NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 315

TOXICOLOGY AND CARCINOGENESIS STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

(CAS NO. 2058-46-0)

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

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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. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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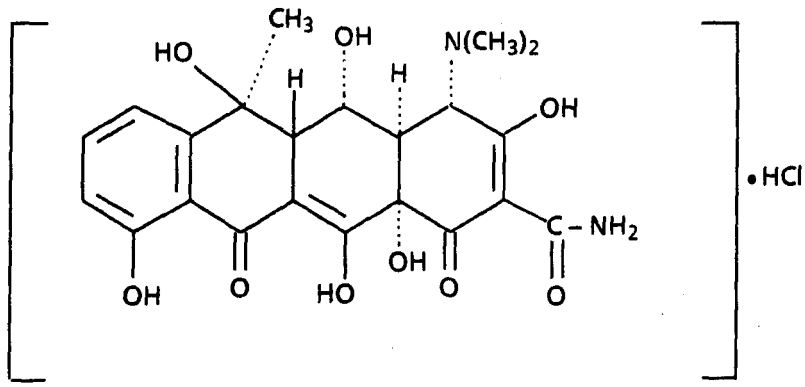

OXYTETRACYCLINE HYDROCHLORIDE

CAS No. 2058-46-0

2-Naphthacenecarboxamide,4(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-monohydrochloride

$C_{22}H_{24}N_2O_9 \cdot HCl$ Molecular weight 496.9

Synonyms: Biosolvomycin; Hydrocyclin; Liquamycin; Otetryn; Oxlopar; 5-Hydroxytetracycline Hydrochloride; Terramycin Hydrochloride; Tetramine; Tetran Hydrochloride

ABSTRACT

Toxicology and carcinogenesis studies were conducted on oxytetracycline hydrochloride (greater than 98.8% pure), a broad-spectrum antibiotic. Groups of F344/N rats and B6C3F$_1$ mice were fed diets containing oxytetracycline hydrochloride for a series of 14-day, 13-week, and 2-year studies. In the 14-day studies, no compound-related gross pathologic effects were seen in rats or mice (groups of five animals per sex per species) given up to 100,000 ppm in their feed. The final mean body weight of male rats receiving 100,000 ppm in feed was 27% lower than that of the controls. Final mean body weights of mice that received 25,000, 50,000, or 100,000 ppm were lower (male: 11%; 16%; 17%; female: 6%; 5%; 17%) than those of the controls. In the 13-week studies, groups of 10 male and 10 female rats and mice were fed diets containing up to 50,000 ppm in feed, and no chemically related gross or histopathologic effects were observed in mice of either sex or in female rats. In male rats, fatty metamorphosis of minimal severity was diagnosed in the liver of 5/10 animals at 6,300, 12,500, and 50,000 ppm and in 2/10 animals at 3,100 and 25,000 ppm. None was seen in the controls. Oxytetracycline levels in bones of rats and mice (as determined fluorometrically) at the end of the 13-week studies increased with dose, the highest levels (3-10 times background levels) being observed at 50,000 ppm.

The 2-year toxicology and carcinogenesis studies were conducted by administering diets containing 0, 25,000, or 50,000 ppm oxytetracycline hydrochloride to groups of 50 male and 50 female rats and diets containing 0, 6,300, or 12,500 ppm oxytetracycline hydrochloride to groups of 50 male and 50 female mice for 103 weeks. The highest dose selected for rats was considered to be the maximum level that would not affect the nutritional value of dosed feed. The dietary concentrations correspond to the following approximate doses: rats--0, 1,000, or 2,000 mg/kg body weight per day; mice--0, 650, or 1,400 mg/kg per day.

Mean body weights were approximately 5%-8% lower than those of controls in high dose male rats during weeks 4-47, in high dose male mice after week 31, and in high dose female mice after week 26. The mean body weights of dosed female rats and low dose male and female mice were comparable to those of controls. The survival of control male rats was lower than that of the high dose group (22/50 vs 38/50). No significant differences in survival were observed between the remaining groups of rats or between any groups of mice.

Pheochromocytomas of the adrenal gland occurred with positive trends in male rats (control, 10/50; low dose, 18/50; high dose, 24/50), and the incidence in the high dose group was greater than that in the controls. Two additional control males and one additional low dose male had malignant pheochromocytomas. The incidence of adrenal gland medullary hyperplasia was elevated slightly but not significantly in dosed male rats (7/50; 14/50; 9/50).

Adenomas and adenomas or adenocarcinomas (combined) of the pituitary gland in female rats occurred with positive trends, and the incidences in the high dose group were greater than that in the controls (adenomas: 19/50; 17/50; 30/50; adenomas or adenocarcinomas [combined]: 20/50; 24/50; 32/50). The incidence of pituitary gland hyperplasia was slightly decreased in dosed female rats (16/50; 10/50; 11/50).

No compound-related increases in nonneoplastic or neoplastic lesions were observed in male or female mice.

Oxytetracycline hydrochloride was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 when assayed according to the preincubation protocol. Oxytetracycline hydrochloride was mutagenic in L5178Y/TK$^{+/-}$ mouse lymphoma cells in the presence but not in the absence of Aroclor 1254-induced male F344 rat liver S9. In cultured Chinese hamster ovary cells, oxytetracycline hydrochloride was weakly positive in inducing sister-chromatid exchanges both with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 but did not induce chromosomal aberrations.

An audit of the experimental data was conducted for these 2-year carcinogenesis studies of oxytetracycline hydrochloride. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year feed studies of oxytetracycline hydrochloride, there was *equivocal evidence of carcinogenicity** for male F344/N rats, as indicated by increased incidences of pheochromocytomas of the adrenal gland. There was *equivocal evidence of carcinogenicity* for female F344/N rats fed diets containing oxytetracycline hydrochloride, as indicated by increased incidences of adenomas of the pituitary gland. There was *no evidence of carcinogenicity* for male or female B6C3F$_1$ mice fed diets containing 6,300 or 12,500 ppm oxytetracycline hydrochloride for 2 years.

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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 13.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Oxytetracycline Hydrochloride is based on the 13-week studies that began in March 1980 and ended in June 1980 and on the 2-year studies that began in November 1980 and ended in November 1982 at Physiological Research Laboratories.

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The members of the Peer Review Panel who evaluated the draft Technical Report on oxytetracycline hydrochloride on December 9, 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 OXYTETRACYCLINE HYDROCHLORIDE

On December 9, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of oxytetracycline hydrochloride 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 at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. K. Abdo, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (equivocal evidence of carcinogenicity in rats; no evidence of carcinogenicity in mice).

Dr. Jones, a principal reviewer, agreed with the conclusions as written.

As a second principal reviewer, Dr. Perera did not agree with the conclusions in rats. She stated that in males both a positive trend for pheochromocytomas and significant increases in pheochromocytomas in the high dose group compared with controls provided adequate support for raising the conclusion to some evidence of carcinogenicity. Likewise, in females, a positive trend for pituitary gland neoplasms and a significantly increased incidence of neoplasms in the high dose group compared with controls by the incidental tumor test supported raising the conclusion to some evidence of carcinogenicity. Dr. Abdo explained the rationale for the levels of evidence used. He said that both the adrenal gland and pituitary gland tumors have high and variable spontaneous rates in untreated rats, and, secondly, the increases were considered to be marginal. Also, no increases were observed in the low dose groups. Dr. Turnbull questioned calling the increase in pheochromocytomas in male rats statistically significant as they are common tumors, and the P value was greater than 0.01. Dr. J. Huff, NIEHS, indicated that this marginal increase did not fit the category of no evidence of carcinogenicity.

As a third principal reviewer, Dr. Kociba agreed with the conclusions in mice and with the level of evidence in rats. However, because the conclusions in rats were based on increases in benign tumors, he felt that the conclusions for both sexes should be called equivocal evidence of benign tumor induction. Dr. E. McConnell, NTP, mentioned that pheochromocytomas are benign neoplasms; for the pituitary gland neoplasms, there were 2 adenocarcinomas in the control group versus 10 in the exposed groups. Dr. Huff reminded the Panel that the morphologic type of neoplasms was always given in the conclusion.

In related discussion, Dr. Perera questioned the discounting of statistically significant results (adrenal gland pheochromocytomas in rats) because neither the trend nor the high dose incidence was significant by a newer statistical test, logistic regression analysis. She asked that this decision be better justified here and whenever statistically significant results are downgraded to equivocal evidence of carcinogenicity. Dr. J. Haseman, NIEHS, explained that logistic regression was employed because it does not require the utilization of time intervals and that there was some indication that, for this particular tumor, the survival patterns observed and the specific time intervals used by the incidental tumor test may have unduly influenced the statistical significance. He opined that the increased tumor incidence may have been related to the greater survival in the high dose group (38/50) relative to controls (22/50).

Dr. Jones moved that the Technical Report on oxytetracycline hydrochloride be accepted with the conclusions as written for male and female rats, equivocal evidence of carcinogenicity, and for male and female mice, no evidence of carcinogenicity. Dr. Swenberg seconded the motion, and it was approved by nine affirmative votes to one negative vote (Dr. Turnbull) with one abstention (Dr. Purchase).

I. INTRODUCTION

Physical and Chemical Properties

Production

Use

Absorption, Distribution, and Excretion

Acute Toxicity

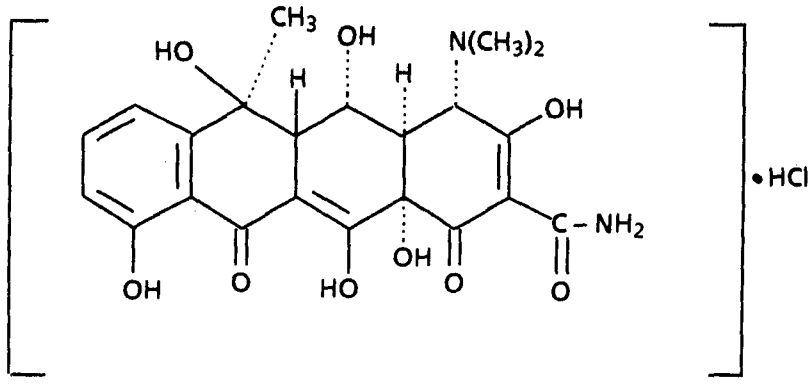
Chronic Toxicity and Carcinogenicity

Reproductive Effects and Teratogenicity

Mutagenicity

Study Rationale

I. INTRODUCTION



OXYTETRACYCLINE HYDROCHLORIDE

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2-Naphthacenecarboxamide,4(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-monohydrochloride

$C_{22}H_{24}N_2O_9 \cdot HCl$ Molecular weight 496.9

Synonyms: Biosolvomycin; Hydrocyclin; Liquamycin; Otetryn; Oxlopar; 5-Hydroxytetracycline Hydrochloride; Terramycin Hydrochloride; Tetramine; Tetran Hydrochloride

Oxytetracycline hydrochloride, a broad-spectrum antibiotic produced by the actinomycete *Streptomyces rimosus*, exerts antibiotic activity by inhibiting protein synthesis. This inhibition apparently takes place when oxytetracycline binds to 30S ribosomes, preventing aminoacyl tRNA from reaching the mRNA-ribosome complex (Sande and Mandell, 1980).

