	(50)	(50)	(49)
Leukocytosis, NOS	1 (2%)		
#Liver	(50)	(49)	(50)
Leukocytosis, NOS	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Hematopoiesis	3 (6%)		5 (10%)
#Cecum	(50)	(49)	(49)
Hyperplasia, lymphoid			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	9 (18%)	9 (18%)	9 (18%)
#Urinary bladder	(49)	(48)	(50)
Hyperplasia, lymphoid	2 (4%)		4 (8%)
#Thymus	(39)	(39)	(38)
Atrophy, NOS			1 (3%)
Angiectasis		1 (3%)	
Hyperplasia, lymphoid	2 (5%)		
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis			1 (2%)
#Mesenteric lymph node	(50)	(50)	(49)
Lymphangiectasis	1 (2%)		
#Iliac lymph node	(50)	(50)	(49)
Lymphangiectasis	1 (2%)		
#Lung	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Heart	(50)	(50)	(49)
Thrombosis, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
#Myocardium	(50)	(50)	(49)
Fibrosis, focal		1 (2%)	
Degeneration, NOS	1 (2%)	1 (2%)	
#Uterus	(50)	(48)	(50)
Thrombosis, NOS	1 (2%)		2 (4%)
#Ovary	(49)	(47)	(48)
Thrombosis, NOS	1 (2%)		1 (2%)
#Thymus	(39)	(39)	(38)
Thrombosis, NOS		1 (3%)	
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(50)	(48)
Fibrosis, diffuse		1 (2%)	
Atrophy, NOS		1 (2%)	
Atrophy, focal			1 (2%)
#Liver	(50)	(49)	(50)
Inflammation, suppurative			1 (2%)
Abscess, NOS			1 (2%)
Inflammation, chronic focal			1 (2%)
Granuloma, NOS	1 (2%)	4 (8%)	2 (4%)
Fibrosis, focal			1 (2%)
Degeneration, NOS			1 (2%)
Necrosis, NOS		1 (2%)	
Necrosis, focal	1 (2%)	2 (4%)	3 (6%)
Metamorphosis, fatty	1 (2%)	1 (2%)	1 (2%)
Pigmentation, NOS	1 (2%)	1 (2%)	1 (2%)
Mitotic alteration			7 (14%)
Focal cellular change	1 (2%)	1 (2%)	5 (10%)
Pleomorphism			1 (2%)
Hepatocytomegaly			1 (2%)
Angiectasis			3 (6%)
#Hepatic capsule	(50)	(49)	(50)
Abscess, NOS			1 (2%)
#Liver/hepatocytes	(50)	(49)	(50)
Degeneration, NOS			1 (2%)
#Bile duct	(50)	(49)	(50)
Inflammation, chronic			3 (6%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(50)	(49)	(50)
Dilatation/ducts	1 (2%)		3 (6%)
Inflammation, chronic			1 (2%)
Atrophy, NOS	1 (2%)		
#Pancreatic duct	(50)	(49)	(50)
Inflammation, chronic			1 (2%)
Pigmentation, NOS			1 (2%)
#Stomach	(50)	(48)	(50)
Hyperkeratosis	1 (2%)		
#Glandular stomach	(50)	(48)	(50)
Inflammation, acute focal		1 (2%)	
Necrosis, focal		1 (2%)	
Hyperplasia, focal	1 (2%)		
#Forestomach	(50)	(48)	(50)
Inflammation, acute focal	1 (2%)		
Inflammation, chronic focal			1 (2%)
Hyperkeratosis	8 (16%)	5 (10%)	2 (4%)
Acanthosis	1 (2%)	2 (4%)	1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Mineralization		1 (2%)	
Hydronephrosis	1 (2%)	2 (4%)	2 (4%)
Abscess, NOS	1 (2%)		1 (2%)
Inflammation, chronic	7 (14%)	5 (10%)	6 (12%)
Inflammation, chronic focal	5 (10%)	5 (10%)	1 (2%)
Inflammation, chronic diffuse			3 (6%)
Fibrosis			1 (2%)
Glomerulosclerosis, NOS	1 (2%)		
Necrosis, focal	1 (2%)		1 (2%)
Infarct, NOS		2 (4%)	1 (2%)
Infarct, focal			1 (2%)
Amyloidosis	1 (2%)		
Pigmentation, NOS	1 (2%)		2 (4%)
Focal cellular change			1 (2%)
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis		1 (2%)	
#Kidney/tubule	(50)	(50)	(50)
Cast, NOS	1 (2%)		
Degeneration, NOS		1 (2%)	
Necrosis, focal	1 (2%)		
#Urinary bladder	(49)	(48)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)
Hyperplasia, epithelial	1 (2%)		3 (6%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(47)	(50)
Cyst, NOS	1 (2%)		
Degeneration, NOS	1 (2%)		
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	3 (6%)	1 (2%)	
Hyperplasia, diffuse		1 (2%)	
#Adrenal/capsule	(50)	(50)	(50)
Hyperplasia, NOS	3 (6%)		
Hyperplasia, focal	4 (8%)		2 (4%)
Hyperplasia, diffuse	2 (4%)		1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(50)	(50)
Degeneration, NOS	3 (6%)		1 (2%)
Cytoplasmic vacuolization		3 (6%)	
Atrophy, NOS	4 (8%)		1 (2%)
Hypertrophy, focal			1 (2%)
Hyperplasia, NOS			1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)	
Hypertrophy, NOS	1 (2%)		
Hyperplasia, focal			2 (4%)
#Periadrenal tissue	(50)	(50)	(50)
Steatitis	1 (2%)		
Inflammation, chronic	1 (2%)		
#Parathyroid	(42)	(36)	(37)
Embryonal rest		1 (3%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cystic ducts	1 (2%)		1 (2%)
#Uterus	(50)	(48)	(50)
Mineralization	1 (2%)		
Hydrometra		2 (4%)	1 (2%)
Cyst, NOS	2 (4%)		
Inflammation, acute	1 (2%)	2 (4%)	1 (2%)
Abscess, NOS	6 (12%)	1 (2%)	5 (10%)
Inflammation, chronic	2 (4%)		2 (4%)
Perforation, inflammatory			1 (2%)
Necrosis, focal	1 (2%)	1 (2%)	
#Cervix uteri	(50)	(48)	(50)
Inflammation, chronic		1 (2%)	1 (2%)
Fibrosis	1 (2%)		
Hyperkeratosis		1 (2%)	1 (2%)
Acanthosis	1 (2%)	2 (4%)	3 (6%)
#Uterus/endometrium	(50)	(48)	(50)
Cyst, NOS	2 (4%)	1 (2%)	5 (10%)
Inflammation, acute			1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, cystic	38 (76%)	39 (81%)	33 (66%)
#Uterus/myometrium	(50)	(48)	(50)
Hypertrophy, NOS			1 (2%)
#Fallopian tube	(50)	(48)	(50)
Abscess, NOS			1 (2%)
#Ovary/parovarian	(49)	(47)	(48)
Abscess, NOS	1 (2%)		
#Ovary	(49)	(47)	(48)
Cyst, NOS	9 (18%)	8 (17%)	13 (27%)
Multilocular cyst	1 (2%)	1 (2%)	
Hemorrhage	1 (2%)	2 (4%)	2 (4%)
Inflammation, acute	1 (2%)	2 (4%)	
Abscess, NOS	5 (10%)	1 (2%)	6 (13%)
Inflammation, chronic	1 (2%)		1 (2%)
Fibrosis			1 (2%)
Degeneration, NOS		1 (2%)	1 (2%)
Pigmentation, NOS			1 (2%)
Atrophy, NOS		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	Low Dose	High Dose
NERVOUS SYSTEM			
*Cauda equina	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Sternum	(50)	(50)	(50)
Fibrous osteodystrophy	10 (20%)	17 (34%)	14 (28%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage		1 (2%)	
*Abdominal cavity	(50)	(50)	(50)
Steatitis	1 (2%)	1 (2%)	1 (2%)
Necrosis, fat		1 (2%)	3 (6%)
*Mesentery	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Abscess, NOS	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Abscess, NOS	1 (2%)		
Inflammation, chronic diffuse	1 (2%)		
Adipose tissue			
Abscess, NOS	2	1	1
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		1	
Auto/necropsy/histo perf	1		1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Skin: Keratoacanthoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	14.6%	11.7%	12.0%
Terminal Rates (c)	2/24 (8%)	3/32 (9%)	3/25 (12%)
Week of First Observation	98	97	104
Life Table Tests (d)	P=0.418N	P=0.495N	P=0.495N
Incidental Tumor Tests (d)	P=0.471N	P=0.542N	P=0.554N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test (d)		P=0.643	P=0.500N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	14.4%	12.5%	12.0%
Terminal Rates (c)	3/24 (13%)	4/32 (13%)	3/25 (12%)
Week of First Observation	75	104	104
Life Table Tests (d)	P=0.401N	P=0.495N	P=0.481N
Incidental Tumor Tests (d)	P=0.415N	P=0.610N	P=0.495N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test (d)		P=0.643N	P=0.500N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	3.1%	10.0%
Terminal Rates (c)	0/24 (0%)	1/32 (3%)	1/25 (4%)
Week of First Observation		104	88
Life Table Tests (d)	P=0.053	P=0.557	P=0.119
Incidental Tumor Tests (d)	P=0.062	P=0.557	P=0.120
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	14.4%	15.6%	21.3%
Terminal Rates (c)	3/24 (13%)	5/32 (16%)	4/25 (16%)
Week of First Observation	75	104	88
Life Table Tests (d)	P=0.313	P=0.616N	P=0.380
Incidental Tumor Tests (d)	P=0.313	P=0.563	P=0.373
Cochran-Armitage Trend Test (d)	P=0.309		
Fisher Exact Test (d)		P=0.500	P=0.370
Subcutaneous Tissue: Fibrosarcoma or Neurofibrosarcoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	4.2%	3.1%	10.0%
Terminal Rates (c)	1/24 (4%)	1/32 (3%)	1/25 (4%)
Week of First Observation	104	104	88
Life Table Tests (d)	P=0.193	P=0.697N	P=0.304
Incidental Tumor Tests (d)	P=0.206	P=0.697N	P=0.309
Cochran-Armitage Trend Test (d)	P=0.201		
Fisher Exact Test (d)		P=0.753	P=0.309
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	4.2%	3.1%	13.7%
Terminal Rates (c)	1/24 (4%)	1/32 (3%)	2/25 (8%)
Week of First Observation	104	104	88
Life Table Tests (d)	P=0.093	P=0.697N	P=0.182
Incidental Tumor Tests (d)	P=0.102	P=0.697N	P=0.185
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.753	P=0.181

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	620 ppm	1,250 ppm
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	18.5%	15.6%	25.0%
Terminal Rates (c)	4/24 (17%)	5/32 (16%)	5/25 (20%)
Week of First Observation	75	104	88
Life Table Tests (d)	P=0.323	P=0.457N	P=0.393
Incidental Tumor Tests (d)	P=0.323	P=0.560N	P=0.387
Cochran-Armitage Trend Test (d)	P=0.318		
Fisher Exact Test (d)		P=0.630	P=0.380
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	0.0%	9.4%	18.5%
Terminal Rates (c)	0/24 (0%)	3/32 (9%)	3/25 (12%)
Week of First Observation		104	100
Life Table Tests (d)	P=0.019	P=0.175	P=0.036
Incidental Tumor Tests (d)	P=0.014	P=0.175	P=0.021
Cochran-Armitage Trend Test (d)	P=0.023		
Fisher Exact Test (d)		P=0.121	P=0.028
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	0.0%	12.5%	18.5%
Terminal Rates (c)	0/24 (0%)	4/32 (13%)	3/25 (12%)
Week of First Observation		104	100
Life Table Tests (d)	P=0.025	P=0.104	P=0.036
Incidental Tumor Tests (d)	P=0.019	P=0.104	P=0.021
Cochran-Armitage Trend Test (d)	P=0.029		
Fisher Exact Test (d)		P=0.059	P=0.028
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	24/50 (48%)	22/50 (44%)	28/50 (56%)
Adjusted Rates (b)	55.7%	54.0%	66.5%
Terminal Rates (c)	6/24 (25%)	14/32 (44%)	12/25 (48%)
Week of First Observation	65	86	72
Life Table Tests (d)	P=0.285	P=0.160N	P=0.330
Incidental Tumor Tests (d)	P=0.216	P=0.524N	P=0.193
Cochran-Armitage Trend Test (d)	P=0.241		
Fisher Exact Test (d)		P=0.421N	P=0.274
Salivary Gland: Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	1/49 (2%)	4/50 (8%)
Adjusted Rates (b)	4.2%	3.2%	14.7%
Terminal Rates (c)	1/24 (4%)	1/31 (3%)	3/25 (12%)
Week of First Observation	104	104	93
Life Table Tests (d)	P=0.094	P=0.704N	P=0.184
Incidental Tumor Tests (d)	P=0.084	P=0.704N	P=0.162
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.747	P=0.181
Salivary Gland: Fibrosarcoma or Neurofibrosarcoma			
Overall Rates (a)	1/50 (2%)	2/49 (4%)	4/50 (8%)
Adjusted Rates (b)	4.2%	6.5%	14.7%
Terminal Rates (c)	1/24 (4%)	2/31 (6%)	3/25 (12%)
Week of First Observation	104	104	93
Life Table Tests (d)	P=0.111	P=0.590	P=0.184
Incidental Tumor Tests (d)	P=0.101	P=0.590	P=0.162
Cochran-Armitage Trend Test (d)	P=0.119		
Fisher Exact Test (d)		P=0.492	P=0.181

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	620 ppm	1,250 ppm
Liver: Neoplastic Nodule			
Overall Rates (a)	2/50 (4%)	21/50 (42%)	23/50 (46%)
Adjusted Rates (b)	8.3%	61.6%	78.6%
Terminal Rates (c)	2/24 (8%)	19/32 (59%)	19/25 (76%)
Week of First Observation	104	97	83
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	9.5%	15.6%	4.0%
Terminal Rates (c)	1/24 (4%)	5/32 (16%)	1/25 (4%)
Week of First Observation	77	104	104
Life Table Tests (d)	P=0.244N	P=0.498	P=0.304N
Incidental Tumor Tests (d)	P=0.277N	P=0.371	P=0.356N
Cochran-Armitage Trend Test (d)	P=0.262N		
Fisher Exact Test (d)		P=0.357	P=0.309N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	5/50 (10%)	22/50 (44%)	23/50 (46%)
Adjusted Rates (b)	17.3%	64.6%	78.6%
Terminal Rates (c)	3/24 (13%)	20/32 (63%)	19/25 (76%)
Week of First Observation	77	97	83
Life Table Tests (d)	P<0.001	P<0.002	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	0/49 (0%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	0.0%	11.3%	24.0%
Terminal Rates (c)	0/24 (0%)	3/32 (9%)	6/25 (24%)
Week of First Observation		88	104
Life Table Tests (d)	P=0.011	P=0.104	P=0.018
Incidental Tumor Tests (d)	P=0.014	P=0.082	P=0.018
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		P=0.061	P=0.014
Rancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	2/49 (4%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	5.9%	13.5%	22.4%
Terminal Rates (c)	0/24 (0%)	2/32 (6%)	5/25 (20%)
Week of First Observation	89	89	92
Life Table Tests (d)	P=0.101	P=0.320	P=0.139
Incidental Tumor Tests (d)	P=0.118	P=0.232	P=0.162
Cochran-Armitage Trend Test (d)	P=0.113		
Fisher Exact Test (d)		P=0.226	P=0.141
Pancreatic Islets: Islet Cell Carcinoma			
Overall Rates (a)	4/49 (8%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	15.0%	3.1%	12.0%
Terminal Rates (c)	3/24 (13%)	1/32 (3%)	3/25 (12%)
Week of First Observation	93	104	104
Life Table Tests (d)	P=0.400N	P=0.109N	P=0.488N
Incidental Tumor Tests (d)	P=0.415N	P=0.114N	P=0.509N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.175N	P=0.489N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	620 ppm	1,250 ppm
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	6/50 (12%)	9/50 (18%)
Adjusted Rates (b)	20.0%	16.4%	34.0%
Terminal Rates (c)	3/24 (13%)	3/32 (9%)	8/25 (32%)
Week of First Observation	89	89	92
Life Table Tests (d)	P=0.232	P=0.446N	P=0.296
Incidental Tumor Tests (d)	P=0.246	P=0.529N	P=0.311
Cochran-Armitage Trend Test (d)	P=0.247		
Fisher Exact Test (d)		P=0.606N	P=0.303
Pituitary: Adenoma			
Overall Rates (a)	17/50 (34%)	22/50 (44%)	19/50 (38%)
Adjusted Rates (b)	52.5%	56.8%	64.6%
Terminal Rates (c)	10/24 (42%)	16/32 (50%)	15/25 (60%)
Week of First Observation	75	74	81
Life Table Tests (d)	P=0.402	P=0.567	P=0.448
Incidental Tumor Tests (d)	P=0.376	P=0.316	P=0.440
Cochran-Armitage Trend Test (d)	P=0.381		
Fisher Exact Test (d)		P=0.206	P=0.418
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	18/50 (36%)	23/50 (46%)	19/50 (38%)
Adjusted Rates (b)	53.9%	58.0%	64.6%
Terminal Rates (c)	10/24 (42%)	16/32 (50%)	15/25 (60%)
Week of First Observation	75	74	81
Life Table Tests (d)	P=0.480	P=0.572N	P=0.527
Incidental Tumor Tests (d)	P=0.462	P=0.308	P=0.544
Cochran-Armitage Trend Test (d)	P=0.462		
Fisher Exact Test (d)		P=0.208	P=0.500
Adrenal: Pheochromocytoma			
Overall Rates (a)	25/50 (50%)	17/50 (34%)	15/50 (30%)
Adjusted Rates (b)	72.6%	46.2%	52.6%
Terminal Rates (c)	15/24 (63%)	13/32 (41%)	12/25 (48%)
Week of First Observation	76	88	78
Life Table Tests (d)	P=0.022N	P=0.010N	P=0.034N
Incidental Tumor Tests (d)	P=0.032N	P=0.017N	P=0.048N
Cochran-Armitage Trend Test (d)	P=0.025N		
Fisher Exact Test (d)		P=0.078N	P=0.033N
Adrenal: Pheochromocytoma, Malignant			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	11.0%	0.0%	0.0%
Terminal Rates (c)	2/24 (8%)	0/32 (0%)	0/25 (0%)
Week of First Observation	93		
Life Table Tests (d)	P=0.032N	P=0.081N	P=0.123N
Incidental Tumor Tests (d)	P=0.038N	P=0.091N	P=0.143N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.122N	P=0.122N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	26/50 (52%)	17/50 (34%)	15/50 (30%)
Adjusted Rates (b)	75.7%	46.2%	52.6%
Terminal Rates (c)	16/24 (67%)	13/32 (41%)	12/25 (48%)
Week of First Observation	76	88	78
Life Table Tests (d)	P=0.013N	P=0.005N	P=0.021N
Incidental Tumor Tests (d)	P=0.019N	P=0.009N	P=0.029N
Cochran-Armitage Trend Test (d)	P=0.016N		
Fisher Exact Test (d)		P=0.053N	P=0.021N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	620 ppm	1,250 ppm
Thyroid: C-Cell Adenoma			
Overall Rates (a)	10/50 (20%)	7/50 (14%)	12/50 (24%)
Adjusted Rates (b)	36.3%	21.9%	41.3%
Terminal Rates (c)	7/24 (29%)	7/32 (22%)	9/25 (36%)
Week of First Observation	91	104	87
Life Table Tests (d)	P=0.363	P=0.118N	P=0.428
incidental Tumor Tests (d)	P=0.404	P=0.146N	P=0.468
Cochran-Armitage Trend Test (d)	P=0.350		
Fisher Exact Test (d)		P=0.298N	P=0.405
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	18.9%	8.5%	12.0%
Terminal Rates (c)	4/24 (17%)	2/32 (6%)	3/25 (12%)
Week of First Observation	91	95	104
Life Table Tests (d)	P=0.268N	P=0.225N	P=0.340N
Incidental Tumor Tests (d)	P=0.259N	P=0.263N	P=0.307N
Cochran-Armitage Trend Test (d)	P=0.284N		
Fisher Exact Test (d)		P=0.357N	P=0.357N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	10/50 (20%)	15/50 (30%)
Adjusted Rates (b)	52.6%	29.9%	52.3%
Terminal Rates (c)	11/24 (46%)	9/32 (28%)	12/25 (48%)
Week of First Observation	91	95	87
Life Table Tests (d)	P=0.526N	P=0.040N	P=0/559N
Incidental Tumor Tests (d)	P=0.480N	P=0.057N	P=0.498N
Cochran-Armitage Trend Test (d)	P=0.543		
Fisher Exact Test (d)		P=0.178N	P=0.586
Preputial Gland: Carcinoma			
Overall Rates (a)	1/50 (2%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	4.2%	22.7%	13.2%
Terminal Rates (c)	1/24 (4%)	6/32 (19%)	2/25 (8%)
Week of First Observation	104	81	82
Life Table Tests (d)	P=0.194	P=0.047	P=0.189
Incidental Tumor Tests (d)	P=0.198	P=0.035	P=0.185
Cochran-Armitage Trend Test (d)	P=0.190		
Fisher Exact Test (d)		P=0.015	P=0.181
Preputial Gland: Adenoma, Carcinoma, or Squamous Cell Papilloma			
Overall Rates (a)	1/50 (2%)	10/50 (20%)	4/50 (8%)
Adjusted Rates (b)	4.2%	27.8%	13.2%
Terminal Rates (c)	1/24 (4%)	7/32 (22%)	2/25 (8%)
Week of First Observation	104	81	82
Life Table Tests (d)	P=0.210	P=0.018	P=0.189
Incidental Tumor Tests (d)	P=0.201	P=0.012	P=0.185
Cochran-Armitage Trend Test (d)	P=0.206		
Fisher Exact Test (d)		P=0.004	P=0.181
Testis: Interstitial Cell Tumor			
Overall Rates (a)	41/49 (84%)	35/50 (70%)	22/50 (44%)
Adjusted Rates (b)	97.5%	80.9%	61.5%
Terminal Rates (c)	23/24 (96%)	24/32 (75%)	12/25 (48%)
Week of First Observation	73	81	64
Life Table Tests (d)	P<0.001N	P=0.008N	P=0.002N
Incidental Tumor Tests (d)	P<0.001N	P=0.013N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.085N	P<0.001N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

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

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	8.7%	2.8%	2.9%
Terminal Rates (c)	2/31 (6%)	1/36 (3%)	1/35 (3%)
Week of First Observation	91	104	104
Life Table Tests (d)	P=0.178N	P=0.262N	P=0.277N
Incidental Tumor Tests (d)	P=0.207N	P=0.323N	P=0.314N
Cochran-Armitage Trend Test (d)	P=0.203N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	13/50 (26%)	15/50 (30%)	16/50 (32%)
Adjusted Rates (b)	32.6%	34.9%	38.0%
Terminal Rates (c)	6/31 (19%)	9/36 (25%)	10/35 (29%)
Week of First Observation	82	64	73
Life Table Tests (d)	P=0.387	P=0.542	P=0.425
Incidental Tumor Tests (d)	P=0.307	P=0.380	P=0.347
Cochran-Armitage Trend Test (d)	P=0.292		
Fisher Exact Test (d)		P=0.412	P=0.330
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	3/49 (6%)	11/50 (22%)
Adjusted Rates (b)	3.2%	8.3%	31.4%
Terminal Rates (c)	1/31 (3%)	3/36 (8%)	11/35 (31%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.001	P=0.359	P=0.004
Incidental Tumor Tests (d)	P=0.001	P=0.359	P=0.004
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.301	P=0.002
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	0/50 (0%)	3/49 (6%)	5/50 (10%)
Adjusted Rates (b)	0.0%	7.8%	14.3%
Terminal Rates (c)	0/31 (0%)	2/36 (6%)	5/35 (14%)
Week of First Observation		95	104
Life Table Tests (d)	P=0.028	P=0.146	P=0.044
Incidental Tumor Tests (d)	P=0.023	P=0.133	P=0.044
Cochran-Armitage Trend Test (d)	P=0.023		
Fisher Exact Test (d)		P=0.117	P=0.028
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	5/49 (10%)	16/50 (32%)
Adjusted Rates (b)	3.2%	13.2%	45.7%
Terminal Rates (c)	1/31 (3%)	4/36 (11%)	16/35 (46%)
Week of First Observation	104	95	104
Life Table Tests (d)	P<0.001	P=0.138	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.130	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.098	P<0.001
Pituitary: Adenoma			
Overall Rates (a)	31/50 (62%)	34/50 (68%)	23/50 (46%)
Adjusted Rates (b)	83.3%	76.9%	55.7%
Terminal Rates (c)	25/31 (81%)	26/36 (72%)	17/35 (49%)
Week of First Observation	82	64	82
Life Table Tests (d)	P=0.027N	P=0.498N	P=0.035N
Incidental Tumor Tests (d)	P=0.060N	P=0.476	P=0.083N
Cochran-Armitage Trend Test (d)	P=0.063N		
Fisher Exact Test (d)		P=0.338	P=0.080N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	620 ppm	1,250 ppm
Pituitary: Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	5.6%	7.7%	2.9%
Terminal Rates (c)	1/31 (3%)	1/36 (3%)	1/35 (3%)
Week of First Observation	96	99	104
Life Table Tests (d)	P=0.371N	P=0.548	P=0.475N
Incidental Tumor Tests (d)	P=0.484N	P=0.495	P=0.539N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	33/50 (66%)	37/50 (74%)	24/50 (48%)
Adjusted Rates (b)	86.4%	80.3%	58.2%
Terminal Rates (c)	26/31 (84%)	27/36 (75%)	18/35 (51%)
Week of First Observation	82	64	82
Life Table Tests (d)	P=0.018N	P=0.553N	P=0.022N
Incidental Tumor Tests (d)	P=0.044N	P=0.384	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.039N		
Fisher Exact Test (d)		P=0.257	P=0.053N
Adrenal: Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	5.3%	7.9%	5.7%
Terminal Rates (c)	1/31 (3%)	2/36 (6%)	2/35 (6%)
Week of First Observation	87	98	104
Life Table Tests (d)	P=0.557N	P=0.548	P=0.665N
Incidental Tumor Tests (d)	P=0.565	P=0.469	P=0.686
Cochran-Armitage Trend Test (d)	P=0.593N		
Fisher Exact Test (d)		P=0.490	P=0.691
Thyroid: C-Cell Adenoma			
Overall Rates (a)	7/50 (14%)	10/50 (20%)	13/50 (26%)
Adjusted Rates (b)	20.4%	26.0%	36.1%
Terminal Rates (c)	5/31 (16%)	8/36 (22%)	12/35 (34%)
Week of First Observation	96	93	101
Life Table Tests (d)	P=0.127	P=0.409	P=0.160
Incidental Tumor Tests (d)	P=0.079	P=0.367	P=0.107
Cochran-Armitage Trend Test (d)	P=0.085		
Fisher Exact Test (d)		P=0.298	P=0.105
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	2/50 (4%)
Adjusted Rates (b)	6.5%	18.9%	5.7%
Terminal Rates (c)	2/31 (6%)	6/36 (17%)	2/35 (6%)
Week of First Observation	104	100	104
Life Table Tests (d)	P=0.511N	P=0.119	P=0.651N
Incidental Tumor Tests (d)	P=0.542N	P=0.112	P=0.651N
Cochran-Armitage Trend Test (d)	P=0.573N		
Fisher Exact Test (d)		P=0.080	P=0.691N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	16/50 (32%)	15/50 (30%)
Adjusted Rates (b)	26.5%	40.8%	41.6%
Terminal Rates (c)	7/31 (23%)	13/36 (36%)	14/35 (40%)
Week of First Observation	96	93	101
Life Table Tests (d)	P=0.171	P=0.162	P=0.188
Incidental Tumor Tests (d)	P=0.105	P=0.128	P=0.132
Cochran-Armitage Trend Test (d)	P=0.108		
Fisher Exact Test (d)		P=0.083	P=0.12

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	620 ppm	1,250 ppm
Mammary Gland: Fibroadenoma			
Overall Rates (a)	22/50 (44%)	16/50 (32%)	4/50 (8%)
Adjusted Rates (b)	58.5%	38.5%	11.4%
Terminal Rates (c)	16/31 (52%)	11/36 (31%)	4/35 (11%)
Week of First Observation	87	82	104
Life Table Tests (d)	P<0.001N	P=0.081N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.162N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.151N	P<0.001N
Mammary Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	3.2%	8.3%	8.6%
Terminal Rates (c)	1/31 (3%)	3/36 (8%)	3/35 (9%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.277	P=0.359	P=0.349
Incidental Tumor Tests (d)	P=0.277	P=0.359	P=0.349
Cochran-Armitage Trend Test (d)	P=0.240		
Fisher Exact Test (d)		P=0.309	P=0.309
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	3.2%	12.8%	10.0%
Terminal Rates (c)	1/31 (3%)	3/36 (8%)	2/35 (6%)
Week of First Observation	104	95	63
Life Table Tests (d)	P=0.190	P=0.138	P=0.212
Incidental Tumor Tests (d)	P=0.171	P=0.118	P=0.246
Cochran-Armitage Trend Test (d)	P=0.160		
Fisher Exact Test (d)		P=0.102	P=0.181
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	23/50 (46%)	17/50 (34%)	7/50 (14%)
Adjusted Rates (b)	61.3%	41.0%	20.0%
Terminal Rates (c)	17/31 (55%)	12/36 (33%)	7/35 (20%)
Week of First Observation	87	82	104
Life Table Tests (d)	P<0.001N	P=0.078N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.156N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.154N	P<0.001N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	24/50 (48%)	20/50 (40%)	10/50 (20%)
Adjusted Rates (b)	64.0%	47.1%	26.3%
Terminal Rates (c)	18/31 (58%)	14/36 (39%)	8/35 (23%)
Week of First Observation	87	82	63
Life Table Tests (d)	P=0.001N	P=0.145N	P=0.001N
Incidental Tumor Tests (d)	P=0.003N	P=0.267N	P=0.002N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.273N	P=0.003N
Clitoral Gland: Carcinoma			
Overall Rates (a)	4/50 (8%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	11.3%	13.9%	16.5%
Terminal Rates (c)	2/31 (6%)	5/36 (14%)	5/35 (14%)
Week of First Observation	82	104	99
Life Table Tests (d)	P=0.369	P=0.578	P=0.432
Incidental Tumor Tests (d)	P=0.299	P=0.518	P=0.323
Cochran-Armitage Trend Test (d)	P=0.309		
Fisher Exact Test (d)		P=0.500	P=0.370

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID (Continued)

	Control	620 ppm	1,250 ppm
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	11.3%	13.9%	19.3%
Terminal Rates (c)	2/31 (6%)	5/36 (14%)	7/35 (17%)
Week of First Observation	82	104	99
Life Table Tests (d)	P=0.261	P=0.578	P=0.323
Incidental Tumor Tests (d)	P=0.203	P=0.518	P=0.229
Cochran-Armitage Trend Test (d)	P=0.209		
Fisher Exact Test (d)		P=0.500	P=0.262
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	6/50 (12%)	15/49 (31%)	10/50 (20%)
Adjusted Rates (b)	17.8%	39.1%	27.5%
Terminal Rates (c)	5/31 (16%)	13/36 (36%)	9/35 (26%)
Week of First Observation	58	86	88
Life Table Tests (d)	P=0.271	P=0.051	P=0.276
Incidental Tumor Tests (d)	P=0.274	P=0.040	P=0.315
Cochran-Armitage Trend Test (d)	P=0.197		
Fisher Exact Test (d)		P=0.021	P=0.207

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences 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 exact tests 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 CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	6/50 (12%)	7/50 (14%)	7/50 (14%)
Adjusted Rates (b)	14.9%	19.2%	19.1%
Terminal Rates (c)	4/37 (11%)	1/28 (4%)	2/29 (7%)
Week of First Observation	69	65	47
Life Table Tests (d)	P=0.326	P=0.358	P=0.375
Incidental Tumor Tests (d)	P=0.515N	P=0.598N	P=0.531N
Cochran-Armitage Trend Test (d)	P=0.442		
Fisher Exact Test (d)		P=0.500	P=0.500
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	6/50 (12%)	9/50 (18%)	7/50 (14%)
Adjusted Rates (b)	14.9%	25.2%	19.1%
Terminal Rates (c)	4/37 (11%)	3/28 (11%)	2/29 (7%)
Week of First Observation	69	65	47
Life Table Tests (d)	P=0.318	P=0.172	P=0.375
Incidental Tumor Tests (d)	P=0.533N	P=0.377	P=0.531N
Cochran-Armitage Trend Test (d)	P=0.446		
Fisher Exact Test (d)		P=0.288	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	7/50 (14%)	8/50 (16%)
Adjusted Rates (b)	20.0%	19.2%	21.7%
Terminal Rates (c)	6/37 (16%)	1/28 (4%)	2/29 (7%)
Week of First Observation	69	65	47
Life Table Tests (d)	P=0.410	P=0.546	P=0.454
Incidental Tumor Tests (d)	P=0.417N	P=0.387N	P=0.441N
Cochran-Armitage Trend Test (d)	P=0.555		
Fisher Exact Test (d)		P=0.500N	P=0.607
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	9/50 (18%)	8/50 (16%)
Adjusted Rates (b)	20.0%	25.2%	21.7%
Terminal Rates (c)	6/37 (16%)	3/28 (11%)	2/29 (7%)
Week of First Observation	69	65	47
Life Table Tests (d)	P=0.398	P=0.321	P=0.454
Incidental Tumor Tests (d)	P=0.438N	P=0.576	P=0.441N
Cochran-Armitage Trend Test (d)	P=0.553N		
Fisher Exact Test (d)		P=0.500	P=0.607
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	11/50 (22%)	2/49 (4%)	7/50 (14%)
Adjusted Rates (b)	29.7%	6.2%	20.4%
Terminal Rates (c)	11/37 (30%)	1/28 (4%)	4/29 (14%)
Week of First Observation	104	84	41
Life Table Tests (d)	P=0.286N	P=0.028N	P=0.393N
Incidental Tumor Tests (d)	P=0.197N	P=0.013N	P=0.298N
Cochran-Armitage Trend Test (d)	P=0.155N		
Fisher Exact Test (d)		P=0.008N	P=0.218N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	5/50 (10%)	2/49 (4%)	3/50 (6%)
Adjusted Rates (b)	13.5%	7.1%	9.1%
Terminal Rates (c)	5/37 (14%)	2/28 (7%)	1/29 (3%)
Week of First Observation	104	104	90
Life Table Tests (d)	P=0.396N	P=0.340N	P=0.488N
Incidental Tumor Tests (d)	P=0.320N	P=0.340N	P=0.354N
Cochran-Armitage Trend Test (d)	P=0.276N		
Fisher Exact Test (d)		P=0.227N	P=0.358N