Physical and Chemical Properties

Recrystallized from water as yellow platelets, oxytetracycline hydrochloride has a melting point of 190°-194° C; it is very soluble in water (1 g/ml), soluble in absolute alcohol (12 mg/ml), and insoluble in ether, petroleum ether, and benzene. Aqueous solutions of oxytetracycline hydrochloride with a pH of 1.0-2.5 are stable for 30 days at 25° C, and those with a pH of 3.0-9.0 are stable for approximately the same time when stored at 5° C. When oxytetracycline hydrochloride crystals were stored at 56° C for 4 months, the potency was reduced by less than 5% (Merck, 1983; Spector, 1957).

Production

The 1983 production of tetracycline for all uses was 7.2 million pounds; data on the specific amounts of oxytetracycline hydrochloride produced are not available (USITC, 1984). In 1974, 1.1×10^5 kg of oxytetracycline hydrochloride was produced; the major producers were International Rectifier Corp., Rochelle Laboratories, and Pfizer, Inc. (Directory of Chemical Producers, 1977).

Use

Oxytetracycline hydrochloride is administered orally and intravenously in humans to treat infectious diseases caused by a wide variety of micro-organisms such as rickettsiae, *Mycoplasma pneumoniae*, spirochetes, gram-negative bacteria (*Pasteurella pestis, Bartonella bacilliformis*, Brucella sp.), and gram-positive bacteria (Streptococcus sp., *Staphlococcus aureus, Neisseria gonorrhoeae*) (Modern Drug Encyclopedia and Therapeutic Index, 1977). Topical

application is recommended only for ophthalmic uses because of the high risk of sensitization (Weinstein, 1970). The oral dose for adults ranges from 1 to 2 g per day in four equal doses. When infections are considered severe, oxytetracycline hydrochloride may be administered intravenously in doses of 1-2 g daily in two equal portions at 12-hour intervals. This antibiotic is available as capsules, tablets, injectable solutions, or syrup and is also sold in combination with other drugs (cortisone, nystatin, polymyxin) as an ophthalmic suspension (5%) or ointment (3%) (Modern Drug Encyclopedia and Therapeutic Index, 1977; PDR, 1980). Adverse effects of oxytetracycline hydrochloride observed in humans include local irritation after intramuscular injection; anorexia, nausea, vomiting, glossitis, dysphagia, and enterocolitis after oral or parenteral administration; and permanent discoloration of the teeth in infants and children under 8 years of age after prolonged use (PDR, 1980).

Injectable preparations of oxytetracycline hydrochloride (200 mg/ml) are administered to beef cattle and nonlactating dairy cows to treat the shipping fever complex associated with Pasteurella sp. and Hemophilus sp., foot rot and diphtheria caused by *Spherophorus necrophorus*, bacterial scours caused by *Escherichia coli*, "wooden" tongue caused by *Actinobacillus lignieresi*, leptospirosis caused by *Leptospira pomona*, and anthrax caused by *Bacillus anthracis*. These preparations are also used in swine to treat infectious enteritis and in poultry to treat sacculitis and fowl cholera caused by *Mycoplasma gallisepticum* and infectious synovitis caused by *M. synoviae*. The recommended dose is 3-5 mg per pound body weight per day. Oxytetracycline hydrochloride boluses fortified with vitamins A and D and niacin are used to treat scours in calves, dysentery in lambs, and necrotic enteritis in swine. This drug is also used for the treatment of acute/chronic mastitis in lactating dairy cows (Aronson, 1983).

Absorption, Distribution, and Excretion

Oxytetracycline hydrochloride is incompletely absorbed from the gastrointestinal tract; the amount of absorption in humans is about 60% when administered orally (Fabre et al., 1971). The percentage of absorbed oxytetracycline hydrochloride seems to be inversely related to the amount administered (Barza and Scheife, 1977). Absorption is decreased in the presence of calcium, magnesium, and iron due to chelation (Banerjee and Chakrabarti, 1976). The amount of oxytetracycline hydrochloride absorbed varies with the age of the subject. Single oral doses of 5 mg/kg were more completely absorbed in 1-day-old chicks than in chickens that were 1 week old; the highest concentrations of oxytetracycline hydrochloride were found in the kidneys and liver and the lowest in the lungs and serum (Black, 1977). The peak plasma concentration occurs soon after administration. In humans, the peak plasma concentration was reached 2-4 hours after a single oral dose and 2.5 hours after repeated dosing (Sande and Mandell, 1980; Green et al., 1976). In mares given an intravenous injection of 5 mg/kg oxytetracycline hydrochloride, the peak plasma concentration was attained in 30 minutes; the chemical was also detected in the synovial and peritoneal fluids. The concentration of oxytetracycline hydrochloride reached a peak of 1,565 µg/ml in the urine 30 minutes after administration (Brown et al., 1981).

The tetracyclines are stored in the reticuloendothelial cells of the liver, spleen, and bone marrow and in the bone, dentine, and enamel of unerupted teeth. They have been detected in the brain, saliva, pleural fluid, semen, prostatic fluid, placenta, and fetal tissue (Weinstein, 1970; Milch et al., 1957). Tetracyclines also have been observed to concentrate and persist in implanted tumor tissue in rats and mice (Rall et al., 1957). Tetracyclines are excreted primarily via the kidney; up to 55% of an oral dose or up to 60% of an intravenous injection is excreted in the urine, and some is excreted in the feces (Sande and Mandell, 1980). Oxytetracycline is excreted in high concentrations by the liver into the bile. The concentration in bile is 6-10 times greater than that in blood (Fabre et al., 1971). The volume of distribution of oxytetracycline hydrochloride is greater than that of body water because it binds to plasma proteins. The volume of distribution in dogs given a single intravenous injection of 5 mg/kg was 2 liters/kg body weight (Baggot et al., 1977). In humans given seven daily oral doses of 500 mg each, the volume of distribution was 4.07 liters/kg (Green et al., 1976).

Acute Toxicity

The acute LD_{50} values of oxytetracycline hydrochloride were reported to be 7,200 mg/kg (oral) in Swiss mice and less than 4.84 g/kg (intramuscular) in Wistar rats (P'an et al., 1950; Szumigowska et al., 1967).

Male Sprague-Dawley rats (300 g body weight) given 100 mg oxytetracycline hydrochloride by intraperitoneal injection for 14 days showed evidence of renal disease (interstitial infiltration, primarily of lymphocytes) and a loss of body weight (Tarara et al., 1976). A synergistic polyuric effect was seen in female Sprague-Dawley rats administered oxytetracycline hydrochloride (37.5 or 75 mg/kg per day by intraperitoneal injection) and methoxyflurane (1% concentration in air). These rats showed shrinkage of the glomeruli with a widening of the space in Bowman's capsule and deposition of protein in the tubules (Rosenberg and Wahlstrom, 1974). Two dogs (strain not specified) receiving 160 or 240 mg/kg body weight oxytetracycline hydrochloride by intramuscular injection died after 18 or 6 days and exhibited impaired renal functions 1-4 days before death. Histologic examination revealed cloudy swelling of the liver and fatty metamorphosis of the kidney (P'an et al., 1950).

Wistar rats injected intramuscularly with oxytetracycline hydrochloride (300 mg/kg) over an 8-hour period showed severe damage of the epithelium of the small intestine and fatty infiltration of the liver (De Jonge, 1973). Oxytetracycline hydrochloride (0.1 ml of 1% solution) injected intratympanically into albino guinea pigs caused sensory hair cell loss and inflammation of the middle ear mucosa (Parker and James, 1978). An intramuscular injection of 0.6 ml of a 50 mg/ml solution caused necrosis at the site of injection in white Leghorn hens (Blom and Rasmussen, 1976). Reduced bone mineralization occurred in 23-day-old Wistar rats receiving intraperitoneal injections of 2.8 mg in 0.5 ml water every 12 hours for 7 days. Concentrations of calcium and phosphorus in femurs of dosed rats were reduced 22% and 23% when compared with controls; collagen synthesis was not affected (Engesaeter et al., 1980).

Chronic Toxicity and Carcinogenicity

No adverse effects were observed on growth rate, feed consumption, and the formed elements of blood when 20 male and 20 female Sprague-Dawley rats were fed diets containing 100 or 1,000 ppm oxytetracycline hydrochloride for up to 2 years (Deichmann et al., 1964). The mean survival time for dosed rats was 11% greater than that of the controls. Mammary adenofibromas were observed in 12/17 female rats receiving 100 ppm and in 10/17 female rats receiving 1,000 ppm oxytetracycline hydrochloride compared with 1/9 controls. In a second study, groups of 100 male Osborne-Mendel rats fed diets containing 100, 1,000, or 3,000 ppm oxytetracycline hydrochloride gained weight more rapidly, had fewer deaths (control, 43%; 3,000 ppm, 13%), and lived longer than the controls (group of 180). No compound-related histopathologic effects were observed at 12, 15, or 18 months. The increased survival in the two studies cited above was thought to be due to the protective action of this antibiotic.

The incidence of liver tumors increased in Sprague-Dawley rats receiving oxytetracycline hydrochloride (1,000 ppm) and nitrite (1,000 ppm) in drinking water as compared with rats receiving oxytetracycline hydrochloride alone (Taylor and Lijinsky, 1975). The incidences were 1/15 for dosed males and 3/15 for dosed females. No liver tumors were observed in rats receiving oxytetracycline hydrochloride alone. Proliferation of Zajdela ascites hepatoma cells grown in adult male Wistar rats weighing about 200 g was arrested by intravenous infusion of 5 mg/kg per day oxytetracycline hydrochloride (van den Bogert et al., 1981).

Reproductive Effects and Teratogenicity

An increase in conception rate was observed in female rats ingesting 2 g/kg oxytetracycline hydrochloride (Elliot and Whitehall, 1957). Fetal litter weight from the exposed dams was elevated, but not significantly. No effect on reproductive performance (sperm volume and morphology, fertility, or hatchability of fertile eggs) was observed in turkeys given diets supplemented with Neomycin Terramycin (220 mg

neomycin plus 220 mg oxytetracycline hydrochloride) 1 day out of every 28 days, or 55 mg neomycin plus 55 mg oxytetracycline hydrochloride given continuously (Touchburn and Nestor, 1971).

Litter size and body weights of pups were reduced in litters obtained from albino rat dams injected with 200 mg/kg oxytetracycline hydrochloride (Takayama, 1965). Malformations in fetuses obtained from dosed dams increased by 11%; no malformations were noted in control fetuses. Administration of oxytetracycline hydrochloride to Wistar rats at doses of up to 0.48 g/kg (route unspecified) from the 1st to the 21st day of pregnancy resulted in reduced ossification in the anterior extremities of fetuses and an increase in fetal resorption (Szumigowska-Szrajber and Jeske, 1970, 1973). Daily intramuscular injections (41.5 mg/kg) to rats on days 7 through 18 of gestation had no effect on the number of implantations, the number of live and normal fetuses, the number or percentage of resorptions, or fetal body weight; no macroscopic malformations were observed (Savini et al., 1968).

In studies conducted for the NTP, oxytetracycline hydrochloride was found to be nonteratogenic when administered in corn oil by gavage during the time of organogenesis (gestational days 6-15) at doses of 1,325, 1,670, or 2,100 mg/kg per day to pregnant CD-1 mice and 1,200, 1,350, or 1,500 mg/kg per day to pregnant CD rats (Wolkoski-Tyl et al., 1983; Morrissey et al., 1986). Maternal toxic effects observed included death, reduced body weight, and reduced liver weights.

Mutagenicity

Oxytetracycline hydrochloride was not mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, or TA100 with or without metabolic activation (Andrews et al., 1980). However, after nitrosation with nitrous acid, oxytetracycline hydrochloride was mutagenic in all the aforementioned strains except TA1535. Further, in the host-mediated assay with randomly bred male and female Swiss mice, intraperitoneal doses of oxytetracycline hydrochloride of up to 100 mg/kg or of potassium nitrite at 150 µg/kg were not mutagenic in *S. typhimurium* strain G46, but a mutagenic response was obtained when the two compounds were tested in combination (Blitek et al., 1983). In the micronucleus test, oxytetracycline hydrochloride administered by gavage to Swiss mice at doses of up to 2 × 500 µg/kg produced significant increases in the frequency of micronuclei in bone marrow polychromatic erythrocytes both in the presence and absence of potassium nitrite. However, the investigators speculated that they may have failed to observe a dose-response relationship in these micronucleus tests because of changes in the ratio of erythrocytes to nucleated cells which resulted from bone marrow cytotoxicity associated with kinetically undefined nitrosodimethylamine formation.

In studies performed for the NTP, oxytetracycline hydrochloride at doses of up to 1 µg/plate was not mutagenic in *S. typhimurium* strains TA100, TA1535, TA1537, and TA98 with or without metabolic activation by Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Appendix G, Table G1). Oxytetracycline hydrochloride at doses of 100 and 200 µg/ml was mutagenic in L5178Y/TK$^{+/-}$ mouse lymphoma cells in the presence, but not in the absence, of Aroclor 1254-induced male F344 rat liver S9 (Tables G2 and G3). In cultured Chinese hamster ovary cells, oxytetracycline hydrochloride was weakly positive in inducing sister-chromatid exchanges both with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 but did not induce chromosomal aberrations (Tables G4 and G5).

Study Rationale

Oxytetracycline hydrochloride was nominated for toxicity and carcinogenicity testing by the National Cancer Institute because of extensive human exposure through its use as an antibiotic and because it had been inadequately studied (NCI, 1977). Because of the stability of this compound and because human exposure is usually via the oral route, oxytetracycline hydrochloride was given in feed to both rats and mice.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF OXYTETRACYCLINE HYDROCHLORIDE

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF OXYTETRACYCLINE HYDROCHLORIDE

USP-grade oxytetracycline hydrochloride was obtained in two lots from American Roland Corporation (New York, New York) (Table 1). The supplier provided documentation that both lots conformed to USP specifications (CFR, 1977). Purity and identity analyses were conducted at Midwest Research Institute (Appendix H). The identity of oxytetracycline hydrochloride was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectroscopic data were consistent with the structure of oxytetracycline hydrochloride. The purity of both lots of oxytetracycline hydrochloride was determined to be greater than 98% by elemental analysis, water analysis, nonaqueous titration of amines and acidic functional groups, thin-layer chromatography, and high-performance liquid chromatography. Water content of both lots ranged from 0.4% to 1%. Each lot contained an impurity of approximately 0.3%-0.4% which was not identified. Both lots of study material were determined to conform to USP specifications and to contain 100% oxytetracycline hydrochloride when compared with a USP standard by high-performance liquid chromatography.

Oxytetracycline hydrochloride was stable in storage for 2 weeks at 25° C (Appendix H). Oxytetracycline hydrochloride was stored at the study laboratory in the dark at 5° C. Periodic characterization of oxytetracycline hydrochloride by infrared spectroscopy, amine titration, and a ferric chloride potency assay detected no deterioration over the course of the studies.

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

The homogeneity of a formulated diet mixture was evaluated (Appendix I). Further studies showed that oxytetracycline hydrochloride at 10,000 ppm was stable in feed when stored for 2 weeks at 45° C. The formulated diets were prepared by adding a dry premix of feed and oxytetracycline hydrochloride to the appropriate amount of feed (Table 2). Formulated diets were stored at 25° C for no longer than 14 days. Periodic analysis for oxytetracycline hydrochloride in feed mixtures was performed by the study and analytical chemistry laboratories to determine if the formulated diets contained the correct concentrations of oxytetracycline hydrochloride (Table 3; Appendix J). Because 56/56 mixtures analyzed were within 10% of the target concentration, it is estimated that the feed mixtures were prepared within specifications 100% of the time (Appendix K, Table K1).

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers	304-G-004	304-G-004	304-G-004; 69150380
Date of Initial Use	9/17/79	3/24/80	Lot no. 304-G-004: rats--11/17/80; mice--11/10/80; lot no. 69150380: NA
Supplier	American Roland Corp. (New York, NY)	Same as 14-d studies	Same as 14-d studies

TABLE 2. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	The premix was prepared by weighing a quantity of chemical into a beaker and thoroughly mixing by spatula with weighed amount of feed. This process was repeated three times with additional weighed amounts of feed. The bulk mixing was carried out by mixing the premix with the appropriate amount of feed in a Patterson-Kelly® 8-quart twin-shell blender for 5 min with intensifier bar followed by 10 min mixing without the intensifier bar.	Similar to that of the 14-d studies	Similar to that of the 14-d studies
Maximum Storage Time	14 d	14 d	14 d
Storage Conditions	4° C in the dark	4° C in the dark	25° C

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

	Concentrations of Oxytetracycline Hydrochloride in Feed for Target Concentration (ppm)			
	6,300	12,500	25,000	50,000
Mean (ppm)	6,415	12,586	25,093	50,093
Standard deviation	233	440	783	1,450
Coefficient of variation (percent)	3.6	3.5	3.1	2.9
Range (ppm)	6,100-6,800	11,500-13,200	23,400-26,800	48,000-52,300
Number of samples	14	14	14	14

FOURTEEN-DAY STUDIES

Four- to five-week old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 2 weeks before the studies began.

Groups of five rats and mice of each sex were fed diets containing 0, 6,300, 12,500, 25,000, 50,000, or 100,000 ppm oxytetracycline hydrochloride for 14 consecutive days.

Rats and mice were observed twice per day and weighed once per week. Further details on animal maintenance are given in Table 4.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to oxytetracycline hydrochloride and to determine the concentrations to be used in the 2-year studies.

Five- to seven-week old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 18 days, separated according to weight class, and then assigned to cages according to a table of random numbers. Cages were assigned to exposed and control groups according to another table of random numbers.

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
0, 6,300, 12,500, 25,000, 50,000, or 100,000 ppm oxytetracycline hydrochloride in feed	0, 3,100, 6,300, 12,500, 25,000, or 50,000 ppm oxytetracycline hydrochloride in feed	Rats--0, 25,000, or 50,000 ppm oxytetracycline hydrochloride in feed; mice--0, 6,300, or 12,500 ppm oxytetracycline hydrochloride in feed
Date of First Dose		
9/17/79	3/24/80	Rats--11/17/80; mice--11/10/80
Date of Last Dose		
9/30/79	6/22/80	Rats--11/07/82; mice--10/31/82
Duration of Dosing		
14 consecutive d	13 wk	103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed on d 1 and 1 × wk thereafter; feed consumption determined 1 × wk	Same as 14-d studies	Observed 2 × d; weighed on d 1, 1 × wk for 14 wk, and monthly thereafter; feed consumption determined monthly. Palpation at weighing beginning on wk 41
Necropsy and Histologic Examination		
Necropsy performed on all animals; 10% of the animals examined histologically	Necropsy performed on all animals; histologic exam performed on all control animals, all dosed animals dying before the scheduled kill, all animals in the highest dose groups, and all dosed animals in which lesions were found at necropsy. Special studies--fluorescence was determined on extracts of the left femur from 5 rats and mice of each sex from the 0-, 3,100-, 12,500-, and 50,000-ppm groups.	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions, skin, mandibular lymph node, mammary gland, salivary gland, thigh muscle, sciatic nerve, sternebrae, vertebrae or femur including marrow, costochondrial junction (rib), oral cavity, thymus, larynx and pharynx, trachea, lungs and bronchi, heart and aorta, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, tongue, tissue masses and regional lymph nodes, ileum, colon, cecum, rectum, mesenteric lymph nodes, liver, gallbladder (mice), kidneys, adrenal glands, pancreas, spleen, urinary bladder, seminal vesicles/prostate/testes/epididymis or ovaries/uterus, nasal cavity and nasal turbinates, brain, pituitary gland, spinal cord, eyes, and preputial or clitoral gland
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)	Same as 14-d studies
Study Laboratory		
Physiological Research Laboratories	Same as 14-d studies	Same as 14-d studies
Method of Animal Identification		
Rats--tail mark; mice--ear punch	Toe clip	Toe and ear clip