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

	Control	620 ppm	1,250 ppm
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	4/49 (8%)	9/50 (18%)
Adjusted Rates (b)	40.5%	13.1%	25.9%
Terminal Rates (c)	15/37 (41%)	3/28 (11%)	5/29 (17%)
Week of First Observation	104	84	41
Life Table Tests (d)	P=0.202N	P=0.023N	P=0.291N
Incidental Tumor Tests (d)	P=0.112N	P=0.012N	P=0.159N
Cochran-Armitage Trend Test (d)	P=0.081N		
Fisher Exact Test (d)		P=0.005N	P=0.121N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	2.7%	9.7%	9.6%
Terminal Rates (c)	1/37 (3%)	2/28 (7%)	1/29 (3%)
Week of First Observation	104	84	99
Life Table Tests (d)	P=0.179	P=0.227	P=0.233
Incidental Tumor Tests (d)	P=0.238	P=0.357	P=0.258
Cochran-Armitage Trend Test (d)	P=0.240		
Fisher Exact Test (d)		P=0.309	P=0.309
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	8.1%	0.0%	2.6%
Terminal Rates (c)	3/37 (8%)	0/28 (0%)	0/29 (0%)
Week of First Observation	104		83
Life Table Tests (d)	P=0.233N	P=0.174N	P=0.380N
Incidental Tumor Tests (d)	P=0.154N	P=0.174N	P=0.230N
Cochran-Armitage Trend Test (d)	P=0.178N		
Fisher Exact Test (d)		P=0.122N	P=0.309N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	10.8%	12.0%	11.9%
Terminal Rates (c)	4/37 (11%)	2/28 (7%)	1/29 (3%)
Week of First Observation	104	81	83
Life Table Tests (d)	P=0.455	P=0.510	P=0.522
Incidental Tumor Tests (d)	P=0.505N	P=0.553N	P=0.634N
Cochran-Armitage Trend Test (d)	P=0.574		
Fisher Exact Test (d)		P=0.643N	P=0.643N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	5/50 (10%)	9/49 (18%)	10/50 (20%)
Adjusted Rates (b)	13.5%	30.1%	33.3%
Terminal Rates (c)	5/37 (14%)	8/28 (29%)	9/29 (31%)
Week of First Observation	105	30	102
Life Table Tests (d)	P=0.038	P=0.077	P=0.047
Incidental Tumor Tests (d)	P=0.041	P=0.081	P=0.050
Cochran-Armitage Trend Test (d)	P=0.111		
Fisher Exact Test (d)		P=0.185	P=0.131
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	9/50 (18%)	17/49 (35%)	20/50 (40%)
Adjusted Rates (b)	22.1%	46.5%	51.8%
Terminal Rates (c)	6/37 (16%)	9/28 (32%)	11/29 (38%)
Week of First Observation	70	75	60
Life Table Tests (d)	P=0.004	P=0.018	P=0.005
Incidental Tumor Tests (d)	P=0.023	P=0.084	P=0.038
Cochran-Armitage Trend Test (d)	P=0.012		
Fisher Exact Test (d)		P=0.048	P=0.013

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

	Control	620 ppm	1,250 ppm
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	13/50 (26%)	23/49 (47%)	27/50 (54%)
Adjusted Rates (b)	32.2%	61.4%	70.6%
Terminal Rates (c)	10/37 (27%)	14/28 (50%)	18/29 (62%)
Week of First Observation	70	30	60
Life Table Tests (d)	P<0.001	P=0.006	P<0.001
Incidental Tumor Tests (d)	P=0.003	P=0.028	P=0.005
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Test (d)		P=0.025	P=0.004
Thyroid: Follicular Cell Adenoma			
Overall Rates (a)	0/50 (0%)	0/47 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	9.1%
Terminal Rates (c)	0/37 (0%)	0/28 (0%)	2/29 (7%)
Week of First Observation			67
Life Table Tests (d)	P=0.030	(e)	P=0.093
Incidental Tumor Tests (d)	P=0.039	(e)	P=0.120
Cochran-Armitage Trend Test (d)	P=0.038		
Fisher Exact Test (d)		(e)	P=0.121
Harderian Gland: Papillary Adenoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.1%	0.0%	0.0%
Terminal Rates (c)	3/37 (8%)	0/28 (0%)	0/29 (0%)
Week of First Observation	104		
Life Table Tests (d)	P=0.059N	P=0.174N	P=0.167N
Incidental Tumor Tests (d)	P=0.059N	P=0.174N	P=0.167N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Harderian Gland: Papillary Adenoma or Cystadenoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	13.5%	7.1%	0.0%
Terminal Rates (c)	5/37 (14%)	2/28 (7%)	0/29 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.034N	P=0.340N	P=0.057N
Incidental Tumor Tests (d)	P=0.034N	P=0.340N	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.218N	P=0.028N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences 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 exact tests 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 reported because no tumors were observed in the 620-ppm and control groups.

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control	620 ppm	1,250 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	0.0%	10.3%	10.5%
Terminal Rates (c)	0/39 (0%)	4/39 (10%)	3/35 (9%)
Week of First Observation		104	74
Life Table Tests (d)	P=0.047	P=0.063	P=0.054
Incidental Tumor Tests (d)	P=0.050	P=0.063	P=0.066
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.059	P=0.059
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	2.6%	12.8%	16.1%
Terminal Rates (c)	1/39 (3%)	5/39 (13%)	5/35 (14%)
Week of First Observation	104	104	74
Life Table Tests (d)	P=0.034	P=0.103	P=0.045
Incidental Tumor Tests (d)	P=0.037	P=0.103	P=0.053
Cochran-Armitage Trend Test (d)	P=0.049		
Fisher Exact Test (d)		P=0.102	P=0.056
Hematopoietic System: Malignant Lymphoma, Undifferentiated Type			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	7.7%	0.0%	2.7%
Terminal Rates (c)	3/39 (8%)	0/39 (0%)	0/35 (0%)
Week of First Observation	104		102
Life Table Tests (d)	P=0.198N	P=0.121N	P=0.341N
Incidental Tumor Tests (d)	P=0.199N	P=0.121N	P=0.336N
Cochran-Armitage Trend Test (d)	P=0.178N		
Fisher Exact Test (d)		P=0.122N	P=0.309N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	9.1%	2.5%	5.7%
Terminal Rates (c)	2/39 (5%)	0/39 (0%)	2/35 (6%)
Week of First Observation	76	103	104
Life Table Tests (d)	P=0.273N	P=0.191N	P=0.380N
Incidental Tumor Tests (d)	P=0.222N	P=0.214N	P=0.306N
Cochran-Armitage Trend Test (d)	P=0.241N		
Fisher Exact Test (d)		P=0.181N	P=0.339N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	7.7%	4.5%	9.5%
Terminal Rates (c)	3/39 (8%)	0/39 (0%)	1/35 (3%)
Week of First Observation	104	69	74
Life Table Tests (d)	P=0.379	P=0.510N	P=0.456
Incidental Tumor Tests (d)	P=0.496	P=0.518N	P=0.533
Cochran-Armitage Trend Test (d)	P=0.416		
Fisher Exact Test (d)		P=0.500N	P=0.500
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	6/50 (12%)	12/50 (24%)	6/50 (12%)
Adjusted Rates (b)	15.4%	30.8%	16.4%
Terminal Rates (c)	6/39 (15%)	12/39 (31%)	5/35 (14%)
Week of First Observation	104	104	90
Life Table Tests (d)	P=0.465	P=0.091	P=0.544
Incidental Tumor Tests (d)	P=0.491	P=0.091	P=0.578
Cochran-Armitage Trend Test (d)	P=0.551N		
Fisher Exact Test (d)		P=0.096	P=0.620N

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

	Control	620 ppm	1,250 ppm
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	16/50 (32%)	15/50 (30%)	13/50 (26%)
Adjusted Rates (b)	38.6%	35.5%	31.8%
Terminal Rates (c)	14/39 (36%)	12/39 (31%)	8/35 (23%)
Week of First Observation	76	69	74
Life Table Tests (d)	P=0.409N	P=0.509N	P=0.448N
Incidental Tumor Tests (d)	P=0.298N	P=0.534N	P=0.339N
Cochran-Armitage Trend Test (d)	P=0.292N		
Fisher Exact Test (d)		P=0.500N	P=0.330N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.6%	8.1%
Terminal Rates (c)	0/39 (0%)	1/39 (3%)	2/35 (6%)
Week of First Observation		104	90
Life Table Tests (d)	P=0.051	P=0.500	P=0.105
Incidental Tumor Tests (d)	P=0.074	P=0.500	P=0.136
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	2/49 (4%)	3/50 (6%)
Adjusted Rates (b)	5.1%	5.1%	8.6%
Terminal Rates (c)	2/39 (5%)	2/39 (5%)	3/35 (9%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.360	P=0.695	P=0.450
Incidental Tumor Tests (d)	P=0.360	P=0.695	P=0.450
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test (d)		P=0.684	P=0.500
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	5/49 (10%)	4/50 (8%)
Adjusted Rates (b)	2.6%	12.4%	10.3%
Terminal Rates (c)	1/39 (3%)	4/39 (10%)	2/35 (6%)
Week of First Observation	104	97	87
Life Table Tests (d)	P=0.131	P=0.106	P=0.154
Incidental Tumor Tests (d)	P=0.183	P=0.090	P=0.215
Cochran-Armitage Trend Test (d)	P=0.161		
Fisher Exact Test (d)		P=0.098	P=0.181
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	7/49 (14%)	7/50 (14%)
Adjusted Rates (b)	7.7%	17.4%	18.5%
Terminal Rates (c)	3/39 (8%)	6/39 (15%)	5/35 (14%)
Week of First Observation	104	97	87
Life Table Tests (d)	P=0.100	P=0.161	P=0.123
Incidental Tumor Tests (d)	P=0.133	P=0.143	P=0.160
Cochran-Armitage Trend Test (d)	P=0.137		
Fisher Exact Test (d)		P=0.151	P=0.159
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	0/48 (0%)	0/50 (0%)
Adjusted Rates (b)	7.7%	0.0%	0.0%
Terminal Rates (c)	3/39 (8%)	0/38 (0%)	0/35 (0%)
Week of First Observation	104		
Life Table Tests (d)	P=0.044N	P=0.126N	P=0.141N
Incidental Tumor Tests (d)	P=0.044N	P=0.126N	P=0.141N
Cochran-Armitage Trend Test (d)	P=0.039N		
Fisher Exact Test (d)		P=0.129N	P=0.121N

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

	Control	620 ppm	1,250 ppm
Pituitary: Adenoma			
Overall Rates (a)	12/48 (25%)	4/47 (9%)	3/50 (6%)
Adjusted Rates (b)	30.8%	10.2%	8.6%
Terminal Rates (c)	12/39 (31%)	3/37 (8%)	3/35 (9%)
Week of First Observation	104	77	104
Life Table Tests (d)	P=0.009N	P=0.035N	P=0.019N
Incidental Tumor Tests (d)	P=0.008N	P=0.028N	P=0.019N
Cochran-Armitage Trend Test (d)	P=0.004N		
Fisher Exact Test (d)		P=0.029N	P=0.009N
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	13/48 (27%)	4/47 (9%)	3/50 (6%)
Adjusted Rates (b)	32.4%	10.2%	8.6%
Terminal Rates (c)	12/39 (31%)	3/37 (8%)	3/35 (9%)
Week of First Observation	91	77	104
Life Table Tests (d)	P=0.005N	P=0.022N	P=0.012N
Incidental Tumor Tests (d)	P=0.003N	P=0.021N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.017N	P=0.005N
Mammary Gland: Adenoma, Papillary Cystadenoma, or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	7.2%	2.9%
Terminal Rates (c)	0/39 (0%)	2/39 (5%)	1/35 (3%)
Week of First Observation		77	104
Life Table Tests (d)	P=0.356	P=0.121	P=0.478
Incidental Tumor Tests (d)	P=0.380	P=0.162	P=0.478
Cochran-Armitage Trend Test (d)	P=0.382		
Fisher Exact Test (d)		P=0.121	P=0.500
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	2/50 (4%)	1/48 (2%)	3/50 (6%)
Adjusted Rates (b)	5.1%	2.4%	6.5%
Terminal Rates (c)	2/39 (5%)	0/39 (0%)	0/35 (0%)
Week of First Observation	104	97	63
Life Table Tests (d)	P=0.379	P=0.497N	P=0.477
Incidental Tumor Tests (d)	P=0.491	P=0.546N	P=0.601
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.515N	P=0.500

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences 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 exact tests 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 B6C3F$_1$ MICE RECEIVING NO TREATMENT

TABLE F1. HISTORICAL INCIDENCE OF SALIVARY GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Sarcoma	Fibrosarcoma	Neurofibrosarcoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL (b)	1/1,689 (0.1%)	1/1,689 (0.1%)	1/1,689 (0.1%)
SD (c)	0.35%	0.37%	0.35%
Range (d)			
High	1/49	1/46	1/49
Low	0/89	0/89	0/89

(a) Data as of August 3, 1984, for studies of at least 104 weeks; no more than one tumor was observed in any control group.
(b) One mixed tumor, malignant, was also observed. The inclusion of this tumor does not affect the reported range.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F2. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	24/1,723 (1.4%)	13/1,723 (0.8%)	35/1,723 (2.0%)
SD (b)	1.82%	1.47%	2.02%
Range (c)			
High	3/49	3/50	3/49
Low	0/89	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F3. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Neoplastic Nodule	Carcinoma	Neoplastic Nodule or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	61/1,719 (3.5%)	12/1,719 (0.7%)	73/1,719 (4.2%)
SD (b)	3.34%	0.98%	3.45%
Range (c)			
High	6/49	1/49	7/49
Low	0/50	0/90	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F4. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 48/1,727 (2.8%)	(c) 57/1,727 (3.3%)	(b,c) 105/1,727 (6.1%)
SD (d)	3.75%	2.98%	4.62%
Range (e)			
High	8/50	5/50	8/50
Low	0/90	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Total includes one papillary adenoma and one cystadenoma.
(c) Total includes two squamous cell carcinomas, seven adenocarcinomas, and two sebaceous adenocarcinomas.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL ADENOMAS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.	
Overall Historical Incidence	
TOTAL	(b) 3/1,667 (0.2%)
SD (c)	0.59%
Range (d)	
High	1/47
Low	0/88

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) No acinar cell carcinomas have been observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF ADRENAL GLAND MEDULLARY TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
No 2-year studies by Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	338/1,702 (19.9%)	20/1,702 (1.2%)	358/1,702 (21.0%)
SD (b)	9.87%	1.49%	9.63%
Range (c)			
High	20/49	3/48	21/49
Low	2/50	0/50	3/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F7. HISTORICAL INCIDENCE OF TESTICULAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence of Interstitial Cell Tumors in Controls
No 2-year studies by Hazleton Laboratories America, Inc., are included in the historical data base.	
Overall Historical Incidence	
TOTAL	(b) 1,511/1,703 (88.7%)
SD (c)	7.79%
Range (d)	
High	49/50
Low	34/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes one malignant interstitial cell tumor
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F8. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Neoplastic Nodule	Carcinoma	Neoplastic Nodule or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	46/1,766 (2.6%)	3/1,766 (0.2%)	48/1,766 (2.7%)
SD (b)	2.77%	0.75%	2.99%
Range (c)			
High	4/50	2/50	5/50
Low	0/50	0/88	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F9. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	743/1,704 (43.6%)	62/1,704 (3.6%)	805/1,704 (47.2%)
SD (b)	11.71%	4.24%	11.01%
Range (c)			
High	33/47	8/49	33/47
Low	7/39	0/50	9/39

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F10. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 492/1,772 (27.8%)	(c) 45/1,772 (2.5%)	(b,c) 520/1,772 (29.3%)
SD (d)	9.61%	2.45%	9.29%
Range (e)			
High	24/49	4/49	24/49
Low	5/50	0/50	6/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Total includes 12 adenomas, 6 cystadenomas, 2 papillary cystadenomas, and 4 cystfibroadenomas.
(c) Total includes one squamous cell carcinoma, six papillary adenocarcinomas, and one papillary cystadenocarcinoma.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F11. HISTORICAL INCIDENCE OF UTERINE TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence of Endometrial Stromal Polyps in Controls
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.	
Overall Historical Incidence	
TOTAL	383/1,750 (21.9%)
SD (b)	7.57%
Range (c)	
High	18/49
Low	4/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F12. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	179/1,784 (10.0%)	377/1,784 (21.1%)	540/1,784 (30.3%)
SD (b)	7.36%	6.54%	8.04%
Range (c)			
High	(d) 22/50	16/50	(e) 29/50
Low	0/49	4/50	7/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest, 9/50
(e) Second highest, 20/50

TABLE F13. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 26/1,680 (1.5%)	2/1,680 (0.1%)	28/1,680 (1.7%)
SD (c)	2.06%	0.49%	2.09%
Range (d)			
High	3/42	1/47	3/42
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Total includes one papillary adenoma and one cystadenoma.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F14. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	215/1,780 (12.1%)	87/1,780 (4.9%)	296/1,780 (16.6%)
SD (b)	6.80%	4.06%	8.22%
Range (c)			
High	14/50	8/48	17/50
Low	1/50	0/50	1/49

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F15. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	87/1,777 (4.9%)	36/1,777 (2.0%)	122/1,777 (6.9%)
SD (b)	3.86%	1.98%	4.44%
Range (c)			
High	7/50	3/50	8/50
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F16. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at Hazleton Laboratories America, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 133/1,542 (8.6%)	(c) 7/1,542 (0.5%)	(b,c) 140/1,542 (9.1%)
SD (d)	8.99%	1.06%	8.73%
Range (e)			
High	12/40	2/44	12/40
Low	0/46	0/49	0/46

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes all adenomas diagnosed as NOS, chromophobe, acidophil, or basophil
(c) Includes adenocarcinomas, NOS, and carcinomas diagnosed as NOS or chromophobe
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

GENETIC TOXICOLOGY OF CHLORENDIC ACID

TABLE G1. MUTAGENICITY OF CHLORENDIC ACID IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	102 ± 3.5	135 ± 2.2	134 ± 2.0
	100	98 ± 5.0	136 ± 11.3	151 ± 8.7
	333	106 ± 10.1	140 ± 13.3	153 ± 6.4
	1,000	104 ± 6.4	139 ± 2.6	128 ± 0.9
	3,333	92 ± 7.0	137 ± 5.9	134 ± 4.9
	7,690	91 ± 1.2	172 ± 13.3	141 ± 3.4
TA1535	0	10 ± 0.9	9 ± 2.3	13 ± 2.1
	100	10 ± 4.4	11 ± 1.5	13 ± 0.9
	333	13 ± 5.4	10 ± 2.1	12 ± 0.3
	1,000	8 ± 1.8	12 ± 1.5	10 ± 1.2
	3,333	10 ± 0.9	12 ± 3.8	11 ± 0.6
	7,690	10 ± 4.7	9 ± 2.0	13 ± 0.7
TA1537	0	3 ± 0.3	4 ± 1.8	5 ± 1.2
	100	3 ± 1.5	5 ± 1.0	5 ± 1.0
	333	4 ± 1.2	5 ± 1.2	6 ± 0.9
	1,000	4 ± 1.5	3 ± 0.7	6 ± 0.9
	3,333	3 ± 0.7	5 ± 1.2	6 ± 0.9
	7,690	Toxic	4 ± 0.9	4 ± 1.0
TA98	0	20 ± 3.3	26 ± 4.2	56 ± 4.2
	100	15 ± 3.2	24 ± 2.3	70 ± 8.3
	333	15 ± 2.6	31 ± 5.5	61 ± 6.6
	1,000	14 ± 2.0	27 ± 1.9	63 ± 1.7
	3,333	20 ± 5.6	35 ± 2.4	70 ± 10.9
	7,690	13 ± 2.6	29 ± 5.9	63 ± 13.2

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (dimethyl sulfoxide) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

TABLE G2. MUTAGENICITY OF CHLORENDIC ACID IN L5178Y MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO					
	1%	118	109	16	36
		134	98	15	46
		112	114	16	33
		75	105	13	24
Methylmethane-sulfonate					
	15	520	69	34	253
		628	60	33	347
Chlorendic acid					
	1,300	96	94	66	34
		109	98	71	37
	1,400	113	119	76	32
		139	105	49	44
	1,500	121	93	69	43
		131	117	69	37
	1,600	116	91	75	43
		113	113	73	33
	1,700	520	55	4	315
		598	77	6	258

(a) Experiments were performed twice, and all doses were tested in duplicate, except the solvent control (dimethyl sulfoxide), which was tested in triplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C . After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

APPENDIX H

CHEMICAL CHARACTERIZATION OF

CHLORENDIC ACID

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Chlorendic Acid Performed by the Analytical Chemistry Laboratory

	Determined	Literature values
A. Lot No. 6287		
1. Physical properties		
a. Appearance:	White microcrystalline powder	
b. Melting point:	238° C (open capillary, Büchi mp/bp apparatus). Endotherm, 205°-217° C, with shoulder at 197°-205° C; small endotherm, 245°-247° C (Dupont 900 DTA)	208°-210° C (sealed tube). Loses water, melts as the anhydride at 230°-235° C
2. Spectral data		
a. Infrared		
Instrument:	Beckman IR-12	
Phase:	1.5% Potassium bromide pellet	
Results:	See Figure 5	Consistent with literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Methanol	
Results:	No absorbance from 800-350 nm. No maximum from 350-230 nm, but an increase in the absorbance toward the solvent cutoff.	No literature reference found. Spectrum consistent with the structure.