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

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Time Held Before Study 14 d	18 d	Rats--18 d; mice--20 d
Age When Placed on Study 6-7 wk	Rats--7-8 wk; mice--7-9 wk	Rats--7-8 wk; mice--8-9 wk
Age When Killed 9 wk	Rats--20-21 wk; mice--20-23 wk	Rats--111-112 wk; mice--112-113 wk
Necropsy Dates Rats--10/2/79; mice--10/3/79	Rats--6/23/80-6/25/80; mice--6/25/80-6/27/80	Rats--11/15/82-11/18/82; mice--11/8/82-11/11/82
Method of Animal Distribution Distributed to weight classes and then assigned to cages according to a table of random numbers; cages assigned to groups according to another table of random numbers	Same as 14-d studies	Same as 14-d studies
Feed Rodent Laboratory Chow (Ralston Purina Co., St. Louis, MO)	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding Aspen wood chips (Minnesota Sawdust and Shavings Co., Anoka, MN)	Same as 14-d studies	Aspen wood shavings (Minnesota Sawdust and Shavings Co., Anoka, MN)
Water Automatic watering system (Edstrom Industries, Waterford, WI); softened to <1 grain/gal with sodium zeolite; filtered through spun polyethylene; available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
Cage Filters Reemay® spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 14-d studies	Same as 14-d studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--22.2°-24.4° C; hum--35%-45%; light 12 h/d; 120 room air changes/h	Temp--17.8°-25.0° C; hum--40%-60%; light 12 h/d; 120 room air changes/h	Temp--23.3° ± 1.1° C; hum--50% ± 10%; fluorescent light 12 h/d; 15 room air changes/h

II. MATERIALS AND METHODS

Groups of 10 rats and 10 mice of each sex were given diets containing 0, 3,100, 6,300, 12,500, 25,000, or 50,000 ppm oxytetracycline hydrochloride for 13 weeks. Control diets consisted of NIH 07 Rat and Mouse Ration (Appendix N). Formulated or control diets and water were available ad libitum. Further experimental details are summarized in Table 4.

Animals were observed two times per day; moribund animals were killed. Feed consumption was measured weekly by cage. Individual animal weights were recorded once per week.

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. The fluorescence of extracts of the left femur of five rats and mice of each sex was determined for the 0-, 3,100-, 12,500-, and 50,000-ppm groups.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 25,000, or 50,000 ppm oxytetracycline hydrochloride were fed to groups of 50 rats of each sex for 103 weeks. Diets containing 0, 6,300, or 12,500 ppm were fed to groups of 50 mice of each sex 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 these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the 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 4-5 weeks of age and mice, at 5-6 weeks of age. The animals were quarantined at the study laboratory for 18 days (rats) or 20 days (mice). Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7-8 weeks of age and mice, at 8-9 weeks of age. The health of the animals was monitored during the course of the studies 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 electrophoresis 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

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintence are given in Table 4.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 14 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was

performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. 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.

During necropsy, all organs and tissues were examined for grossly visible lesions. 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 evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The 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 assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. 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 analysis of pathology data, 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 for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain 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 Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: 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 actually examined for tumors 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.) A method for the analysis of incidental tumors based on logistic regression (Dinse and Lagakos, 1983) was also employed as a supplemental test in some instances. This method has the advantage of not requiring time intervals in the statistical evaluation.

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

FOURTEEN-DAY STUDIES

None of the rats died before the end of the studies (Table 5). Feed consumption by male rats that received 100,000 ppm in the diet was 35% lower than that of the controls. The final mean body weight of male rats that received 50,000 ppm or 100,000 ppm was 5% or 27% lower than that of the controls. The final mean body weight of female rats that received 100,000 ppm was 6% lower than that of the controls. No compound-related effects were observed at necropsy.

Based on the mean body weight depression observed at the 100,000-ppm concentration in both males and females, concentrations of 0, 3,100, 6,300, 12,500, 25,000, and 50,000 ppm oxytetracycline hydrochloride were selected for the 13-week studies in rats.

TABLE 5. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d)	(e)
MALE							
0	5/5	103 ± 4	178 ± 5	+75 ± 3	--	13.6	--
6,300	5/5	107 ± 3	188 ± 3	+81 ± 3	106	14.2	104
12,500	5/5	97 ± 2	172 ± 4	+75 ± 3	97	12.3	90
25,000	5/5	104 ± 5	172 ± 6	+68 ± 3	97	12.8	94
50,000	5/5	103 ± 2	169 ± 3	+66 ± 3	95	12.8	94
100,000	5/5	98 ± 3	130 ± 3	+32 ± 2	73	8.8	65
FEMALE							
0	5/5	89 ± 2	125 ± 3	+36 ± 1	--	9.5	--
6,300	5/5	90 ± 2	129 ± 2	+39 ± 1	103	9.5	100
12,500	5/5	87 ± 5	130 ± 5	+43 ± 1	104	11.2	118
25,000	5/5	91 ± 2	133 ± 5	+42 ± 3	106	9.5	100
50,000	5/5	90 ± 1	127 ± 3	+37 ± 2	102	8.8	93
100,000	5/5	88 ± 2	118 ± 3	+30 ± 2	94	8.2	86

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change ± standard error of the mean
(d) Grams of feed consumed per animal per day averaged over the 2-week period; not corrected for scatter. The estimated doses of oxytetracycline hydrochloride consumed per day, based on the average feed consumption and the mean of the initial and final body weights, are 604, 1,138, 2,319, 4,706, and 7,719 mg/kg for males and 544, 1,290, 2,109, 4,055, and 7,961 mg/kg for females.
(e) Percent feed consumption relative to controls

THIRTEEN-WEEK STUDIES

None of the rats died before the end of the studies (Table 6). Final mean body weights and feed consumption of dosed and control groups were comparable.

Degenerative vacuolization (diagnosed as periacinar fatty metamorphosis) of minimal severity was diagnosed in the liver of 5/10 males at 50,000 ppm, 2/10 males at 25,000 ppm, 5/10 males at 12,500 ppm, 5/10 males at 6,300 ppm, and 2/10 males at 3,100 ppm. Except for those males in the 3,100-ppm group, levels of oxytetracycline hydrochloride in bone as measured by fluorometric analysis generally increased with increase in dose (Table 7).

Dose Selection Rationale: Because oxytetracycline hydrochloride at the concentrations studied did not result in life-threatening toxic effects and because 5% chemical (except for dietary constituents) is considered to be the highest dietary dose that rats and mice can receive without reducing the nutritional value of the diet, concentrations of 0, 25,000, and 50,000 ppm oxytetracycline hydrochloride in feed were selected for the 2-year rat studies.

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

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d)	(e)
MALE							
0	10/10	128 ± 1	322 ± 6	+194 ± 6	--	15.7	--
3,100	10/10	131 ± 1	325 ± 8	+194 ± 8	101	14.6	93
6,300	10/10	129 ± 1	323 ± 4	+194 ± 4	100	14.2	90
12,500	10/10	152 ± 1	338 ± 6	+186 ± 7	105	15.3	97
25,000	10/10	141 ± 2	327 ± 8	+186 ± 9	102	14.8	94
50,000	10/10	132 ± 1	317 ± 3	+185 ± 3	98	15.1	96
FEMALE							
0	10/10	104 ± 1	186 ± 1	+82 ± 1	--	10.2	--
3,100	10/10	112 ± 1	191 ± 3	+79 ± 3	103	10.3	101
6,300	10/10	106 ± 1	191 ± 2	+85 ± 2	103	10.2	100
12,500	10/10	117 ± 1	202 ± 3	+85 ± 2	109	10.9	107
25,000	10/10	111 ± 1	191 ± 2	+80 ± 2	103	10.8	106
50,000	10/10	115 ± 1	197 ± 3	+82 ± 2	106	10.9	107

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change ± standard error of the mean
(d) Grams of feed consumed per animal per day not corrected for scatter; average of weeks 4 and 12. The estimated doses of oxytetracycline hydrochloride consumed per day, based on the average feed consumption and the mean of the initial and final body weights, are 198, 394, 778, 1,576, and 3,352 mg/kg for males and 210, 431, 854, 1,780, and 3,494 mg/kg for females.
(e) Percent feed consumption relative to controls

TABLE 7. OXYTETRACYCLINE CONCENTRATION IN BONE OF RATS IN THE THIRTEEN-WEEK FEED STUDIES AS DETERMINED BY A FLUORESCENCE ASSAY (a)

Concentration (ppm)	Male (μg/g)	Female (μg/g)
0	142 ± 73.5	44.7 ± 33.0
3,100	135 ± 42.1	154.0 ± 70.0
12,500	217 ± 56.5	(b) 248.0 ± 47.0
50,000	(b) 434 ± 107.0	(b) 452.0 ± 116.0

(a) Micrograms oxytetracycline per gram of bone (left femur)
(b) $P<0.01$ vs controls

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 5%-8% lower than those of the controls from week 4 to week 47 (Table 8 and Figure 1). Mean body weights of low dose and high dose female rats were comparable to those of the controls throughout most of the study. The average daily feed consumption by low dose and high dose rats was 102% and 103% that of the controls for males and 106% and 104% for females (Appendix M, Tables M1 and M2). The average amount of oxytetracycline hydrochloride consumed per day was approximately 1,000 or 2,000 mg/kg.

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

Week on Study	Control Av. Wt. (grams)	Control No. of Survivors	25,000 ppm Av. Wt. (grams)	25,000 ppm Wt. (percent of controls)	25,000 ppm No. of Survivors	50,000 ppm Av. Wt. (grams)	50,000 ppm Wt. (percent of controls)	50,000 ppm No. of Survivors
MALE								
1	135	50	140	104	50	138	102	50
2	186	50	184	99	50	177	95	50
3	210	50	215	102	50	202	96	50
4	240	50	241	100	50	227	95	50
5	264	50	262	99	50	249	94	50
6	282	50	278	99	50	264	94	50
7	296	50	292	99	50	278	94	50
8	311	50	304	98	50	291	94	50
9	325	50	317	98	50	302	93	50
10	335	50	326	97	50	311	93	50
11	345	50	334	97	50	319	92	50
12	356	50	344	97	50	328	92	50
13	364	50	352	97	50	338	93	50
14	372	50	358	96	50	343	92	50
17	400	50	387	97	50	369	92	50
21	411	50	394	96	50	379	92	50
26	429	50	417	97	50	401	93	50
31	425	50	415	98	50	399	94	50
35	430	50	421	98	50	404	94	50
39	443	50	429	97	50	418	94	50
43	450	50	440	98	50	428	95	50
47	453	50	449	99	49	432	95	50
51	460	50	451	98	49	441	96	50
55	461	50	452	98	48	444	96	50
60	472	49	454	96	48	448	95	50
64	464	47	457	98	47	447	96	50
68	461	44	455	99	46	447	97	50
73	454	44	451	99	46	444	98	50
77	453	39	454	100	46	450	99	49
81	448	37	446	100	46	441	98	48
85	449	35	444	99	44	439	98	48
89	451	34	443	98	41	439	97	46
95	436	31	438	100	36	434	100	44
98	430	27	430	100	34	420	98	43
102	423	24	426	101	30	421	100	38
FEMALE								
1	114	50	113	99	50	115	101	50
2	136	50	132	97	50	132	97	50
3	146	50	145	99	50	145	99	50
4	158	50	156	99	50	154	97	50
5	168	50	166	99	50	165	98	50
6	177	50	172	97	50	171	97	50
7	183	50	178	97	50	175	96	50
8	188	50	184	98	50	178	95	50
9	194	50	189	97	50	184	95	50
10	199	50	193	97	50	188	94	50
11	202	50	194	96	50	193	96	50
12	205	50	195	95	50	195	95	50
13	209	50	203	97	50	201	96	50
14	213	50	203	95	50	202	95	50
17	224	50	216	96	50	216	96	50
21	224	50	220	98	50	215	96	50
26	233	50	231	99	50	225	97	50
31	236	50	236	100	50	233	99	50
35	239	50	238	100	50	234	98	50
39	243	50	245	101	50	240	99	50
43	247	50	251	102	50	247	100	50
47	257	50	258	100	50	252	98	50
51	268	50	269	100	50	262	98	50
55	275	50	275	100	49	268	97	50
60	289	50	285	99	49	277	96	49
64	299	50	295	99	49	284	95	49
68	304	50	302	99	49	291	96	49
73	311	50	313	101	49	300	96	48
77	315	50	318	101	49	306	97	47
81	319	50	318	100	48	307	96	47
85	321	50	318	99	46	306	95	44
89	323	47	319	99	43	308	95	42
95	328	41	321	98	39	315	96	39
98	327	38	318	97	36	311	95	37
102	325	34	314	97	31	308	95	35

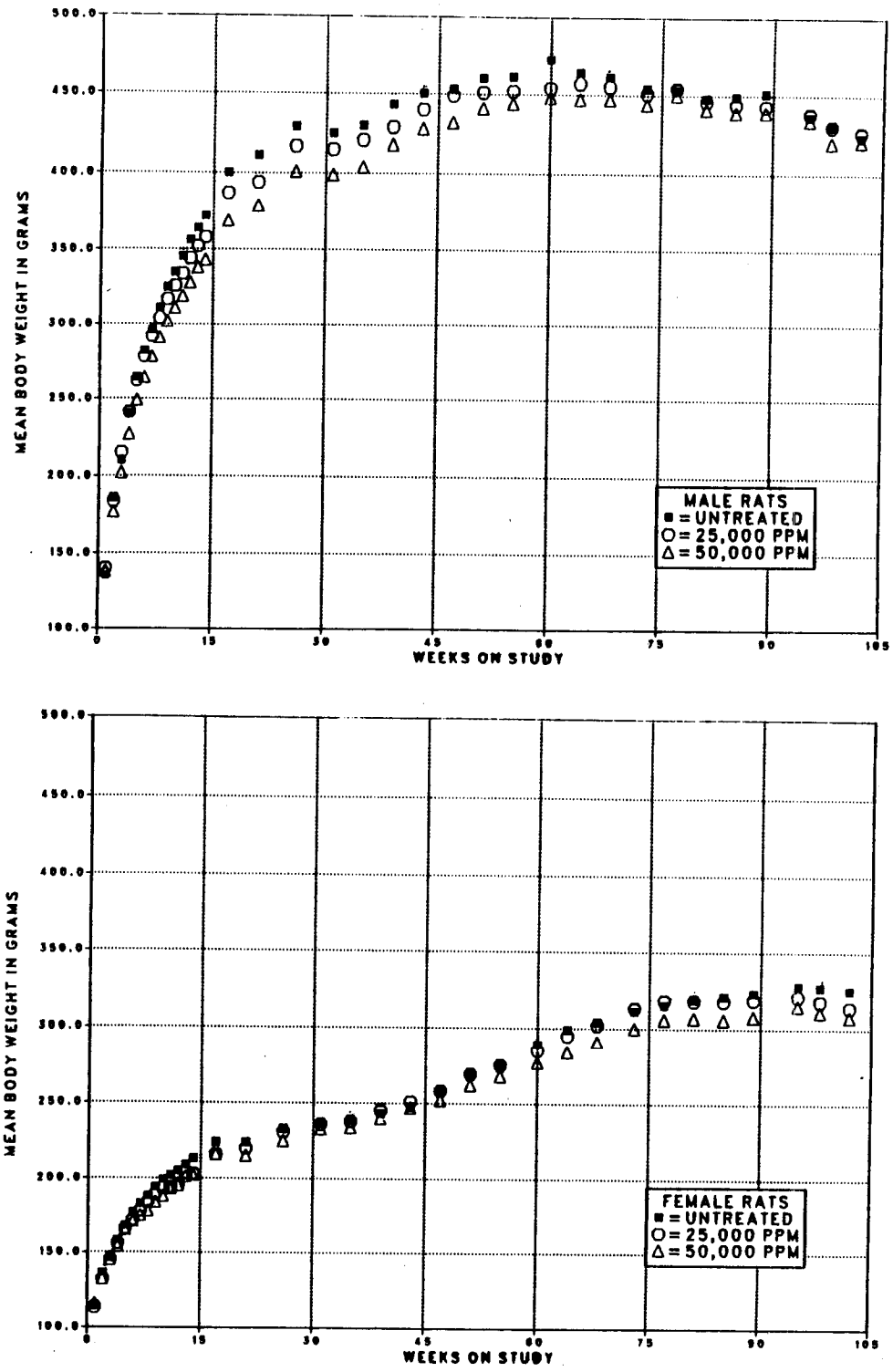


FIGURE 1. GROWTH CURVES FOR RATS FED DIETS CONTAINING OXYTETRACYCLINE HYDROCHLORIDE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing oxytetracycline hydrochloride at the concentrations used in these studies and for controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the control group of male rats was significantly lower than that of the high dose group after week 74 (Table 9). No significant differences were observed between any other groups of either sex.

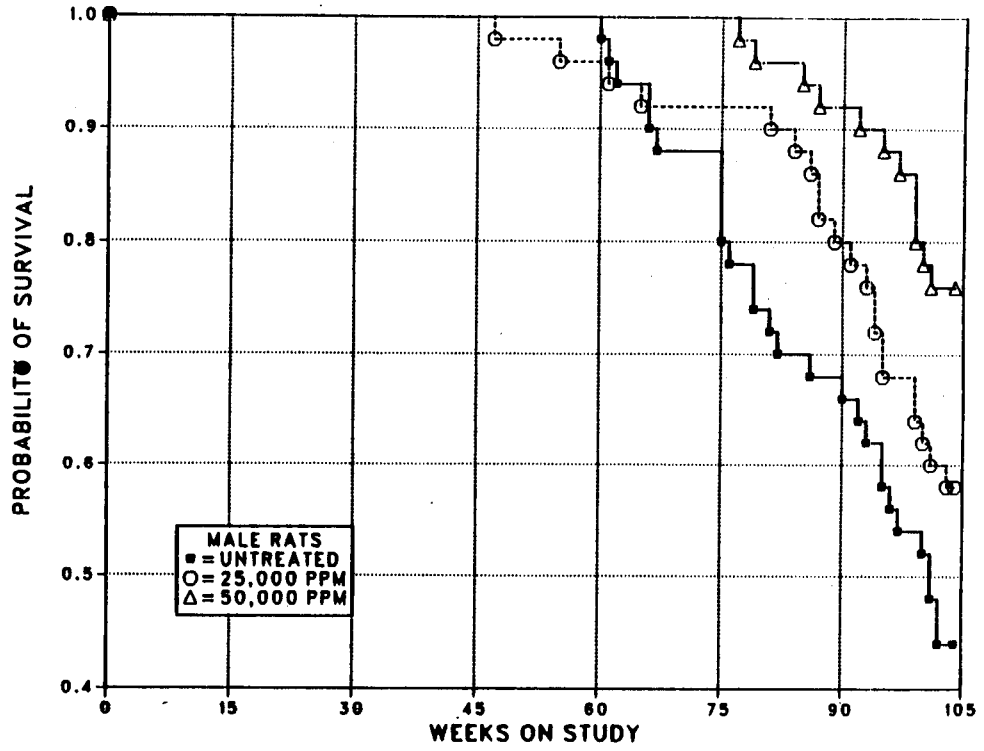
Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the adrenal gland, pituitary gland, and liver. 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 OXYTETRACYCLINE HYDROCHLORIDE

	Control	25,000 ppm	50,000 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	28	21	12
Killed at termination	22	28	38
Died during termination period	0	1	0
Survival P values (c)	0.001	0.173	0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	22	16
Killed at termination	30	28	34
Died during termination period	1	0	0
Survival P values (c)	0.783	0.612	0.836

(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.