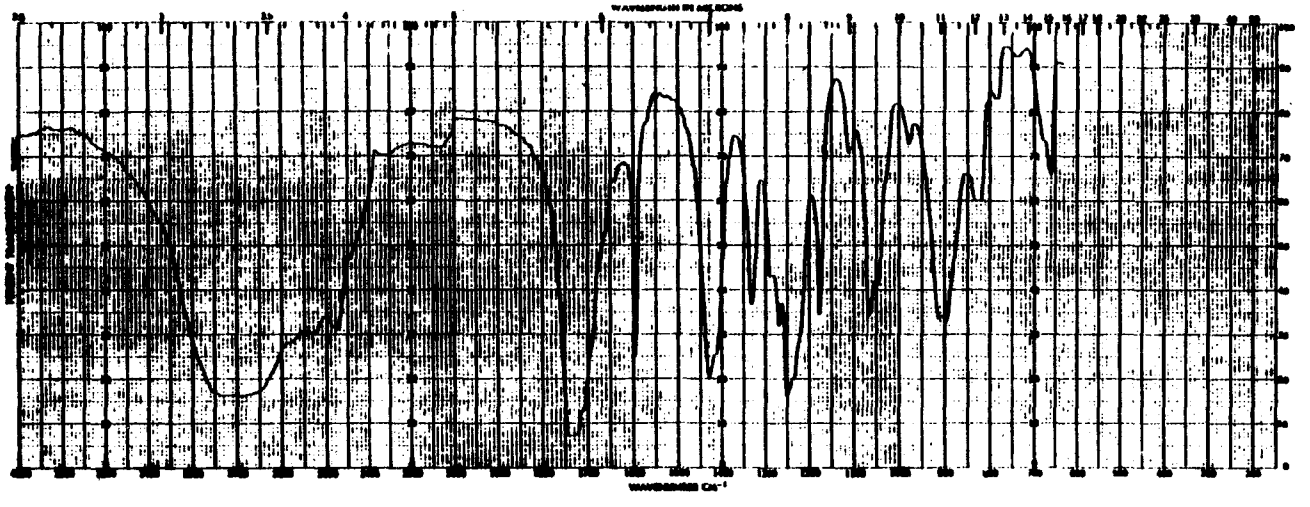

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF CHLORENDIC ACID (LOT NO. 6287)

	Determined	Literature values
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Deuterated dimethyl sulfoxide with internal tetramethylsilane	
Assignments:	See Figure 6	Consistent with literature spectrum. (Sadtler Standard Spectra)
Chemical shift (δ):	a s, 4.02 ppm b broad singlet, 12.70 ppm	
Integration ratios:	a 2.00 b 1.54	
3. Titration:	Titration of two carboxylic acid groups with 0.1N sodium hydroxide, 99.7% ± 0.3(δ)%	
4. Water analysis (Karl Fischer):	0.95% ± 0.04(δ)%	

5. Elemental analysis

Element	C	H	Cl
Theory (T)	27.80	1.04	54.70
Determined (D)	27.35 27.41	0.97 0.99	55.55 55.69
Percent D/T	98.49	94.23	101.68

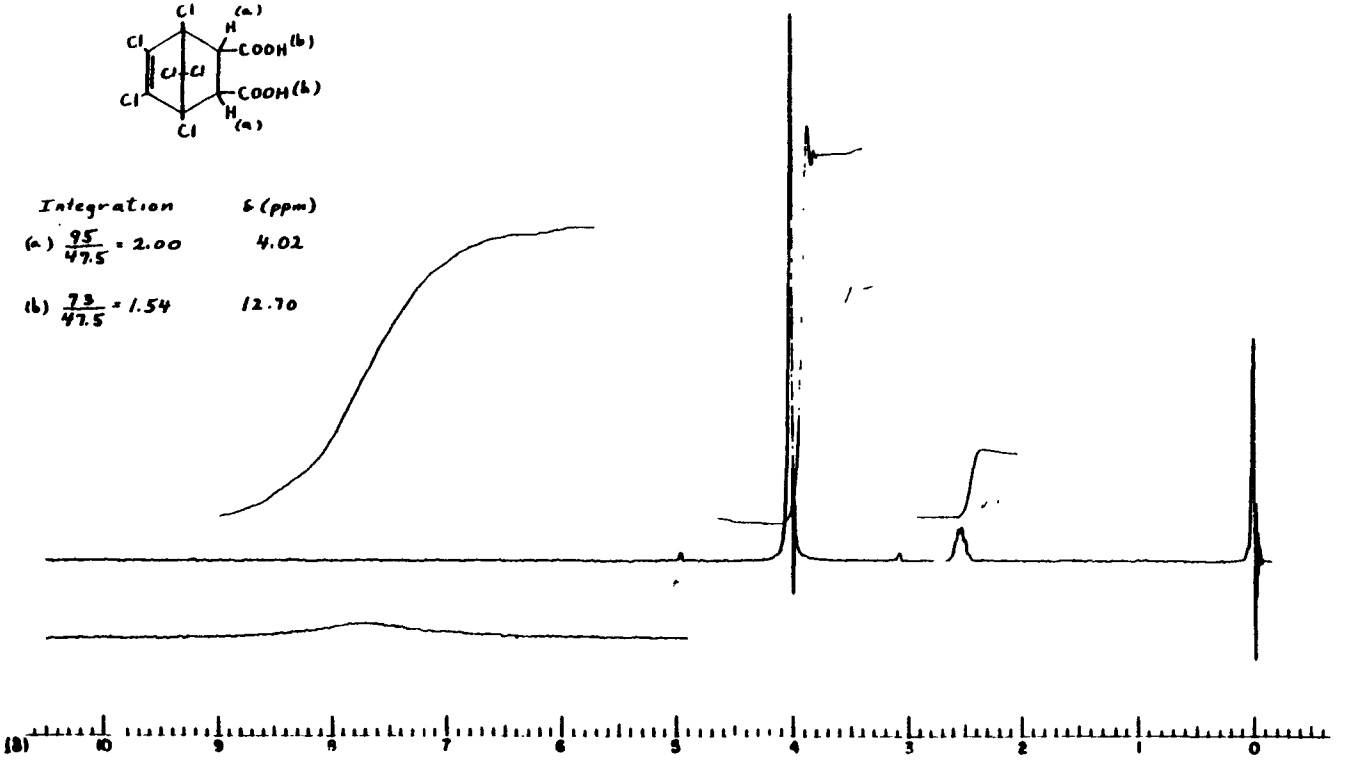

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORENDIC ACID (LOT NO. 6287)

6. **Chromatographic analysis**

a. **Thin-layer chromatography**

Plates: Silica Gel 60 F-254
Reference standard: 2,4,5-Trichlorophenoxypropionic acid (50 µg) (10 mg/ml methanol)
Amount spotted: 100 and 300 µg (10 mg/ml methanol)
Visualization: 254 nm and methyl red acid indicator

System 1: Methanol:acetic acid (98:2)

R_f: 0.63 (origin)
R_{st}: 0.86

System 2: Ethyl acetate:formic acid (98:2)

R_f: 0.67 (ultraviolet and methyl red positive)
R_{st}: 0.95

b. **Gas chromatography**

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 270° C
Carrier gas: Nitrogen, 70 ml/min
Oven temperature program: 50° C for 5 minutes, then 50° to 250° C at 10° C/minute

System 1

Column: 3% SP-2100 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Samples injected: Solutions (3 µl) of 1% and 0.5% chlorendic acid in chloroform to quantitate impurities and check for overloading

Results: Major peak and one impurity after the major peak with a relative area of 0.03%

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	19.8	1.00	100
2	22.8	1.15	0.03

System 2

Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass
Samples injected: Solutions (4 µl) of 1% and 0.5% chlorendic acid in dichloromethane to quantitate impurities and check for overloading

Results: Single homogeneous peak with a retention time of 23.4 minutes

7. **Conclusions:** The results of elemental analysis for carbon was slightly low, for chlorine slightly high, and for hydrogen in agreement with the theoretical value. Titration of two carboxylic acid groups with sodium hydroxide indicated a purity of 99.7% ± 0.3(δ)%. Karl Fischer analysis indicated 0.95% water content. Thin-layer chromatography by two systems indicated a single major component. Gas chromatography with a 3% SP-2100 column indicated one impurity after the major peak with a relative area of 0.03%. A second gas chromatographic system with 3% OV-17 indicated a single homogeneous peak. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of chlorendic acid.

	Determined	Literature values
B. Lot no. 6745		
1. Appearance:	White microcrystalline powder	
2. Spectral data		
a. Infrared		
Instrument:	Perkin-Elmer 283	
Phase:	1% in potassium bromide pellet	
Results:	See Figure 7	Consistent with literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 219	
Solvent:	Methanol	
Results:	No absorbance from 800-350 nm at 10 mg/ml. No maximum from 350 to 202 nm, but an increase in absorbance toward the solvent cutoff at a concentration of 0.0001 mg/ml	No literature reference found. Spectrum consistent with structure.
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Deuterated dimethyl sulfoxide with internal tetramethylsilane	
Assignments:	See Figure 8	Consistent with literature spectrum (Sadtler Standard Spectra)
Chemical shift (δ):	a s, 4.00 ppm b broad singlet, 12.17 ppm	
Integration ratios:	a 2.00 b 1.72	

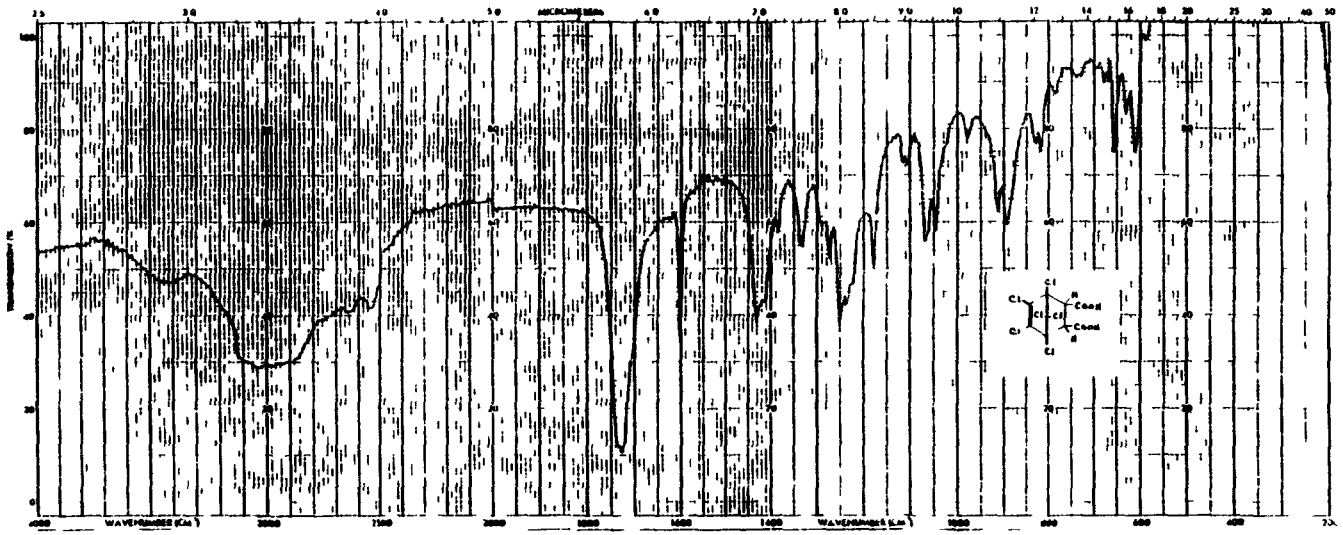

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF CHLORENDIC ACID (LOT NO. 6745)

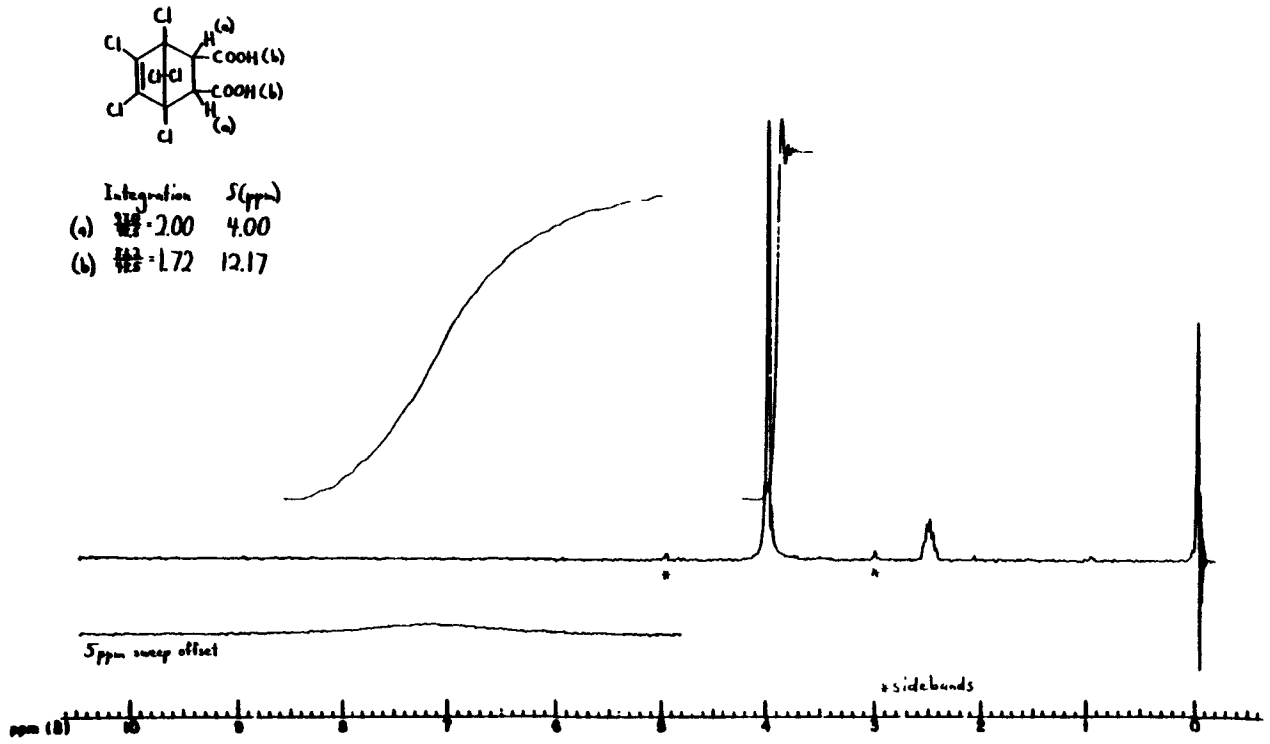

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORENDIC ACID (LOT NO. 6745)

3. **Titration:** Titration of two carboxylic acid groups in deionized water with 0.1 N sodium hydroxide; monitored potentiometrically with a combination pH/mV electrode, 98.8% ± 0.2(δ)%

4. **Water analysis (Karl Fischer):** 0.05% ± 0.01(δ)%

5. **Elemental analysis**

Element	C	H	Cl
Theory (T)	27.80	1.04	54.70
Determined (D)	27.73	1.15	54.46
	27.80	1.16	54.34
Percent D/T	99.86	111.5	99.45

6. **Chromatographic analysis**

   a. **Thin-layer chromatography**

   Plates: Silica Gel 60-F254, 0.25-mm layer
   Reference standard: 2,4,5-Trichlorophenoxypropionic acid, 10 µg (1 µl of a 10 µg/µl solution in methanol)
   Amount spotted: 100 and 300 µg (10 and 30 µl of a 10 µg/µl solution in methanol)
   Visualization: 254 nm and methyl red acid indicator

   System 1: Methanol:acetic acid (98:2)

Spot Intensity	R_f	R_{st}
Major	0.60	0.87
Slight trace (a)	0.43	0.62
Reference	0.69	--

   System 2: Ethyl acetate:formic acid (98:2)

Spot Intensity	R_f	R_{st}
Major	0.49	0.83
Trace (a)	Origin	--
Reference	0.59	--

(a) This impurity spot was not detected until the plates were resprayed 2 days after development.

b. Gas chromatography

Instrument: Varian 3700
Detector: Flame ionization
Detector temperature: 270° C
Carrier gas: Nitrogen, 70 ml/min
Oven temperature program: 50° C for 5 minutes, then 50° to 250° C at 10° C/minute

System 1

Column: 3% SP-2100 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Inlet temperature: 200° C
Samples injected: A 5.0% solution (4 µl) of chlorendic acid in chloroform to quantitate impurities and solutions of 1.0% and 0.5% chlorendic acid in chloroform to quantitate the major peak and check for detector overload

Results: Major peak and one impurity after the major peak with a relative area of 0.02%

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	20.1	1.00	100
2	22.6	1.12	0.02

System 2

Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass
Inlet temperature: 210° C
Samples injected: Solutions (4 µl) of 1.0% and 0.5% chlorendic acid in dichloromethane to quantitate impurities and check for detector overload

Results: Major peak and one impurity before the major peak with a relative area of 0.02%

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	22.3	0.97	0.02
2	23.0	1.00	100

7. **Conclusions:** The results of elemental analysis for carbon, hydrogen, and chlorine were in agreement with the theoretical values. Karl Fischer analysis indicated 0.05% ± 0.01(δ)% water, compared with 0.95% ± 0.04(δ)% for lot no. 6287. Titration of two carboxylic acid groups with sodium hydroxide indicated a purity of 98.8% ± 0.2(δ)%; lot no. 6287 indicated a purity of 99.7% ± 0.3(δ)%. Thin-layer chromatography indicated a single major spot in each of two systems when developed in the same manner as lot no. 6287, which gave the same results. Treatment of the plates from lot no. 6745 2 days after development indicated a slight trace impurity on one system and a trace impurity on the second system. Gas chromatography with a 3% SP-2100 column indicated one impurity after the major peak with a relative area of 0.02%. One impurity was reported for lot no. 6287 on this column, after the major peak, with a relative area of 0.03%. A second gas chromatographic system with a 3% OV-17 column indicated one impurity before the major peak with an area of 0.02% relative to the major peak area. For lot no. 6287 on this system, there was a single homogeneous peak. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of chlorendic acid and with the spectra obtained for lot no. 6287.