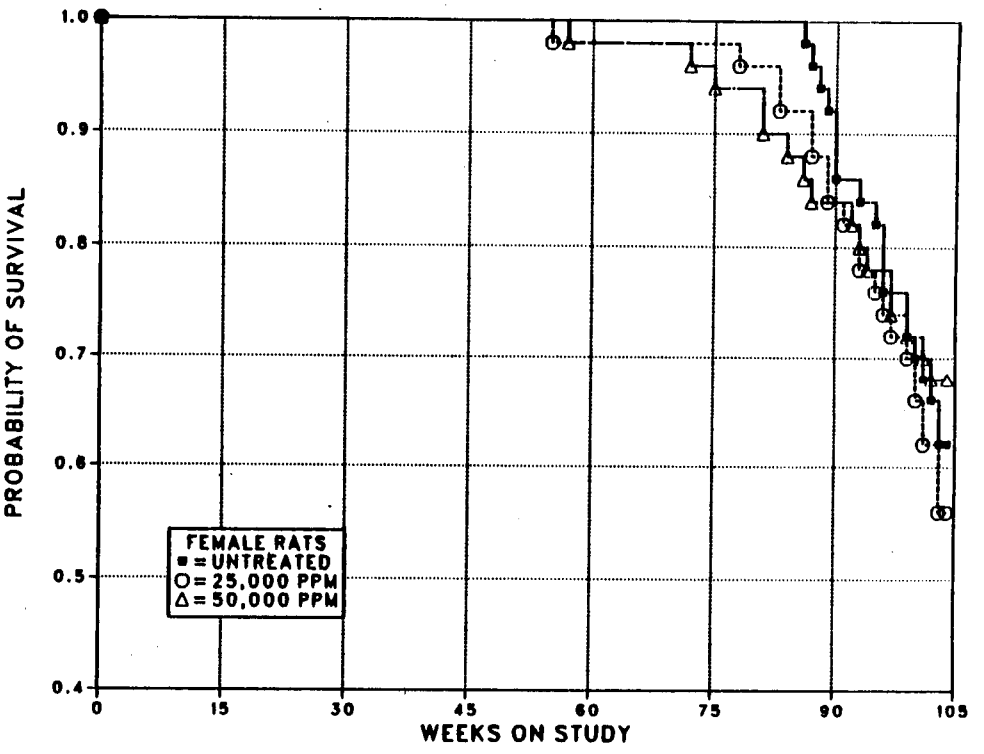


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING OXYTETRACYCLINE HYDROCHLORIDE FOR TWO YEARS

Adrenal Gland: The incidence of adrenal gland medullary hyperplasia in low dose male rats was greater than that in the controls (Table 10). Pheochromocytomas and pheochromocytomas or malignant pheochromocytomas (combined) in male rats occurred with significant positive trends ($P<0.05$) by the incidental tumor test, and the incidences in the high dose group were significantly greater ($P<0.05$) than those in the controls by the incidental tumor test. The incidences of pheochromocytomas were lower in dosed female rats than in the controls (control, 6/50; low dose, 4/50; high dose, 3/50).

Further examination of the male rat data revealed a pattern of survival suggesting that the incidental tumor test may have been unduly affected by the incidence of pheochromocytomas in the 53- to 78-week time interval (control, 1/11; high dose, 1/1). Thus, a method for the analysis of incidental tumors based on logistic regression (Dinse and Lagakos, 1983) was used as a supplemental test. This method of analysis does not require time intervals and indicated no significant ($P<0.05$) effects for the combined incidence of pheochromocytomas or malignant pheochromocytomas (Table 10).

TABLE 10. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF OXYTETRACYCLINE HYDROCHLORIDE (a)

	Control	25,000 ppm (b)	50,000 ppm (b)
Adrenal Medullary Hyperplasia			
Overall Rates	7/50 (14%)	14/50 (28%)	9/50 (18%)
Pheochromocytoma			
Overall Rates	10/50 (20%)	18/50 (36%)	24/50 (48%)
Adjusted Rates	37.2%	51.2%	52.9%
Terminal Rates	6/22 (27%)	12/29 (41%)	17/38 (45%)
Week of First Observation	95	94	77
Life Table Tests	P=0.161	P=0.221	P=0.166
Incidental Tumor Tests	P=0.014	P=0.135	P=0.015
Logistic Regression Analysis	P=0.027	P=0.149	P=0.024
Malignant Pheochromocytoma			
Overall Rates	2/50 (4%)	1/50 (2%)	0/50 (0%)
Pheochromocytoma or Malignant Pheochromocytoma (c)			
Overall Rates	12/50 (24%)	19/50 (38%)	24/50 (48%)
Adjusted Rates	41.0%	52.6%	52.9%
Terminal Rates	6/22 (27%)	12/29 (41%)	17/38 (45%)
Week of First Observation	75	94	77
Life Table Tests	P=0.305	P=0.314	P=0.312
Incidental Tumor Tests	P=0.026	P=0.163	P=0.026
Logistic Regression Analysis	P=0.061	P=0.211	P=0.053

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) The estimated dose in milligrams per kilogram per day is given in Chapter III (Body Weights and Clinical Signs) and in Appendix M.
(c) Historical incidence in NTP studies (mean ± SD): 358/1,702 (21% ± 10%)

Pituitary Gland: Adenomas and adenomas or adenocarcinomas (combined) in female rats occurred with significant positive trends, and the incidences in the high dose group were significantly greater (by the incidental tumor test) than those in the controls (Table 11). The incidence of hyperplasia was slightly decreased in dosed female rats relative to controls.

Liver: The incidence of fatty metamorphosis was increased in low dose male rats (control, 8/50; low dose, 16/50; high dose, 7/50). Accessory structures were observed at increased incidences in dosed female rats (control, 2/50; low dose, 7/50; high dose, 9/50).

TABLE 11. ANALYSIS OF PITUITARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF OXYTETRACYCLINE HYDROCHLORIDE

	Control	25,000 ppm	50,000 ppm
Hyperplasia			
Overall Rates	16/50 (32%)	10/50 (20%)	11/50 (22%)
Adenoma			
Overall Rates	19/50 (38%)	17/50 (34%)	30/50 (60%)
Adjusted Rates	44.9%	52.9%	69.5%
Terminal Rates	9/31 (29%)	13/28 (46%)	21/34 (62%)
Week of First Observation	86	101	57
Life Table Tests	P=0.050	P=0.544N	P=0.066
Incidental Tumor Tests	P=0.012	P=0.477N	P=0.013
Adenocarcinoma			
Overall Rates	2/50 (4%)	7/50 (14%)	3/50 (6%)
Adjusted Rates	5.8%	17.5%	8.4%
Terminal Rates	1/31 (3%)	1/28 (4%)	2/34 (6%)
Week of First Observation	99	83	99
Life Table Tests	P=0.431	P=0.075	P=0.520
Incidental Tumor Tests	P=0.294	P=0.083	P=0.429
Adenoma or Adenocarcinoma (a)			
Overall Rates	20/50 (40%)	24/50 (48%)	32/50 (64%)
Adjusted Rates	47.4%	62.5%	72.6%
Terminal Rates	10/31 (32%)	14/28 (50%)	22/34 (65%)
Week of First Observation	86	83	57
Life Table Tests	P=0.044	P=0.202	P=0.051
Incidental Tumor Tests	P=0.004	P=0.230	P=0.007

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

FOURTEEN-DAY STUDIES

None of the mice died before the end of the studies (Table 12). The final mean body weights of male mice that received 25,000, 50,000, or 100,000 ppm in the diet were 11%-26% lower than that of the controls. The final mean body weight of female mice that received 100,000 ppm was 17% lower than that of the controls. Mice receiving 25,000 ppm or higher lost weight during the studies. During week 1, feed consumption at 50,000 and 100,000 ppm for males and females and at 25,000 ppm for males was 13%-37% lower than those of the corresponding controls. Rough hair coats were observed for males that received 100,000 ppm. No compound-related effects were observed at necropsy.

Based on the reduction in mean body weights of both males and females at 100,000 ppm, concentrations of 0, 3,100, 6,300, 12,500, and 50,000 ppm oxytetracycline hydrochloride were selected for the 13-week studies in mice.

TABLE 12. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d)	(e)
MALE							
0	5/5	26.2 ± 0.8	28.3 ± 0.9	+2.1 ± 0.2	--	3.2	--
6,300	5/5	24.8 ± 0.7	26.3 ± 0.7	+1.5 ± 0.5	92.9	2.7	84
12,500	5/5	25.9 ± 0.9	25.9 ± 0.8	0.0 ± 0.5	91.5	2.7	84
25,000	5/5	25.3 ± 0.7	25.2 ± 0.9	−0.1 ± 0.5	89.0	2.7	84
50,000	5/5	26.1 ± 0.8	23.7 ± 0.5	−2.4 ± 0.4	83.7	2.6	81
100,000	5/5	25.7 ± 0.6	20.8 ± 0.5	−4.9 ± 0.4	73.5	2.2	69
FEMALE							
0	5/5	20.4 ± 1.0	22.1 ± 0.9	+1.7 ± 0.4	--	3.1	--
6,300	5/5	21.5 ± 1.0	23.5 ± 0.7	+2.0 ± 0.5	106.3	3.2	103
12,500	5/5	20.4 ± 0.4	21.5 ± 0.4	+1.1 ± 0.2	97.3	2.8	90
25,000	5/5	21.0 ± 0.5	20.8 ± 0.5	−0.2 ± 0.2	94.1	2.8	90
50,000	5/5	21.5 ± 0.2	20.9 ± 0.4	−0.6 ± 0.2	94.6	3.0	97
100,000	5/5	22.3 ± 1.0	18.4 ± 0.5	−3.9 ± 0.9	83.3	2.5	81

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change ± standard error of the mean
(d) Grams of feed consumed per animal per day averaged over the 2-week period; not corrected for scatter. The estimated doses of oxytetracycline hydrochloride consumed per day, based on the average feed consumption and the mean of the initial and final body weights, are 653, 1,279, 2,624, 5,120, and 9,247 mg/kg for males and 896, 1,641, 3,349, 6,958, and 12,039 mg/kg for females.
(e) Percent feed consumption relative to controls

III. RESULTS: MICE

THIRTEEN-WEEK STUDIES

None of the mice died before the end of the studies (Table 13). The final mean body weights of mice that received 25,000 or 50,000 ppm were 3% or 15% lower than that of the controls for males and 8% or 12% for females. Estimated feed consumption by dosed groups was comparable to that of the controls.

Measurable amounts of oxytetracycline hydrochloride as determined by fluorometric analysis were found in the 3,100-, 12,500-, and 50,000-ppm groups of males and the 50,000-ppm group of females (Table 14); only trace amounts were detected at lower doses in females.