   The sample was identified as chlorendic acid by spectroscopy. Water content was 0.05% ± 0.01(δ)% and titration indicated a purity of 98.8% ± 0.2(δ)%. Gas chromatography by two systems each indicated one impurity with a relative area of 0.02%. This lot is comparable in purity to lot no. 6287.

II. Chemical Stability Study Performed by the Analytical Chemistry Laboratory

A. Sample preparation and storage: Samples were stored for 2 weeks at temperatures of −20°, 5°, 25°, and 60° C in glass tubes with Teflon-lined caps.

B. Analytical method: Samples from each storage temperature were analyzed by the following gas chromatographic system. The sample peak areas were compared with the internal standard peak areas, and the percent of sample recovery from each storage temperature was compared with that for the −20° C sample.

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 270° C
Carrier gas: Nitrogen, 70 ml/min
Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 220° C, isothermal
Samples injected: Solutions of 0.5% chlorendic acid from each storage temperature in chloroform containing 0.1% docosane as an internal standard
Retention times: Chlorendic acid---4.5 minutes
Internal standard (docosane)--2.9 minutes

C. Results

Storage Temperature	Percent Purity
−20° C	100.0 ± 1.5(δ)
5° C	101.1 ± 1.5(δ)
25° C	101.8 ± 1.5(δ)
60° C	100.7 ± 1.5(δ)

D. Conclusion: Chlorendic acid is stable as the bulk chemical, within the limits of experimental error, when stored for 2 weeks at temperatures up to 60° C. This indicates, by extrapolation, that storage of chlorendic acid for up to 24 weeks at room temperature (25° C) would result in no significant decomposition of the material.

III. Chemical Stability Study at the Study Laboratory

A. Analytical method

1. **Purity determination:** Duplicate samples were titrated against sodium hydroxide containing 100 mg of phenolphthalein.

2. **Identity determination:** The infrared absorption spectra of the sample was obtained as potassium bromide disks with a Perkin-Elmer 597.

B. Results

1. **Purity**

Date of Analysis	Lot No.	Percent Chlorendic Acid Reference	Bulk
03/07/79	6287	97.52	--
05/17/79	6287	97.15	97.22
09/11/79	6287	97.39	97.24
01/10/80	6287	97.81	97.42
05/15/80	6287	97.97	--
05/15/80	6745	98.64	
09/24/80	6745	97.69	97.88
01/16/81	6745	97.35	97.70
05/81	6745	96.95	97.89
09/25/81	6745	97.50	97.47
01/27/82	6745	97.76	97.71
05/21/82	6745	97.81	97.81
07/06/82	6745	97.60	97.64

2. **Identity:** The infrared spectra were consistent with that expected for the structure.

C. Conclusion: No notable degradation occurred during the studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Two-week Stability in Feed

A. Preparation procedure

1. **Premix:** Chlorendic acid (1.500 g) was mixed by spatula with about 5 g of feed in a 600-ml beaker. More feed was added in 10- to 20-g amounts, with mixing between additions, until the total weight of the premix was 200 g. The concentration of chlorendic acid in the premix was 7,500 ppm.

2. **Bulk mixing:** A 600-g quantity of feed was layered evenly in the bottom of the Patterson-Kelly® Twin-shell, 4-quart blender with intensifier bar; then the 200-g premix was added in roughly equal amounts to both sides of the blender. 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 then the feed was added to the blender. After an additional 600 g of feed was layered over the premix, the blender ports were sealed.

   Blending was conducted with the intensifier bar turned on for the first 5 minutes and turned off for the next 10 minutes of mixing. At the end of the 15-minute mixing period, approximately 75 g of the blend was sampled from the upper left and right shells and from the bottom discharge port for homogeneity determination, and the remaining feed blend was discharged into a large beaker. The mix was turned several times in the beaker with a spatula; then twelve 20-g samples were weighed into 200-ml centrifuge bottles and sealed with screw caps. Bottles were randomly divided into four sets of three bottles each and were stored for 2 weeks at −20°, 5°, 25°, or 45° C.

B. Analytical procedure

1. **Special reagents:** Extracting solution--Reagent-grade hydrochloric acid in reagent grade acetonitrile (5:495).
   Boron trifluoride-methanol reagent--14% (weight/volume) solution (Pierce Chemical Co., catalog no. 49370).
   Hexane--Pesticide quality.
   Internal standard solution--25 mg of aldrin dissolved in 200 ml of hexane; then 2 ml was further diluted to 500 ml with hexane. Final concentration was 0.50 µg/ml.
   Sodium chloride solution--22% (weight/weight): 22 g of reagent-grade sodium chloride was dissolved in 78 ml of water.
   Chlorendic acid matrix standard solution--100 mg of chlorendic acid was dissolved in extracting solution and diluted to 50 ml. A 5-ml aliquot of this solution was further diluted to 50 ml in blank feed extract, prepared by extracting 20 g of feed with 100 ml of solvent as for samples.

2. **Extraction and analysis:** Samples (20.0 g) and spiked feeds for recovery determinations were extracted with 100 ml of 1% hydrochloric acid in methanol by shaking for 15 minutes on a mechanical shaker. Solids were allowed to settle for a few minutes; then 2-ml aliquots of each extract were pipetted into 16 × 100 mm culture tubes equipped with Teflon®-lined screw caps.

   The sample aliquots were evaporated to dryness by warming the tubes in a 60° C water bath under a gentle stream of nitrogen. When the samples were completely dry, 3 ml of boron trifluoride reagent was added to each tube; then the tubes were tightly sealed and heated in a 70° C oven for 40-48 hours.

The reacted solutions were transferred to 50-ml volumetric flasks with methanol and diluted to 50 ml. After a thorough mixing, 2-ml aliquots were pipetted into 30-ml septum vials containing 5 ml of sodium chloride solution and 20 ml of internal standard solution. The vials were immediately sealed and shaken vigorously for 1 minute. The dimethyl chlorendate content of the upper hexane layer was determined by the gas chromatographic system described below.

Instrument: Varian 3700 eqipped with autosampler and CDS-111 integrator
Detector: Electron capture, ^{63}Ni
Column: 10% SP-2100 on 100/120 Supelcoport, 1.8 m × 2 mm ID, glass
Detector temperature: 280° C
Injector temperature: 250° C
Oven temperature: 221° C, isothermal
Volume injected: 4 µl
Carrier gas: Nitrogen
Retention times: Dimethyl chlorendate--3.8 minutes
Aldrin--3.0 minutes

3. **Quality control:** All analyses were performed by making duplicate injections of triplicate sample extracts and were all related to an internal standard. Results were calculated from electronically measured peak areas by comparison of samples with matrix standards run in triplicate.

4. **Results**

Storage Temperature	Chlorendic Acid Found in Feed (a) (ppm)	Percent Stability (−20° C = 100%) (b)
−20° C	1,040	100 ± 1
5° C	970	93 ± 2
25° C	960	92 ± 4
45° C	930	89 ± 3

(a) Results corrected for a zero-time spiked recovery yield of 97.1% ± 0.8%. The target concentration of chlorendic acid in feed was 1,000 ppm. Values are the mean of three determinations.
(b) Error values are maximum deviations from the main values.

5. **Conclusion:** Chlorendic acid blended into feed at a concentration of 1,000 ppm exhibited no loss of stability at −20° C. Recovery of the chemical from feed stored 2 weeks at 5°, 25°, or 45° C was 93%, 92%, or 89% of the −20° C sample, respectively.

II. Homogeneity Analysis

A. Preparation and analysis: Samples were prepared and analyzed as described in Section I.

B. Quality assurance: Analyses were performed by making duplicate injections of triplicate sample extracts and were related to an internal standard incorporated into each sample solution. Results were corrected for a zero-time spiked recovery of chlorendic acid from feed, determined in triplicate along with the samples. Spiked recovery determinations were prepared as dry spikes (20 g feed + 20 mg chemical), and all results were calculated against a matrix standard solution analyzed along with the samples. Linearity of the detector response was evaluated with derivatized chlorendic acid at concentrations of 1.6, 0.8, and 0.4 µg/ml. The linear coefficient was 0.99732.

C. Results

15-Minute Blend Sampling Location	Chlorendic Acid Found in Feed (a) (ppm)	Percent Recovery (found/target) (b)
Right shell	1,012 ±13	101.2 ± 1.3
Left shell	978 ±9	97.8 ± 0.9
Bottom port	1,006 ±15	100.6 ± 1.5

(a) Results corrected for a zero-time spiked recovery yield of 97.1% ± 0.8%. The target concentration of chlorendic acid in feed was 1,000 ppm. Values are the mean of three determinations.
(b) Error values are maximum deviations from the mean values and represent the sum of the analytical errors plus feed blend variations.

D. Conclusion: Chlorendic acid was blended into feed at a concentration of 1,000 ppm with a variability of ±15 ppm from the mean concentration of the blend.

III. Seven-Day Stability at Room Temperature

A. Sample mixing and storage: Dosed feed samples were prepared in triplicate on three different days such that when they were all analyzed on the 7th day of the study, they represented samples that had been stored 2, 4, and 7 days.

On each mixing day, samples were prepared by blending together 50.0 g of feed with 50-mg quantities of chlorendic acid, weighed to the nearest 0.1 mg, in 1,000-ml Erlenmeyer flasks. After the samples were mixed by rotating the flasks at an angle for a few moments, they were stored at room temperature in the dark until they were analyzed.

B. Extraction and analysis: The analytical method used in this study was the same as was used in the 2-week stability study cited in I.B., except that methylation was accomplished with diazomethane instead of boron trifluoride.

Special reagents

Ethereal diazomethane solution--Reagent-grade potassium hydroxide (2.3 g) was dissolved in 2.3 ml of water in a 50-ml Erlenmeyer flask equipped with a Teflon®-lined screw cap. The solution was cooled to room temperature, and 25 ml of ethyl ether was added. The flask was further cooled in an ice bath; then 1.5 g of N-methyl-N'-nitro-N-nitrosoguanidine (Aldrich no. 12,994-1) was added in small portions for a few minutes. The flask was capped and shaken vigorously after each addition. The yellow ether layer was decanted into a 30-ml septum vial containing a few potassium hydroxide pellets, and the vial was sealed.

Hydrochloric acid-ethyl acetate solution--5 ml of concentrated hydrochloric acid was carefully added and mixed with 5 ml of ethyl acetate.

Samples (50 g in 1-liter Erlenmyer flasks) were extracted with 500 ml of extracting solvent by being shaken for 15 minutes on a mechanical shaker. The feed solids were allowed to settle for a few minutes; then 2-ml aliquots of each extract and the matrix standard were pipetted into individual 16 × 100 mm screw-cap culture tubes (Corning no. 9826).

The aliquots were evaporated to dryness under a stream of nitrogen while being warmed in a 60° C water bath. When the aliquots were dry, 0.5 ml of methanol and one drop of hydrochloric acid-ethyl acetate solution were added to each tube to dissolve the residue. A 2-ml volume of ethereal diazomethane was then added with mixing, and the solutions were allowed to react for 5 minutes, after which the tubes were placed in a 30° C water bath, and the solvent was evaporated under nitrogen to a volume just under 0.5 ml (to eliminate the ether and excess diazomethane).

The concentrated solutions were diluted with methanol to about 8 ml and then transferred to 50-ml volumetric flasks and diluted to volume with methanol. After mixing, 2-ml aliquots were transferred to 30-ml septum vials containing 5 ml of 22% sodium chloride solution and 20 ml of internal standard solution. The vials were sealed and shaken 1 minute; then the dimethyl chlorendate content of the upper hexane layer was determined by the gas chromatographic system described below.

Instrument: Varian 3700 equipped with autosampler and CDS-111 integrator
Column: 10% SP-2100 on 100/120 mesh Supelcoport, 2 mm ID × 1.8 m, glass silanized
Detector: Electron capture, ^{63}Ni
Detector temperature: 280° C
Injector temperature: 250° C
Oven temperature: 221° C, isothermal
Volume injected: 3 µl
Carrier gas: Nitrogen
Retention Times: Dimethyl chlorendate--4.3 minutes
Aldrin--3.5 minutes

C. **Quality control:** Analyses were performed in a random order by making duplicate injections on triplicate sample extracts and were related to an internal standard incorporated into each sample solution. Results were corrected for a zero-time spiked recovery of chlorendic acid from feed, determined in triplicate along with the samples.

D. Results

Storage Duration at Room Temperature	Chlorendic Acid Found (a) (ppm)	Average Percent Concentration Ratio (found/target) (b)
2 days	1,008 ± 5(b)	100.8 ± 0.5
4 days	945 ± 11	94.5 ± 1.1
7 days	973 ± 15	97.3 ± 1.5

(a) Corrected for a zero-time spiked recovery yield of 98.3% ± 1.1% The target concentration of chlorendic acid in feed was 1,000 ppm. Values are the mean of three determinations.
(b) Error values are the maximum deviation from the mean.

E. Discussion: The stability results reported in Section I.B.4 showed some loss of chlorendic acid with time but did not follow a typical temperature profile chemical degradation pattern. A similar pattern was apparent in this study. The triplicate analysis values determined at each sampling time were in close agreement with each other; however, their means were variable and did not follow a well-defined degradation curve.

Based on its structure, chlorendic acid was not expected to be unstable under these mild storage conditions. However, even though a strongly polar solvent (1% hydrochloric acid in acetonitrile) was used to extract the samples, there was a clear tendency to lower recovery of the chemical from feed with time. This phenomenon possibly may be related to some irreversible binding with feed components rather than degradation, which renders the chemical incompletely extractable by solvents after a period of storage.

The data from both studies indicate that quantitative recovery of chlorendic acid from the feed vehicle can only be obtained after 2 days of storage at room temperature or 2 weeks at −20° C.

F. Conclusions: The mean recovery of chlorendic acid from feed dosed at 1,000 ppm was 97.3% ± 1.5% after 7 days of room temperature storage in the dark. The results from this study and from the 2-week variable temperature study (Section I) suggest that the chemical is probably not degrading but is possibly binding with feed ingredients during storage which renders it incompletely extractable even by strongly polar solvents. Quantitative recovery values were obtained only from samples of the mix stored for 2 days at room temperature or 2 weeks at −20° C.

APPENDIX J

METHODS OF ANALYSIS OF FORMULATED DIETS

APPENDIX J. METHODS OF ANALYSIS

I. Study Laboratory

Two different derivatization methods were used for the analysis of chlorendic acid. Both of these methods are described below.

A. Procedure (method of 6/9/80): Individual 10-g feed samples were extracted in 50-ml centrifuge tubes with 50 ml of 1% (v/v) aqueous hydrochloric acid in methanol. The samples were shaken for 15 minutes on a mechanical shaker and centrifuged for 15 minutes at 25,000 rpm. Aliquots of 2 ml each were transferred into 5-ml test tubes and dried in a 60° C sand bath. When the samples were totally dry, 3 ml of boron trifluoride reagent was delivered to each tube and sealed tightly. The samples were heated in an oven at 70° C for 48 hours.

The derivatized samples were transferred individually to 50-ml volumetric flasks with methanol and diluted to the mark; further dilutions of about 1:25 with methanol were made depending on the concentration. Aliquots of 0.5 ml were pipetted into 100-ml septum vials containing 5 ml of sodium chloride (22% w/w solution prepared by dissolving 22 g in 78 ml of water) and 20 ml of an internal standard (0.05 µg/ml of aldrin in hexane) sealed and shaken for 1 minute before 2-µl portions of the hexane layer were injected into the gas chromatograph.