No compound-related clinical signs or gross or microscopic pathologic effects were observed.

Dose Selection Rationale: Because mean body weight gains of mice receiving 25,000 ppm or more oxytetracycline hydrochloride in feed were lower than those of the controls, concentrations of 0, 6,300, and 12,500 ppm oxytetracycline hydrochloride were selected for the 2-year studies.

TABLE 13. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d)	(e)
MALE							
0	10/10	22.7 ± 0.4	30.5 ± 0.4	+7.8 ± 0.5	--	4.2	--
3,100	10/10	24.1 ± 0.4	32.8 ± 0.6	+8.7 ± 0.4	107.5	3.6	86
6,300	10/10	25.5 ± 0.4	34.0 ± 0.5	+8.5 ± 0.9	111.5	3.5	83
12,500	10/10	20.5 ± 0.6	30.3 ± 0.7	+9.8 ± 1.0	99.3	3.8	90
25,000	10/10	24.7 ± 0.2	29.6 ± 0.4	+4.9 ± 0.3	97.0	4.1	98
50,000	10/10	23.6 ± 0.3	25.8 ± 0.3	+2.2 ± 0.3	84.6	4.1	98
FEMALE							
0	10/10	19.7 ± 0.2	25.6 ± 0.3	+5.9 ± 0.4	--	3.0	--
3,100	10/10	17.0 ± 0.3	23.5 ± 0.4	+6.5 ± 0.3	91.8	3.0	100
6,300	10/10	18.1 ± 0.3	24.4 ± 0.4	+6.3 ± 0.4	95.3	2.9	97
12,500	10/10	19.6 ± 0.2	25.0 ± 0.2	+5.4 ± 0.3	97.7	3.3	110
25,000	10/10	18.6 ± 0.2	23.5 ± 0.3	+4.9 ± 0.3	91.8	3.3	110
50,000	10/10	18.9 ± 0.3	22.4 ± 0.3	+3.5 ± 0.3	87.5	3.3	110

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change ± standard error of the mean
(d) Grams of feed consumed per animal per day not corrected for scatter; average of weeks 4 and 12. The estimated doses of oxytetracycline hydrochloride consumed per day, based on the average feed consumption and the mean of the initial and final body weights, are 392, 741, 1,845, 3,821, and 8,300 mg/kg for males and 459, 845, 1,850, 3,860, and 7,990 mg/kg for females.
(e) Percent feed consumption relative to controls

TABLE 14. OXYTETRACYCLINE CONCENTRATION IN BONE OF MICE IN THE THIRTEEN-WEEK FEED STUDIES AS DETERMINED BY A FLUORESCENCE ASSAY (a)

Concentration (ppm)	Male (μg/g)	Female (μg/g)
3,100	44.2	Trace
12,500	32.9	Trace
50,000	134.0	38.9

(a) Micrograms oxytetracycline per gram of bone (left femur)

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The mean body weights of high dose male mice were 5%-8% lower than those of the controls after week 31 (Table 15 and Figure 3). Mean body weights of low dose and control male mice were comparable throughout the studies. The mean body weights of high dose female mice were 5%-9% lower than those of the controls after week 26. The average daily feed consumption per mouse by low dose and high dose mice was 100% that of the controls for males and 100% and 103% for females (Appendix M, Tables M3 and M4). The average amount of oxytetracycline hydrochloride consumed per day was approximately 650 or 1,400 mg/kg.

TABLE 15. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

Week on Study	Control Av. Wt. (grams)	Control No. of Survivors	6,300 ppm Av. Wt. (grams)	6,300 ppm Wt. (percent of controls)	6,300 ppm No. of Survivors	12,500 ppm Av. Wt. (grams)	12,500 ppm Wt. (percent of controls)	12,500 ppm No. of Survivors
MALE								
1	25.1	50	25.2	100	50	25.0	100	50
2	26.9	50	27.1	101	50	26.3	98	50
3	27.6	50	27.2	99	50	26.4	96	50
4	28.4	50	28.0	99	50	27.5	97	50
5	29.6	50	28.5	96	50	27.8	94	50
6	30.4	50	30.0	99	50	28.8	95	50
7	31.0	50	30.7	99	50	29.9	96	50
8	31.7	49	31.1	98	50	30.3	96	50
9	31.6	49	31.3	99	50	30.5	97	50
10	32.4	49	32.5	100	50	31.3	97	50
11	31.5	49	31.5	100	50	30.2	96	50
12	32.9	49	32.7	99	50	31.7	96	50
13	33.0	49	33.7	102	50	32.6	99	50
14	33.6	49	33.9	101	50	33.3	99	50
17	35.4	48	37.2	105	49	34.8	98	49
21	36.9	48	38.0	103	48	36.6	99	48
26	37.7	48	38.6	102	47	36.4	97	48
31	39.2	48	38.6	98	46	37.0	94	47
35	38.5	48	38.9	101	45	36.9	96	47
39	39.6	48	39.8	101	45	37.7	95	47
44	39.5	48	39.8	101	45	37.8	96	47
48	40.8	47	41.3	101	45	39.0	96	47
52	41.2	47	41.8	101	45	39.3	95	47
56	42.5	46	42.8	101	45	40.1	94	47
61	42.0	46	42.1	100	45	40.3	96	47
65	41.8	46	41.4	99	44	39.5	94	47
69	42.3	45	41.4	98	44	39.4	93	46
74	41.4	45	40.4	98	44	39.0	94	44
78	41.8	45	41.4	99	42	39.4	94	44
82	41.0	45	40.3	98	42	39.0	95	44
86	40.4	45	39.0	97	42	38.2	95	43
90	40.3	44	38.4	95	41	37.8	94	43
96	38.9	38	37.9	97	36	37.3	96	39
99	39.5	35	38.2	97	34	37.2	94	37
103	40.3	31	38.2	95	33	37.2	92	34
FEMALE								
1	19.7	50	19.5	99	50	19.7	100	50
2	20.6	50	20.6	100	50	20.1	98	50
3	20.5	50	20.2	99	50	20.0	98	50
4	21.0	50	20.8	99	50	20.5	98	50
5	21.8	50	21.6	99	50	21.3	98	50
6	22.0	50	22.2	101	50	21.9	100	50
7	22.4	50	22.5	100	50	22.2	99	50
8	22.8	50	22.7	100	50	22.6	99	50
9	23.2	50	23.2	100	50	22.7	98	50
10	23.2	50	23.7	102	50	23.3	100	50
11	23.5	50	23.6	100	50	23.4	100	50
12	24.3	50	24.8	102	50	24.2	100	50
13	25.4	50	25.6	101	50	24.9	98	50
14	25.7	50	25.7	100	50	25.3	98	50
17	26.0	50	26.2	101	50	26.7	95	50
21	29.0	50	29.4	101	50	28.2	97	50
26	31.4	50	30.4	97	50	28.8	92	50
31	31.8	50	31.2	98	50	29.1	92	50
35	32.3	50	31.1	96	50	29.5	91	50
39	34.2	50	33.8	99	50	32.1	94	50
44	34.7	49	33.5	97	50	32.5	94	50
48	36.3	49	34.7	96	50	33.9	93	50
52	37.8	49	36.5	97	50	35.8	95	50
56	39.4	48	38.4	97	50	37.1	94	50
61	39.3	48	38.7	98	50	37.2	95	50
65	39.2	48	37.8	96	50	36.9	94	50
69	40.5	48	39.1	97	49	38.0	94	50
74	40.3	48	39.0	97	49	38.0	94	50
78	39.8	48	39.0	98	49	38.0	95	50
82	39.4	45	38.7	98	49	37.6	95	49
86	39.5	43	38.4	97	49	37.3	94	49
90	39.6	43	38.3	97	46	37.4	94	48
96	40.2	39	38.5	96	43	38.0	95	43
99	40.2	36	38.4	96	38	37.2	93	41
103	41.3	31	38.8	94	35	38.1	92	36