All samples and standards were processed under the following conditions:

Instrument: Perkin-Elmer Sigma II, equipped with electron capture detector
Column: 3% OV-17 on 100/120 Gas Chrom Q 1.8 m × 4 mm ID, glass
Detection: Electron capture, ^{63}Ni
Column temperature: 221° C
Detector temperature: 350° C
Injector temperature: 240° C
Carrier gas: Nitrogen, 70 ml/minute
Injection volume: 2-4 µl
Detection limit: 0.25 ng
Retention times: Dimethyl chlorendate--9.6 minutes
Aldrin--3.0 minutes for internal standard

B. Procedure (method of 12/5/80): Ten-gram feed samples were weighed in 50-ml centrifuge tubes, in duplicate. Fifty milliliters of 1% (v/v) aqueous hydrochloric acid in methanol was added, and the entire contents were shaken for 15 minutes on a mechanical shaker and centrifuged for 15 minutes at 25,000 rpm. Aliquots (2 ml) were transferred into 5-ml test tubes and dried under a stream of nitrogen in a 60° C sand bath. Three milliliters of boron trifluoride reagent was added, the test tubes were tightly sealed, and the tubes were heated in an oven at 70° C for 48 hours. The samples were transferred to a 50-ml (low concentration) or a 100-ml (high concentration) volumetric flask and diluted to mark. Aliquots (0.5 ml) were pipetted into 100-ml septum vials containing 5 ml of sodium chloride (22% w/w solution) and 20 ml of 0.5 µg/ml aldrin in hexane. The vials were sealed and shaken for 1 minute.

Gas chromatographic conditions were the same as described in I.A.

II. Analytical Chemistry Laboratory

A. Boron trifluoride procedure

1. Special reagents

Extracting solution--Prepared by mixing 10 ml of reagent-grade hydrochloric acid with approximately 700 ml reagent-grade acetonitrile and diluting to 1 liter with acetonitrile.
Boron trifluoride-methanol reagent, 14% (w/v)--Available from Pierce Chemical Co., catalog no. 49370. Stored tightly stoppered at 5° C and discarded when 2 months old.
Sodium chloride solution--22 g reagent-grade sodium chloride dissolved in 78 ml of deionized water

2. **Preparation of spiked feed standards:** Two standard solutions of chlorendic acid were prepared independently in extracting solution. Aliquots (20 ml) of the six standard solutions were pipetted into individual 200-ml centrifuge bottles containing 10 g of undosed feed to make spiked feed standards bracketing the specified concentration range of the referee sample. One 200-ml centrifuge bottle containing 10 g of undosed feed was treated with 20 ml of extracting solution for use as a blank. The spiked feed standards and the feed blank were used immediately in the analysis procedure described below.

3. **Preparation of dosed feed sample:** Triplicate weights of the dosed feed sample (approximately 10 g weighed to the nearest 0.01 g) were transferred to individual 200-ml centrifuge bottles and treated with 20 ml of extracting solution. The samples were analyzed immediately by the procedure described below.

4. **Analysis:** Extracting solution (40 ml) was pipetted into each blank, standard, and dosed feed sample bottle, and the bottles were shaken at maximum stroke for 20 minutes on a wrist-action shaker. After being centrifuged for 10 minutes, 2-ml aliquots of the extracts were pipetted into individual 6-ml septum vials and evaporated to dryness under a gentle stream of nitrogen. Boron triflouride reagent (3 ml) was added to each vial; the vials were then sealed, mixed on a vortex mixer, and heated in a 70° C oven for 40 hours.

   The reacted solutions were cooled, quantitatively transferred to 100-ml volumetric flasks, and diluted to volume with methanol. After being mixed thoroughly, 1-ml aliquots were pipetted into 30-ml septum vials containing 5 ml of sodium chloride solution and 20 ml of internal standard solution (aldrin in pesticide-quality hexane, 0.108 µg/ml). The vials were sealed and shaken vigorously for 1 minute. When the layers separated, the dimethyl chlorendate content of the upper hexane layer was determined by the gas chromatographic system described below.

Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
Column: 10% SP-2100 on 100/120 mesh Supelcoport 1.8 m × 2 mm ID, glass, silanized
Oven temperature: 220° C, isothermal
Detector temperature: 280° C
Inlet temperature: 250° C
Carrier gas: Nitrogen, 30 ml/minute
Injection volume: 4 µl
Retention times: Dimethyl chlorendate--6.0 minutes
Aldrin--5.0 minutes for internal standard

B. Diazomethane procedure

1. Special reagents

Sodium chloride solution, 22% (w/w)--22 g of reagent-grade sodium chloride was in 78 ml of water.
Ethereal diazomethane solution--Reagent-grade potassium hydroxide (2.3 g) was dissolved in 2.3 ml of water in a 50-ml Erlenmeyer flask equipped with a Teflon®-lined screw cap. The solution was cooled to room temperature, and 25 ml of ethyl ether was added. The flask was further cooled in an ice bath; then 1.5 g of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (Aldrich no. 12,994-1) was added in small portions over a period of a few minutes. The flask was capped and shaken vigorously after each addition. The yellow ether layer was decanted into a 30-ml septum vial containing a few potassium hydroxide pellets, and the vial was sealed with a Teflon®-lined septum.
Hydrochloric acid-ethyl acetate solution--5 ml of concentrated hydrochloric acid was carefully added and mixed with 5 ml of ethyl acetate.

2. Analysis: Extracts of the same spiked feed standards, dosed feed samples, and blank feed sample prepared for the boron trifluoride method were used for this analysis. Aliquots (2 ml) of the extracts were pipetted into individual 10-ml septum vials and evaporated to dryness under a gentle stream of nitrogen.

The residues were dissolved in 0.5 ml of methanol containing one drop of hydrochloric acid-ethyl acetate solution. A 2-ml volume of ethereal diazomethane was added with mixing, and the solutions were allowed to react for 5 minutes. At the end of the 5-minute period, the vials were placed in a 30° C water bath and the solvent was evaporated under nitrogen to a volume just under 0.5 ml (to eliminate the ether and excess diazomethane).

The concentrated solutions were diluted with methanol to about 8 ml, transferred to 100-ml volumetric flasks, and diluted to volume with methanol. After the solutions were mixed, 1-ml aliquots were transferred to 30-ml septum vials containing 5 ml of 22% sodium chloride solution and 20 ml of internal standard solution (aldrin in pesticide quality hexane, 0.108 µg/ml). The vials were sealed and shaken 1 minute, and then the dimethyl chlorendate content of the upper hexane layer was determined by the gas chromatographic system described below.

Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
Column: 10% SP-2100 on 100/120 mesh Supelcoport 1.8 m × 2 mm ID, glass, silanized
Detection: Electron capture, ^{63}Ni
Oven temperature: 220° C, isothermal
Detector temperature: 280° C
Inlet temperature: 250° C
Carrier gas: Nitrogen, 30 ml/minute
Injection volume: 2.7 µl
Retention times: Dimethyl chlorendate--6.1 minutes
Aldrin--5.0 minutes for internal standard

C. **Quality assurance measures:** The same quality assurance measures were followed for both the boron trifluoride and the diazomethane methods.

The dosed feed sample was analyzed in triplicate, and the undosed feed sample was analyzed once. Individually spiked portions of undosed feed (six concentrations bracketing the specified concentration of the dosed feed sample) were prepared from two independently weighed standards and were used to obtain standard data. Three injections of each standard and sample were made into the gas chromatograph in a random order. All determinations were related to an internal standard incorporated into the sample solutions.

APPENDIX K

RESULTS OF ANALYSIS OF FORMULATED DIETS

TABLE K1. RESULTS OF HOMOGENEITY ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF CHLORENDIC ACID (a)

Blender Location	Concentration of Chlorendic Acid in Feed (ppm)		Determined as a Percent of Target
	Target	Determined	
Top	620	562	90.6
Middle		586	94.5
Bottom		560	90.3
Top	1,250	1,240	99.2
Middle		1,187	95.0
Bottom		1,168	93.4
Top	2,500	2,305	92.2
Middle		2,346	93.8
Bottom		2,281	91.2
Top	5,000	4,699	94.0
Middle		4,761	95.2
Bottom		4,728	94.6
Top	10,000	9,330	93.3
Middle		9,219	92.2
Bottom		9,020	90.3
Top	20,000	20,760	103.8
Middle		20,700	103.5
Bottom		19,250	96.3

(a) Results of duplicate analysis

TABLE K2. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID (a)

Date Mixed	Determined Concentration for Target Concentration of 620 ppm	Determined Concentration for Target Concentration of 1,250 ppm
06/18/80	--	1,165
06/25/80	580	--
06/30/80	575	
07/02/80	600	1,235
07/14/80	--	(b) 1,095
08/11/80	560	--
09/29/80	--	1,165
11/24/80	630	1,200
01/05/81	680	1,315
02/16/81	625	1,270
04/20/81	710	1,290
08/17/81	595	1,215
10/19/81	(c) 555	1,180
10/28/81	(d) 565	--
12/14/81	620	1,310
02/08/82	610	1,140
03/29/82	(b) 705	1,380
05/17/82	645	1,205
Mean (ppm)	621	1,226
Standard deviation	49.8	78.5
Coefficient of variation (percent)	8.0	6.4
Range (ppm)	555-710	1,095-1,380
Number of samples	14	14

(a) Results of duplicate analysis
(b) Out of specification. Mix was used in the study.
(c) Originally analyzed out of specification. Value presented is the corrected concentration. Mix not used in the study.
(d) Remix. Not included in the mean.

TABLE K3. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm) Study Laboratory	Determined Concentration (ppm) Analytical Laboratory
07/02/80	620	600	(a) 585
01/05/81	1,250	1,315	(a) 1,190
08/17/81	1,250	1,215	(b,c) 1,020
12/14/81	1,250	1,310	(a) 1,090
			(b) 1,150
05/17/82	620	640	(a,d) 537

(a) Boron trifluoride methylation procedure
(b) Diazomethane methylation procedure
(c) Analyzed 24 days after mixing; chemical irreversibly bound to feed.
(d) Analyzed 25 days after mixing; chemical irreversibly bound to feed.

APPENDIX L

SENTINEL ANIMAL PROGRAM

APPENDIX L. SENTINEL ANIMAL PROGRAM

I. 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 study 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 study rooms. These animals are untreated, and these animals and the study 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 B6C3F$_1$ 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:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (12, 18, 24 mo)	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (6 mo) MHV (6, 12 mo)	MHV (mouse hepatitis virus) (18, 24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6, 12, 18 mo)	RCV (rat coronavirus) Sendai (24 mo)	

II. Results

Results are presented in Table L1.

TABLE L1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	10/10	RCV
18	--	None positive
24	3/10	KRV
	1/7	Sendai
	4/10	RCV
MICE		
6	1/7	GDVII
	2/4	MHV
12	--	None positive
18	--	None positive
24	--	None positive

(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 (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX M

FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF CHLORENDIC ACID

TABLE M1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

Week	Control		620 ppm				1,250 ppm			
	Grams Feed/ Day (c)	Body Weight (grams)	Grams Feed/ Day (c)	Body Weight (grams)	Low/ Control (a)	Dose/ Day (b)	Grams Feed/ Day (c)	Body Weight (grams)	High/ Control (a)	Dose/ Day (b)
1	14	199	14	194	1.0	45	14	191	1.0	92
2	16	222	15	214	0.9	43	15	210	0.9	89
3	15	239	14	231	0.9	38	14	227	0.9	77
4	16	252	15	246	0.9	38	16	239	1.0	84
5	15	269	14	259	0.9	34	15	254	1.0	74
6	16	284	15	268	0.9	35	16	266	1.0	75
7	16	296	15	283	0.9	33	15	276	0.9	68
8	16	305	15	292	0.9	32	16	285	1.0	70
9	16	318	16	304	1.0	33	16	294	1.0	68
10	17	323	17	306	1.0	34	16	297	0.9	67
11	17	342	16	320	0.9	31	15	311	0.9	60
12	17	346	16	332	0.9	30	16	306	0.9	65
13	17	355	15	332	0.9	28	15	319	0.9	59
17	16	379	16	359	1.0	28	16	345	1.0	58
21	16	396	15	368	0.9	25	15	352	0.9	53
25	13	401	15	380	1.2	24	14	364	1.1	48
29	16	412	15	391	0.9	24	15	369	0.9	51
33	17	429	16	402	0.9	25	15	381	0.9	49
37	15	440	15	414	1.0	22	15	390	1.0	48
41	15	443	14	417	0.9	21	14	395	0.9	44
45	15	446	15	421	1.0	22	15	401	1.0	47
49	16	453	15	430	0.9	22	14	406	0.9	43
53	16	434	15	410	0.9	23	15	392	0.9	48
57	15	447	13	421	0.9	19	14	398	0.9	44
61	15	444	15	420	1.0	22	15	398	1.0	47
65	17	445	16	424	0.9	23	16	402	0.9	50
69	15	449	14	422	0.9	21	15	406	1.0	46
73	14	447	14	425	1.0	20	14	402	1.0	44
77	15	445	16	430	1.1	23	15	408	1.0	46
81	16	435	15	428	0.9	22	15	399	0.9	47
85	15	437	14	420	0.9	21	14	398	0.9	44
89	15	437	16	426	1.1	23	15	397	1.0	47
93	18	427	14	417	0.8	21	15	392	0.8	48
97	13	417	14	413	1.1	21	15	397	1.2	47
101	18	403	15	409	0.8	23	15	390	0.8	48
104	15	406	15	400	1.0	23	6	384	0.4	20
Mean	15.7	378	15.0	362	1.0	27	14.8	346	0.9	56
SD (d)	1.2		0.8		0.1	7	1.6		0.1	15
CV (e)	7.6		5.3		10.0	25.9	10.8		11.1	26.8

(a) Grams of feed per day for the dosed group divided by that for the controls
(b) Estimated milligrams of chlorendic acid consumed per day per kilogram of body weight
(c) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE M2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control		620 ppm				1,250 ppm			
Week	Grams Feed/ Day (c)	Body Weight (grams)	Grams Feed/ Day (c)	Body Weight (grams)	Low/ Control (a)	Dose/ Day (b)	Grams Feed/ Day (c)	Body Weight (grams)	High/ Control (a)	Dose/ Day (b)
1	10	143	14	143	1.4	61	10	140	1.0	89
2	12	153	13	151	1.1	53	11	147	0.9	94
3	10	159	16	158	1.6	63	10	152	1.0	82
4	11	166	14	164	1.3	53	11	157	1.0	88
5	11	174	13	172	1.2	47	10	164	0.9	76
6	11	179	14	176	1.3	49	11	168	1.0	82
7	10	183	14	180	1.4	48	10	172	1.0	73
8	11	187	14	183	1.3	47	11	174	1.0	79
9	10	192	15	187	1.5	50	11	178	1.1	77
10	12	195	12	186	1.0	40	11	177	0.9	78
11	11	203	14	194	1.3	45	10	183	0.9	68
12	11	203	14	193	1.3	45	11	181	1.0	76
13	11	206	14	197	1.3	44	10	185	0.9	68
17	11	219	14	207	1.3	42	10	194	0.9	64
21	11	226	14	212	1.3	41	10	199	0.9	63
25	10	229	14	214	1.4	41	12	202	1.2	74
29	11	234	14	217	1.3	40	10	204	0.9	61
33	11	241	13	220	1.2	37	10	205	0.9	61
37	11	250	14	228	1.3	38	10	211	0.9	59
41	11	256	15	233	1.4	40	10	214	0.9	58
45	11	264	14	236	1.3	37	11	219	1.0	63
49	11	271	14	243	1.3	36	10	221	0.9	57
53	10	271	15	245	1.5	38	11	221	1.1	62
57	12	286	12	253	1.0	29	10	227	0.8	55
61	12	298	14	260	1.2	33	12	232	1.0	65
65	13	305	14	272	1.1	32	12	237	0.9	63
69	12	319	14	281	1.2	31	11	247	0.9	56
73	12	325	14	283	1.2	31	11	251	0.9	55
77	12	329	14	289	1.2	30	11	250	0.9	55
81	13	330	13	286	1.0	28	12	253	0.9	59
85	12	335	14	294	1.2	30	11	259	0.9	53
89	13	344	15	300	1.2	31	13	267	1.0	61
93	12	350	13	302	1.1	27	11	271	0.9	51
97	13	351	12	302	0.9	25	11	274	0.8	50
101	12	346	14	306	1.2	28	11	273	0.9	50
104	12	346	15	303	1.3	31	14	290	1.2	60
Mean	11.4	252	13.9	230	1.2	39	10.9	211	1.0	66
SD (d)	0.9		0.9		0.1	10	0.9		0.1	12
CV (e)	7.9		6.5		8.3	25.6	8.3		10.0	18.2

(a) Grams of feed per day for the dosed group divided by that for the controls
(b) Estimated milligrams of chlorendic acid consumed per day per kilogram of body weight
(c) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE M3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control		620 ppm				1,250 ppm			
Week	Grams Feed/ Day (c)	Body Weight (grams)	Grams Feed/ Day (c)	Body Weight (grams)	Low/ Control (a)	Dose/ Day (b)	Grams Feed/ Day (c)	Body Weight (grams)	High/ Control (a)	Dose/ Day (b)
1	5	26.3	5	26.7	1.0	116	6	25.3	1.2	296
2	5	27.8	5	27.2	1.0	114	5	26.8	1.0	233
3	5	28.3	5	27.1	1.0	114	5	26.7	1.0	234
4	7	29.1	7	27.6	1.0	157	7	28.0	1.0	313
5	5	29.7	6	28.5	1.2	131	6	28.4	1.2	264
6	5	30.2	6	29.3	1.2	127	6	29.3	1.2	256
7	5	31.3	6	30.2	1.2	123	6	30.3	1.2	248
8	5	30.6	5	31.0	1.0	100	5	30.8	1.0	203
9	5	31.6	5	30.4	1.0	102	5	30.5	1.0	205
10	5	32.2	5	30.4	1.0	102	5	30.6	1.0	204
11	5	32.4	6	31.8	1.2	117	6	31.4	1.2	239
12	5	33.0	4	31.7	0.8	78	4	31.4	0.8	159
13	4	32.9	4	31.9	1.0	78	4	31.3	1.0	160
17	4	35.0	4	33.2	1.0	75	4	33.1	1.0	151
21	5	36.6	6	34.3	1.2	108	5	33.9	1.0	184
25	4	35.7	4	34.0	1.0	73	4	33.2	1.0	151
29	4	36.7	4	34.3	1.0	72	4	34.3	1.0	146
33	4	37.2	4	34.4	1.0	72	4	33.8	1.0	148
37	4	38.9	4	35.5	1.0	70	4	36.1	1.0	139
41	4	38.9	4	36.4	1.0	68	4	35.3	1.0	142
45	4	40.9	4	37.6	1.0	66	4	37.3	1.0	134
49	4	40.0	5	37.4	1.3	83	5	36.0	1.3	174
53	4	41.2	7	38.0	1.8	114	7	37.1	1.8	236
57	4	41.0	5	39.0	1.3	79	5	37.0	1.3	169
65	4	41.2	4	40.5	1.0	61	4	38.5	1.0	130
69	4	41.6	4	40.0	1.0	62	4	38.1	1.0	131
73	4	41.0	5	39.2	1.3	79	4	37.2	1.0	134
77	4	40.8	4	39.5	1.0	63	5	37.7	1.3	166
81	5	40.4	4	38.4	0.8	65	5	36.7	1.0	170
85	4	40.1	4	38.3	1.0	65	5	37.4	1.3	167
89	4	40.0	4	38.0	1.0	65	5	37.0	1.3	169
97	4	39.4	4	37.6	1.0	66	4	37.1	1.0	135
101	3	40.0	4	38.0	1.3	65	4	38.0	1.3	132
103	4	40.0	4	37.0	1.0	67	4	36.0	1.0	139
104	5	40.0	6	36.3	1.2	102	6	36.7	1.2	204
Mean	4.5	36.1	4.8	34.3	1.1	89	4.9	33.7	1.1	185
SD (d)	0.7		0.9		0.2	25	0.9		0.2	50
CV (e)	15.6		18.8		18.2	28.1	18.4		18.2	27.0

(a) Grams of feed per day for the dosed group divided by that for the controls
(b) Estimated milligrams of chlorendic acid consumed per day per kilogram of body weight
(c) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE M4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF CHLORENDIC ACID

	Control		620 ppm				1,250 ppm			
Week	Grams Feed/ Day (c)	Body Weight (grams)	Grams Feed/ Day (c)	Body Weight (grams)	Low/ Control (a)	Dose/ Day (b)	Grams Feed/ Day (c)	Body Weight (grams)	High/ Control (a)	Dose/ Day (b)
1	5	20.4	5	19.0	1.0	163	6	19.3	1.2	389
2	6	21.0	5	19.6	0.8	158	6	20.6	1.0	364
3	5	22.1	6	21.3	1.2	175	5	19.8	1.0	316
4	7	22.7	7	21.6	1.0	201	6	21.2	0.9	354
5	5	23.6	6	22.5	1.2	165	6	22.4	1.2	335
6	6	24.0	6	23.2	1.0	160	6	23.2	1.0	323
7	6	24.8	6	24.7	1.0	151	6	24.9	1.0	301
8	5	24.0	5	24.2	1.0	128	5	23.7	1.0	264
9	5	24.8	5	24.4	1.0	127	5	23.6	1.0	265
10	5	24.9	6	25.2	1.2	148	5	24.3	1.0	257
11	5	25.8	6	25.5	1.2	146	6	25.1	1.2	299
12	4	27.2	4	26.0	1.0	95	4	25.3	1.0	198
13	4	26.9	4	26.0	1.0	95	4	25.2	1.0	198
17	4	28.5	4	28.5	1.0	87	4	27.2	1.0	184
21	4	30.4	4	29.6	1.0	84	4	28.2	1.0	177
25	4	31.8	4	30.1	1.0	82	4	32.7	1.0	153
29	4	32.7	4	30.8	1.0	81	4	29.6	1.0	169
33	4	33.1	4	31.9	1.0	78	4	30.4	1.0	164
37	4	35.5	4	34.6	1.0	72	4	32.1	1.0	156
41	4	36.2	4	35.2	1.0	70	4	32.8	1.0	152
45	4	38.8	4	36.9	1.0	67	4	34.9	1.0	143
49	3	37.4	4	36.5	1.3	68	4	35.3	1.3	142
53	4	38.3	4	36.8	1.0	67	5	34.3	1.3	182
57	4	39.0	4	38.0	1.0	65	4	37.0	1.0	135
65	4	38.7	4	38.4	1.0	65	4	36.9	1.0	136
69	4	39.0	4	39.1	1.0	63	4	36.7	1.0	136
73	4	38.3	4	37.4	1.0	66	4	35.3	1.0	142
77	4	37.6	4	38.2	1.0	65	4	36.3	1.0	138
81	5	37.8	4	36.6	0.8	68	5	34.4	1.0	182
85	4	37.2	4	36.3	1.0	68	4	35.0	1.0	143
89	4	38.0	4	37.0	1.0	67	5	35.0	1.3	179
97	4	39.3	4	37.8	1.0	66	4	35.3	1.0	142
101	4	39.0	4	38.0	1.0	65	3	36.0	0.8	104
103	4	38.0	4	36.0	1.0	69	4	34.0	1.0	147
104	6	37.6	6	35.8	1.0	104	5	34.3	0.8	182
Mean	4.5	31.8	4.6	30.9	1.0	100	4.6	29.8	1.0	207
SD (d)	0.9		0.9		0.1	42	0.8		0.1	80
CV (e)	20.0		19.6		10.0	42.0	17.4		10.0	38.6

(a) Grams of feed per day for the dosed group divided by that for the controls
(b) Estimated milligrams of chlorendic acid consumed per day per kilogram of body weight
(c) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX N

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Meal Diet: June 1980 to July 1982

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE N1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NIH, 1978; NCI, 1976
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE N2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
d-α-Tocopheryl acetate	20,000 IU	
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Folic acid	2.2 g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
B_{12}	4,000 µg	
Biotin	140.0 mg	*d*-Biotin
K_3	2.8 g	Menadione activity
Choline	560.0 g	Choline chloride
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE N3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.20 ± 1.00	22.6-26.3	24
Crude fat (percent by weight)	5.02 ± 0.46	4.2-6.0	24
Crude fiber (percent by weight)	3.48 ± 0.41	2.4-4.3	24
Ash (percent by weight)	6.66 ± 0.41	5.97-7.42	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,087 ± 1,723	7,200-17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	18.8 ± 0.36	7.4-26.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.27 ± 0.19	0.81-1.6	24
Phosphorus (percent)	1.00 ± 0.08	0.84-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine.

TABLE N4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.39 ± 0.17	0.13-0.93	24
Cadmium (ppm) (a)	<0.1		24
Lead (ppm)	1.09 ± 0.72	0.33-2.93	24
Mercury (ppm) (a)	0.05		24
Selenium (ppm)	0.30 ± 0.07	0.16-0.48	24
Aflatoxins (ppb) (a,b)	<10		24
Nitrate nitrogen (ppm) (c)	8.50 ± 4.39	0.6-18.0	24
Nitrite nitrogen (ppm) (c)	2.05 ± 1.28	0.4-5.3	24
BHA (ppm) (d,e)	3.68 ± 2.71	0.4-11.0	24
BHT (ppm) (d)	2.65 ± 1.13	1.2-4.9	24
Aerobic plate count (CFU/g) (f)	70,729 ± 49,351	7,000-210,000	21
Coliform (MPN/g) (g)	731 ± 880	<3-2,400	24
E. coli (MPN/g)	7.50 ± 7.68	<3-23	24
Total nitrosamines (ppb) (h,i)	7.24 ± 6.70	1.8-24.5	22
Total nitrosamines (ppb) (h,j)	17.03 ± 28.20	1.8-101.6	24
N-Nitrosodimethylamine (ppb) (h,k)	5.55 ± 6.07	0.7-20.0	22
N-Nitrosodimethylamine (ppb) (h,l)	13.29 ± 26.86	0.7-99	24
N-Nitrosopyrrolidine (ppb)	1.32 ± 0.81	0.3-3.5	24
Pesticides (ppm)			
α-BHC (a,m)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (n)	<0.01	0.05 (7/14/81)	24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (n)	<0.05	0.13 (8/25/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (o)	0.08 ± 0.05	<0.05-0.25	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE N4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: Soy oil and fish meal
(e) Two batches contained less than 0.5 ppm.
(f) CFU = colony-forming unit
(g) MPN = most probable number
(h) All values were corrected for percent recovery.
(i) Mean, standard deviation, and range exclude two very high values of 101.6 and 100.3 ppb for batches produced on 1/26/81 and 4/27/81.
(j) Mean, standard deviation, and range include the very high values given in footnote i.
(k) Mean, standard deviation, and range exclude two very high values of 97.9 and 99 ppb for batches produced on 1/26/81 and 4/27/81.
(l) Mean, standard deviation, and range include the high values given in footnote k.
(m) BHC = hexachlorocyclohexane or benzene hexachloride
(n) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(o) Nine batches contained more than 0.05 ppm.

APPENDIX O

DISPOSITION AND EXCRETION OF CHLORENDIC ACID IN FISCHER 344 RATS

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DISPOSITION AND EXCRETION OF CHLORENDIC ACID IN FISCHER 344 RATS

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The absorption, distribution, and excretion of a highly chlorinated dicarboxylic acid, chlorendic acid, was studied in the male Fischer 344 rat. [^{14}C]Chlorendic acid was absorbed after an oral dose of 7.7 μmol per kilogram of body weight. The distribution in various tissues was similar whether the treatment was by the oral or the intravenous route. The major site of [^{14}C]chlorendic acid deposition was the liver, with smaller amounts found in the blood, muscle, skin, and kidneys. Chlorendic acid-derived radioactivity was excreted primarily through the bile and into the feces. The urine contained less than 6% of the total dose. Within 1 d, more than 75% of the total dose was excreted in the feces, primarily as metabolites. Radioactivity in the liver was also primarily metabolites of chlorendic acid. Thus, chlorendic acid was absorbed, metabolized, and excreted primarily in the feces as metabolites. The rapid metabolism and biliary excretion of chlorendic acid contrast with observations for the closely related lipophilic compounds aldrin and dieldrin.

INTRODUCTION

1,4,5,6,7,7-Hexachlorendo-5-norbornene-2,3-dicarboxylic acid (chlorendic acid) is used as a fire retardant in unsaturated polyester fibers and has been suggested for fireproofing polymers of chlorethylene, styrene, and urethan (NTP, 1980). Approximately 1.5 million kilograms of chlorendic acid are produced yearly. There are no data on its fate in laboratory animals, humans, or the environment.

Chlorendic acid is structurally related to the highly chlorinated insecticide aldrin and its environmentally persistent degradation product dieldrin (IARC, 1975). Unlike aldrin or dieldrin, chlorendic acid contains two carboxylic acid groups and is thus a polar representative of a highly chlorinated class of compounds. It was of interest to study the fate of radiolabeled chlorendic acid in the rat after a single oral dose or injection. The distribution in body tissues, excretion, and metabolism were also determined.

METHODS

Male adult Fischer 344 rats weighing 176–215 g were used. They were purchased from Charles River Breeding Laboratories (Wilmington,

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Mass.), housed under a 12-h light cycle for at least 1 wk before use, and fed Purina Rat Chow and offered water *ad libitum.*

[U-^{14}C]Chlorendic acid (12 mCi/mmol) was purchased from Pathfinder Laboratories (St. Louis, Mo.). Radiochemical purity was determined by radio-gas-liquid chromatography on 3% QF-1 by Dr. Phillip Albro, Laboratory of Environmental Chemistry, National Institute of Environmental Health Sciences. The radiolabeled compound was ≥99% radiochemically pure. The dose solution was made up by dissolving [^{14}C]chlorendic acid in a 1:1 mixture of Emulfor, a polyoxyethylated vegetable oil (GAF Corp., New York), and ethanol along with unlabeled chlorendic acid (K & K Laboratories, Irvine, Calif), ≥99% pure by nuclear magnetic resonance (NMR), determined by Dr. Phillip Albro. Distilled water was then added to give a final chlorendic acid concentration of 3.0 mg per milliliter of the mixture of Emulfor, ethanol, and water (1:1:8 by volume). [^{14}C]Chlorendic acid solution was injected iv into the tail vein of rats (3 mg/kg, 7.7 μmol/kg, 11 μCi/kg, 1 ml/kg), which were held for 15 min to 7 d, after which they were sacrificed by cervical dislocation. For absorption studies, rats received the same dose as in the iv study by oral intubation and were sacrificed by cervical dislocation after 1 d. All injections and intubations were made between 9 and 10 a.m.

Three animals were exsanguinated by cardiac puncture at each time point, dissected immediately, and the tissues weighed and stored in a freezer until they could be prepared for analysis by oxidation to $^{14}CO_2$ in a Packard model 306B biological oxidizer (Packard Instrument Co., Downers Grove, Ill.). Recovery of $^{14}CO_2$ radioactivity was determined and corrected for quenching in a Beckman model LS8100 liquid scintillation system (Beckman Instruments, Fullerton, Calif.). In each case, a section of the tail injection site with 0.5 cm^2 of surrounding tissue was removed and the residual radioactivity determined. When the injection site contained as much as 5% of the [^{14}C]chlorendic acid dose, the animal was discarded and another treated for the respective time period. Approximately 5% of the animals were discarded. Most of the tissue samples were finely minced before oxidation. However, blood (0.2 ml drawn with a heparinized syringe from the heart), adipose tissue (50 mg perirenal), and skin (100 mg portion from the ears) were oxidized directly. The skin weight and weight of adipose tissue depots of Fisher 344 rats are 16 and 11% of body weight, respectively (Brinbaum et al., 1980). Estimates of blood volume and muscle weight, 8 and 50% of body weight, respectively, were based on literature values for rats (Matthews and Anderson, 1975).

Animals held for 1 d or longer were housed in individual metabolism cages with food and water *ad libitum*; feces and urine were collected daily. The feces were air-dried, weighed, and ground into a powder

with mortar and pestle; two 100-mg samples of each daily collection were oxidized. [^{14}C]Chlorendic acid-derived radioactivity in the urine was quantified by determining the volume of each urine collection and counting two 0.1-ml samples directly into Aquasol (New England Nuclear Corp., Boston, Mass.). Liquid scintillation counting efficiencies were determined by use of an appropriate [^{14}C]chlorendic acid standard and corrected for quench in all cases.

Bile duct cannulation experiments were carried out by first anesthetizing rats with pentobarbital (Matthews and Anderson, 1975). The common bile duct was cannulated with PE-10 tubing and bile collected at timed intervals for 6 h. Excretion in bile was determined by counting duplicate 10-μl samples for each time point in 10 ml Aquasol in a liquid scintillation spectrometer.

Radioactivity was extracted from 6-g samples of liver, 2 g from each of three 1-d animals, with organic solvents before and after acid hydrolysis (Matthews and Anderson, 1975). Tissue extracts were concentrated to 10 ml by rotary evaporation under vacuum and further concentrated under N_2. Concentrated extracts were chromatographed as a band on 20 X 20 cm silica gel G thin-layer plates (Analtech, Inc., Newark, Del.) for 15 cm. The solvent systems used were (1) *n*-butanol, acetic acid, and water (12:3:5 by volume) and (2) ethyl acetate and acetic acid (9:1 by volume). An authentic standard of [^{14}C]chlorendic acid (R_f = 0.69 in both solvent systems) was chromatographed on the same plate with each tissue extract. After chromatography, the silica gel was scraped from the plates in 1-cm bands, placed into liquid scintillation vials, shaken vigorously with 20 ml Aquasol, and counted.

Bile samples were analyzed by thin-layer chromatography with the solvent systems described above both before and after hydrolysis in 1 *N* HCl at 90°C for 1 h. Bile samples were also treated with β-glucuronidase or aryl sulfatase and then a portion of the unextracted sample was subjected to thin-layer chromatography as described above. Approximately 20 μl bile containing approximately 30,000 cpm was incubated at 37°C for 17 h in 0.1 *M* acetate buffer, pH 5.0, containing 200 U/ml β-glucuronidase (bovine liver, type B10, Sigma Chemical Co., St. Louis, Mo.) or 30 U/ml aryl sulfatase (abalone entrails, type VIII, Sigma Chemical Co.).

Feces were extracted in a Soxhlet apparatus (Matthews and Anderson, 1975) and the extracts analyzed by thin-layer chromatography as described above. Urine was analyzed after extraction with ether (Matthews and Anderson, 1975).

Tissue distribution data were analyzed by a nonlinear regression analyses computer program (Morales et al., 1979) based on the exponential decay curves. The number of exponential terms was determined by best fit. Data are expressed as the mean ± SD, $n \geq 3$.

TABLE 1. Specific Activity of Chlorendic Acid-derived Radioactivity in Tissues of the Rat after iv Administration

Tissue	Percent of dose per gram of tissue ($n > 3$ animals)					
	15 min	30 min	1 h	3 h	7 h	1 d
Blood	1.19 ± 0.17	1.13 ± 0.65	1.21 ± 0.15	0.24 ± 0.17	0.03 ± 0.01	0.04 ± 0.006
Liver	6.87 ± 0.71	4.85 ± 1.19	3.68 ± 0.18	1.39 ± 0.18	0.522 ± 0.033	0.206 ± 0.122
Kidney	3.23 ± 0.588	2.08 ± 0.175	1.46 ± 0.183	0.340 ± 0.040	0.075 ± 0.014	0.019 ± 0.014
Thymus	0.141 ± 0.098	0.432 ± 0.423	0.089 ± 0.019	0.014 ± 0.009	0	0
Adrenals	9.99 ± 5.85	6.70 ± 1.65	3.69 ± 1.83	0.350 ± 0.606	0	0
Spleen	0.480 ± 0.062	0.500 ± 0.07	0.212 ± 0.032	0.286 ± 0.440	0.008 ± 0.013	0
Testes	0.085 ± 0.015	0.499 ± 0.720	0.060 ± 0.004	0.022 ± 0.004	0	0
Lungs	0.508 ± 0.125	0.750 ± 0.684	0.212 ± 0.032	0.078 ± 0.055	0.010 ± 0.006	0
Small intestine	0.438 ± 0.196	1.00 ± 1.64	7.99 ± 3.57	1.14 ± 0.751	0.266 ± 0.149	0.010 ± 0.018
Contents	0.301 ± 0.170	3.55 ± 1.65	10.49 ± 2.04	19.6 ± 11.25	2.49 ± 1.90	0.122 ± 0.039
Large intestine	0.213 ± 0.112	0.081 ± 0.016	0.177 ± 0.112	0.592 ± 0.292	1.14 ± 0.315	0.035 ± 0.019
Contents	0.227 ± 0.192	0.128 ± 0.027	0.028 ± 0.016	4.95 ± 1.18	26.7 ± 9.53	1.76 ± 1.19
Skin	0.386 ± 0.081	0.280 ± 0.037	0.183 ± 0.066	0.020 ± 0.001	0	0
Brain	0.079 ± 0.049	0.045 ± 0.013	0.020 ± 0.024	0	0.002 ± 0.003	0
Adipose	0.004 ± 0.003	0.004 ± 0.007	0.003 ± 0.001	0	0	0
Muscle	0.161 ± 0.028	0.091 ± 0.008	0.058 ± 0.011	0.004 ± 0.004	0	0
Heart	0.352 ± 0.054	0.228 ± 0.081	0.142 ± 0.043	0.036 ± 0.014	0.009 ± 0.015	0

RESULTS

Intravenous Administration

The dose of [^{14}C]chlorendic acid (7.7 μmol/kg) was sufficient to allow accurate determination of tissue concentrations and caused no overt signs of toxicity. Major organs and tissues were analyzed for radioactive content at selected time points after chlorendic acid administration. Liver, blood, muscle, skin, and kidneys were the most important depots for chlorendic acid, especially at early time points (Table 1). Since the organ with the greatest amount of radioactivity was the liver, the nature of the radioactivity in this tissue was determined after 1 h and 1 d by extraction and thin-layer chromatography. The total radioactivity extracted from liver was 66.7%. Only 4% of the total radioactivity was present as chlorendic acid. Additional radioactivity was released (62.6%) after acid treatment; this was mostly (85%) [^{14}C]chlorendic acid. The balance of radioactivity (33.3%) was associated with liver and could not be extracted; this was apparently an artifact of the procedure since this radioactivity was obviously readily cleared by the intact animal (see below). Radioactivity associated with the other tissue depots was insufficient for analysis.

The major organ deposition site of chlorendic acid-derived radioactivity

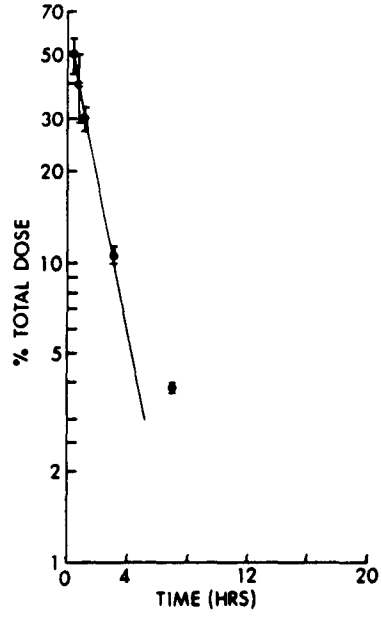

FIGURE 1. Percent of total chlorendic acid dose in liver versus time. Animals were given 7.7 μmol/kg [^{14}C]chlorendic acid iv. Each point represents the mean ± SD for three animals. The line is the computer-drawn one-component exponential decay curve.

at early times after injection was the liver. More than 50% of the total dose was found in this organ within 15 min (Fig. 1). Radioactivity was rapidly removed from the liver, and by 7 h less than 4% of the dose remained. The loss of radioactivity from the liver can be described by a single-component exponential computer-fitted decay curve (Fig. 1). The half-life of chlorendic acid-derived radioactivity in the liver was 1.19 h. Radioactivity removed from the liver was found primarily in bile (see below).

Another major compartment for radioactivity at early time points was the blood. At 15 min more than 16% and by 1 h nearly 20% of the total dose was found in blood (Fig. 2). Thereafter the radioactivity declined exponentially, and by 7 h less than 0.5% of the dose could be detected in the blood. The half-life of chlorendic acid-derived radioactivity in the blood was 0.84 h.

Muscle tissue of rats accounts for a large percentage of the body weight and was another major depot for radioactivity at early time points (Table 1). At 15 min, 14% of the dose was located in this tissue, followed by a rapid single-component exponential decay, with less than 6% of the dose remaining at 1 h. The half-life of chlorendic acid-derived radioactivity in muscle tissue was 0.57 h. Slightly more than 10% of the total dose was found in the skin at 15 min, and it

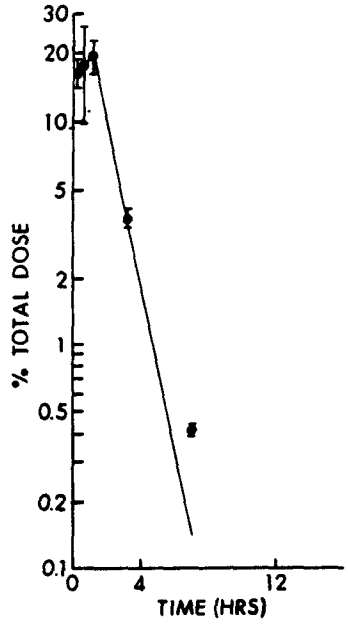

FIGURE 2. Percent of total chlorendic acid dose in blood versus time. Animals were given 7.7 μmol/kg [^{14}C] chlorendic acid iv. Each point represents the mean ± SD for three animals. The line from 1 to 7 h is the computer-drawn one-component exponential decay curve.

followed a single-component exponential decay with a half-life of 0.87 h. At 15 min less than 5% of the total dose could be detected in the kidneys, and the amount decreased exponentially thereafter with a half-life of 0.62 h (Table 1).

In addition, radioactivity was measured in thymus, adrenals, spleen, testes, lungs, small and large intestines and their contents, brain, perirenal adipose tissue, and heart (Table 1). The thymus, spleen, testes, lungs, skin, brain, adipose tissue, muscle, and heart did not account for a significant portion of the total dose; on a specific activity basis (percent of dose per gram of tissue), the amount never exceeded one-tenth that observed for liver (Table 1). At early time points, the liver had a high specific activity; at 15 min it was approximately equivalent to 0.11 μmol/g. The adrenals had a greater specific activity than the liver at early time points, but the concentration of chlorendic acid in the adrenals became undetectable within 7 h. The kidneys also showed a high specific activity at the early time points, followed by blood from 15 min to 1 h.

At 15 min the small and large intestines and their respective contents contained small amounts of radioactivity (Table 1). However, from 30 min to 7 h, the highest specific activity of all tissues was found in the contents of the small and large intestines. This increase at later time points was associated with removal of radioactivity from the liver into the bile.

Oral Administration

Since exposure to chlorendic acid is more likely to occur by ingestion, it was of interest to observe the absorption and distribution of chlorendic acid after oral administration. Three animals were each given an oral dose of 3.0 mg/kg (7.7 μmol/kg), held in individual metabolism cages for 1 d, sacrificed, and the tissues and excreta assayed for radioactivity and metabolites as described in Methods. These data are compared with data from three animals that received similar iv doses and treatment in Table 2. Total recovery of administered radioactivity was more than 90% in each instance. The animals given the oral dose had slightly more of the dose associated with the liver and less with the blood than the animals given an iv dose. By 1 d, most of the radioactivity was excreted in the feces and a substantial portion remained in the large intestines of both treatment groups. Analysis of the radioactivity revealed predominance of metabolites of chlorendic acid (see below). Comparable percentages of the dose were excreted in the urine of both treatment groups. There was also no detectable difference in the percentages of the dose found in kidneys in both treatment groups. Other tissues examined at this time period, including muscle, skin, and adipose tissue, had no detectable radioactivity.

TABLE 2. Distribution of Radioactivity 1 d after Administration of [^{14}C]Chlorendic Acid

Tissue	Percent of total dose ($n \geq 3$ animals)	
	Oral	Intravenous
Blood	0.033 ± 0.014	0.524 ± 0.026
Liver	1.08 ± 0.035	0.524 ± 0.026
Kidney	0.018 ± 0.008	0.021 ± 0.016
Small intestine	0.188 ± 0.137	0.036 ± 0.062
Contents	0.460 ± 0.194	0.266 ± 0.157
Large intestine	1.16 ± 0.394	0.070 ± 0.035
Contents	12.7 ± 2.76	5.57 ± 2.93
Feces	73.00 ± 5.93	77.80 ± 13.10
Urine	2.98 ± 1.35	5.94 ± 2.14

Excretion

Excretion of [^{14}C]chlorendic acid-derived radioactivity was analyzed by daily collection of urine and feces from individual animals held for 1 d or longer after treatment (Table 2). The major route of excretion of chlorendic acid was the feces, and approximately 78% of the dose was excreted in the first 24 h (Table 2). Most of the urinary excretion also occurred within the first 24 h, and less than 0.1% of the dose appeared in the urine on subsequent days (data not shown). Thus, by the first day, more than 73% of the total dose was recovered in the excreta (Table 2). Since the feces were the major

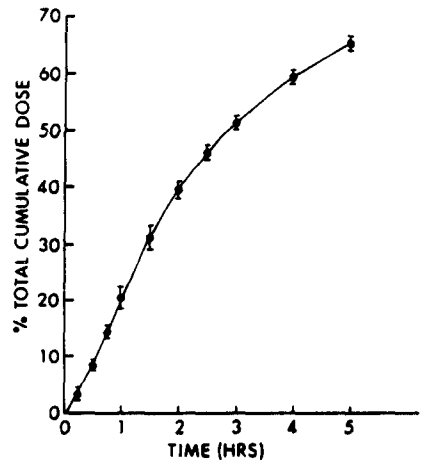

FIGURE 3. Cumulative excretion of chlorendic acid-derived radioactivity in bile. Samples were collected after iv administration of 7.7 μmol/kg [^{14}C]chlorendic acid into the femoral vein. Each point represents the mean ± SD for three animals.

route of elimination, excretion of radioactivity through the bile was studied. As shown in Fig. 3, 65% of an iv dose of [^{14}C]chlorendic acid-derived radioactivity was excreted in the bile within 5 h. This is in close agreement with the fecal excretion data shown in Table 2, suggesting that most of the [^{14}C]chlorendic acid-derived radioactivity in bile was excreted in the feces.

The [^{14}C]chlorendic acid-derived radioactivity in the urine, bile, and feces was examined by extraction and thin-layer chromatography. In the urine, 72% of the radioactivity appeared to represent parent compound. The remainder of the radioactivity was released after acid hydrolysis and then cochromatographed with parent compound, suggesting the presence of conjugates. Similar extraction and analysis of bile collected at time points from 15 min to 5 h indicated that about 20% of the total radioactivity cochromatographed with parent compound. Approximately 25% of the radioactivity extracted from bile chromatographed with an R_f of 0.19 in ethyl acetate and acetic acid (9:1); the remaining radioactivity was at the origin. After acid hydrolysis, all the radioactivity cochromatographed with the parent compound in both systems (R_f = 0.69), indicating the presence of conjugates. Treatment of unhydrolyzed bile with β-glucuronidase or aryl sulfatase did not alter the chromatographic results.

Feces were sequentially extracted with hexane, methylene chloride, and acetone before and after acid hydrolysis; only 34% of the radioactivity in feces could be extracted before acid hydrolysis. After acid hydrolysis, 31% was extracted by hexane. Analysis of this extract by thin-layer chromatography in ethyl acetate and acetic acid (9:1) indicated that 81% of the radioactivity cochromatographed with the parent compound, 7% had an R_f of 0.19, and the remainder was located at the origin. The results suggest that most of the radioactivity excreted in bile, and subsequently in feces, represented metabolites of chlorendic acid.

DISCUSSION

This study was performed to ascertain the absorption, distribution, and excretion of chlorendic acid in rats in order to evaluate its potential for bioaccumulation compared to that of the nonpolar halogenated hydrocarbons aldrin and dieldrin. The data showed that orally administered chlorendic acid was absorbed from the gastrointestinal tract. Chlorendic acid-derived radioactivity was initially distributed to the blood, liver, muscle, skin, and kidney and did not accumulate in adipose tissue, as previously observed for dieldrin (IARC, 1974). Distribution to the tissues was apparently not influenced by route of exposure. Most of the dose was located in the liver. Essentially 96% of the tissue burden may be either acid-labile conjugates of

chlorendic acid or chlorendic acid bound to tissue which required acid for release.

Chlorendic acid-derived radioactivity was rapidly excreted, primarily by the feces, with only 3-6% in the urine. Radioactivity in the urine was primarily parent compound; the remainder was most likely conjugates. In contrast, most of the radioactivity in the bile was conjugates of chlorendic acid and only about 20% was parent compound. After acid hydrolysis, extraction of chlorendic acid-derived radioactivity from bile was nearly complete; however, after acid hydrolysis of feces, less than one-third of the chlorendic acid-derived radioactivity could be extracted. Data for control extractions of chlorendic acid-spiked feces showed approximately 90% extraction of chlorendic acid.

Chlorendic acid was not stored in any of the tissues examined but was rapidly excreted in the bile; active tubular excretion of this chemical by the kidneys apparently had a relatively minor role in its clearance, in contrast to observations for other organic acids (Pitts, 1979). This result also contrasts with similar studies of the structurally related lipophilic insecticides, aldrin and its metabolite, dieldrin. Dieldrin was shown to be present in the environment and bioaccumulated in adipose tissue, liver, brain, and muscle of mammals, birds, fish and invertebrates (IARC, 1974). It accumulates in the food chain and was detected in human milk and adipose tissue (IARC, 1974). [^{14}C]Aldrin was converted to dieldrin after oral administration to male rats, and the dieldrin was stored in adipose tissue (IARC, 1975).

The polarity of chlorendic acid and the ability of the rat to metabolize it and rapidly clear it from the body may explain the lack of storage of this compound or its metabolites in adipose or other lipophilic tissues. Chlorendic acid is an amphipathic molecule with a hydrophilic dicarboxylic acid portion. Apparently the hydrophilic portion of the molecule facilitates its metabolism and excretion.

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APPENDIX P

DATA AUDIT SUMMARY

APPENDIX P. DATA AUDIT SUMMARY

The experimental data, records, and pathology materials from the NTP toxicology and carcinogenesis studies of chlorendic acid in F344/N rats and B6C3F$_1$ mice (feed studies) were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. These studies were performed at Hazleton Laboratories America, Inc., Vienna, Virginia, under a subcontract with Tracor Jitco, Inc., from the National Cancer Institute from June 1980 to June 1982 and were initiated before the requirement of compliance to Good Laboratory Practice standards by the NTP in October 1981. The audit was conducted at Dynamac Corp., Rockville, Maryland, and at the NTP Archives, Research Triangle Park, North Carolina. The audit involved the following Dynamac personnel: F. Garner, D.V.M.; L. Keifer, Ph.D.; J. Konz, M.S.P.H.; C. Sexsmith, B.S.; and E. Zurek. M. Shoaf (Pathology Associates, Inc.) also participated.

The complete audit has been reviewed and approved by NTP personnel and is on file at NIEHS, Research Triangle Park, North Carolina. The audit consisted of an indepth review of the data and pathology materials collected during the conduct of the studies as well as a review of the correspondence. The review of the inlife toxicology data involved examination of 100% of the records on animal receipt and husbandry, mortality, environmental conditions, and dosing and examination of body weight and clinical observation data for 10% of the animals. In the review of the chemistry data, all of the records associated with receipt, initial analysis, and stability testing by Midwest Research Institite were examined. In addition, records pertaining to receipt, use, bulk chemical analysis, and diet preparation and analysis by the laboratory were examined. The audit of the pathology materials included review of 100% of the Individual Animal Data Records (IADRs) for correlation between gross and microscopic diagnoses and clerical errors, examination of the wet tissues of 10% of the animals for unidentified lesions and correct identification, correlation of slides and tissue blocks for all control and high dose groups, and verification of the reported pathologic effects for a 10% sample of the animals. A draft of the NTP Technical Report was available for validation.

Review of the toxicology data indicated that temperature and humidity readings outside the range specified in the protocol were recorded frequently during several months of the studies. Temperatures were above the 66°-74° F range for an average of 9 days each month for 21 months of the studies. The highest recorded temperature was 81° F, and the lowest was 66° F. The relative humidity was below 40% for an average of 8 days each month for 21 months and above 60% for an average of 8 days each month for 21 months. No relationship was found between the periods of poor environmental control and mortality. Clinical observations were consistent or followed a logical progression over the audited period of the studies. Group mean body weights and feed consumption values were recalculated and validated, except for feed consumption values in the low dose female rats.

A complete review of the available analytical chemistry data found that the study material was received and used in the preparation of formulated diets according to the required protocols. Laboratory reports and raw data indicated that the study material and formulated diets were reanalyzed as required.

The review and audit of the pathology materials indicated some discrepancies between gross and microscopic diagnoses, especially in mice, and several untrimmed lesions in the wet tissues. In rats and mice, the majority of these discrepancies involved potential nonneoplastic lesions in target organs or potential tumors in nontarget organs. A post audit tissue review of these discrepancies resulted in additional diagnoses in the liver of rats and mice, which are included in the Technical Report. Examination of wet tissues indicated that 27 rats and 14 mice had ear tags that matched the inlife animal numbers recorded on the bag labels. Positive identification was not possible in 16/43 rats and 23/37 mice because of missing ears or ear tags; no discrepancies were found in the examination of the wet tissues and the inlife study records, indicating little likelihood of errors regarding animal identification.

Overall, the audit identified no problems that would reduce confidence in the data reported. Although some problems and discrepancies were identified, these were adequately resolved or were determined not to affect the outcome of the studies. In conclusion, the data examined in this audit are considered adequate to support the conclusions presented in the Technical Report.

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