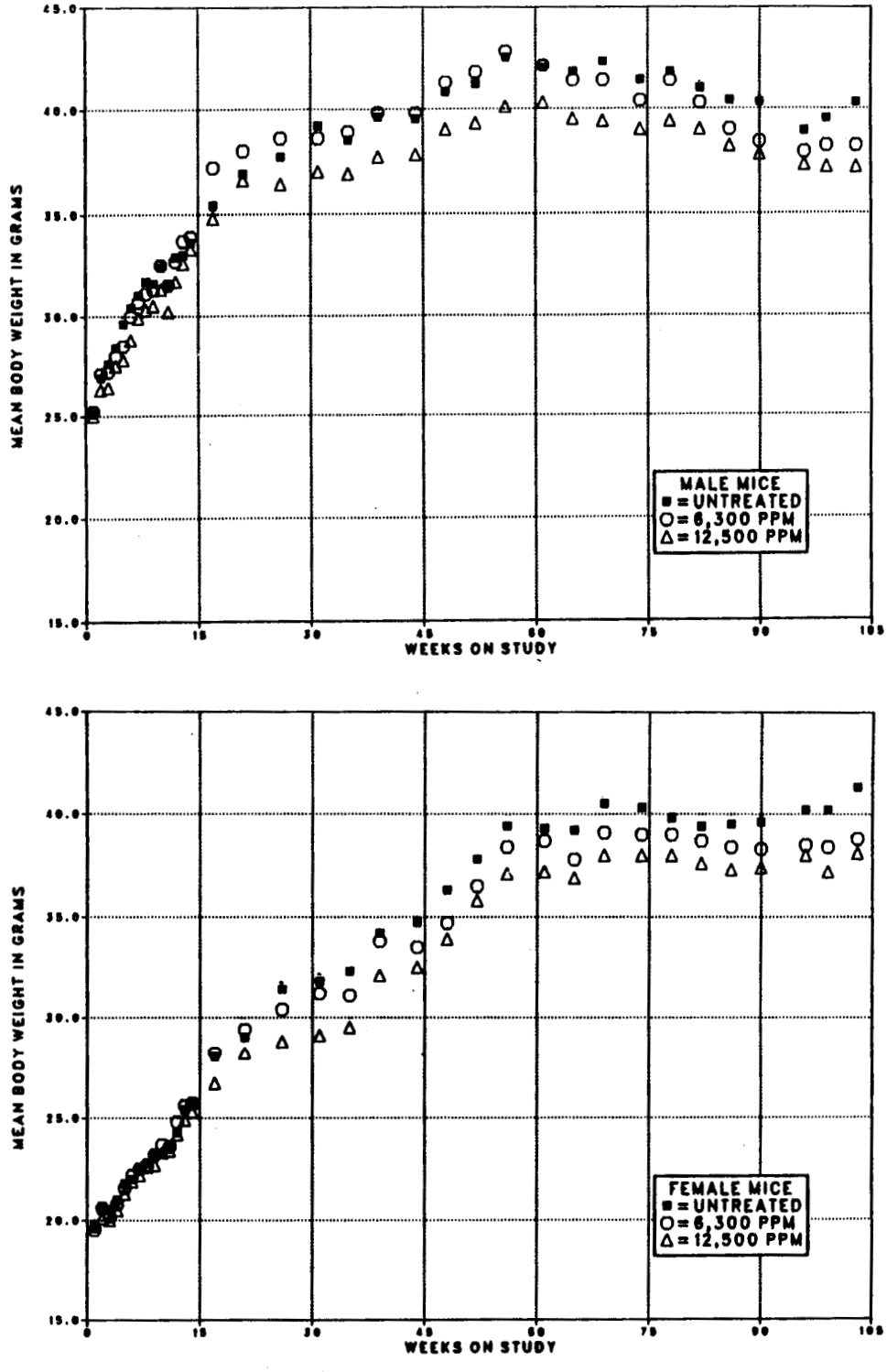


FIGURE 3. GROWTH CURVES FOR MICE FED DIETS CONTAINING OXYTETRACYCLINE HYDROCHLORIDE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing oxytetracycline hydrochloride at the concentrations used in these studies and for controls are shown in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex (Table 16).

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 and hematopoietic system. 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 16. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

	Control	6,300 ppm	12,500 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	17	16
Killed at termination	29	33	33
Died during termination period	2	0	1
Survival P values (c)	0.658	0.957	0.711
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	15	14
Killed at termination	31	34	36
Died during termination period	0	1	0
Survival P values (c)	0.268	0.438	0.315

(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.

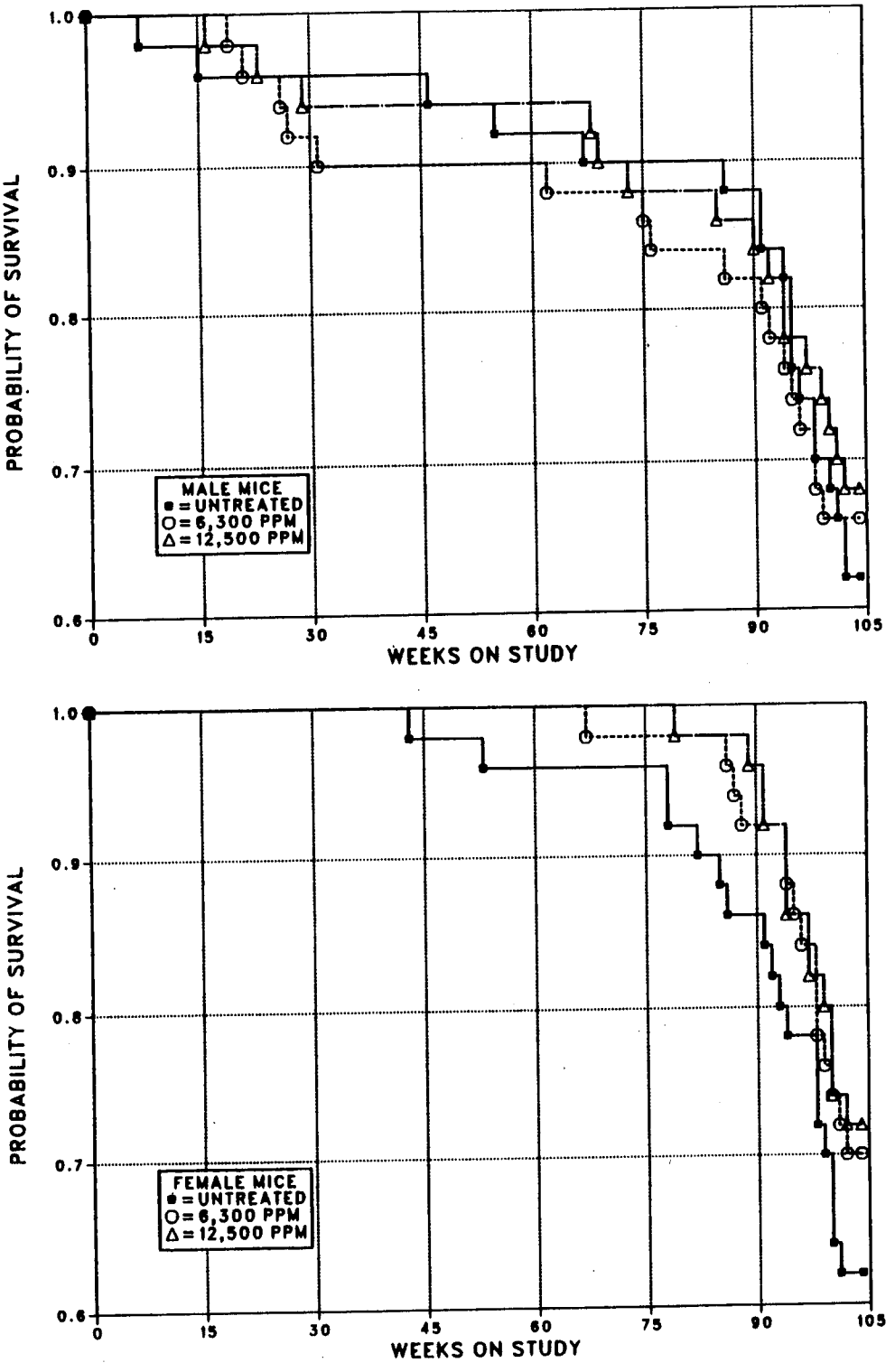


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING OXYTETRACYCLINE HYDROCHLORIDE FOR TWO YEARS

Liver: The incidence of hepatocellular adenomas or carcinomas (combined) in low dose female mice was significantly lower than that in the controls (Table 17).

Hematopoietic System: The incidence of lymphomas in low dose male mice was significantly lower than that in the controls (Table 18).

TABLE 17. ANALYSIS OF HEPATOCELLULAR ADENOMAS OR CARCINOMAS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF OXYTETRACYCLINE HYDROCHLORIDE (a)

	Control	6,300 ppm (b)	12,500 ppm (b)
Overall Rates	6/50 (12%)	0/50 (0%)	2/50 (4%)
Adjusted Rates	17.6%	0.0%	5.1%
Terminal Rates	4/31 (13%)	0/35 (0%)	1/36 (3%)
Week of First Observation	91		99
Life Table Tests	P=0.043N	P=0.013N	P=0.099N
Incidental Tumor Tests	P=0.052N	P=0.018N	P=0.118N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) The estimated dose in milligrams per kilogram per day is given in Chapter III (Body Weights and Clinical Signs) and in Appendix M.

TABLE 18. ANALYSIS OF MALIGNANT LYMPHOMAS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF OXYTETRACYCLINE HYDROCHLORIDE

	Control	6,300 ppm	12,500 ppm
Overall Rates	8/50 (16%)	1/50 (2%)	8/50 (16%)
Adjusted Rates	22.1%	2.4%	19.1%
Terminal Rates	5/31 (16%)	0/33 (0%)	3/34 (9%)
Week of First Observation	55	91	29
Life Table Tests	P=0.527N	P=0.020N	P=0.562N
Incidental Tumor Test	P=0.552	P=0.017N	P=0.597

IV. DISCUSSION AND CONCLUSIONS

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The main effects of oxytetracycline hydrochloride in the 14-day feed studies were reductions in mean body weights and feed consumption of rats and mice at 100,000 ppm; males were more sensitive than females. At this concentration, mean body weights relative to controls were reduced by 27% and 6% for male and female rats and by 26% and 17% for male and female mice; the reduction in average daily feed consumption was 35% and 14% for male and female rats and 31% and 19% for male and female mice. No compound-related deaths or gross pathologic changes were observed in any of the dose groups.

In the 13-week studies, mean body weight reductions (greater than 10%) were noted only in mice at 50,000 ppm (male, 15%; female, 12%). Average daily feed consumption of rats and mice receiving oxytetracycline hydrochloride was comparable to that of the controls. No deaths occurred during the studies. The only compound-related change observed was fatty metamorphosis in the liver of male rats (Appendix C); the incidences were 5/10 at 50,000 ppm, 2/10 at 25,000 ppm, 5/10 at 12,500 ppm, 5/10 at 6,300 ppm, and 2/10 at 3,100 ppm; the severity was judged to be minimal. In other studies, fatty infiltration was noted in Wistar rats injected intramuscularly with oxytetracycline hydrochloride (300 mg/kg) over an 8-hour period (De Jonge, 1973). Humans receiving large doses of aureomycin (chlorotetracycline) orally or intravenously developed hepatic dysfunction and fatty accumulation in the liver (Lepper, 1951).

The administration of oxytetracycline hydrochloride at concentrations of 6,300 or 12,500 ppm in the diet of mice for 2 years did not result in any significant toxic effect. Mean body weights and survival of dosed mice were similar to those of controls.

The administration of oxytetracycline hydrochloride at concentrations of 25,000 or 50,000 ppm in the diet of rats for 2 years did not adversely affect survival. These doses were considered to be the highest that could be given without affecting the nutritional value of the formulated diet. Survival of high dose male rats (38/50) was greater ($P=0.001$) than that of the controls (22/50); there was no clear reason for this difference. Thus, this increased survival may have been due to the administration of the antibiotic. In other studies, increased survival was noted in male and female Sprague-Dawley rats fed diets containing 1,000 ppm and in male Osborne-Mendel rats fed diets containing 3,000 ppm oxytetracycline hydrochloride for 2 years and was thought to be due to the "protective" effect of this antibiotic (Deichmann et al., 1964).

Mean body weights were approximately 5%-8% lower than those of controls in high dose male rats during weeks 4-47, in high dose male mice after week 31, and in high dose female mice after week 26. The mean body weights of dosed female rats and low dose male and female mice were comparable to those of controls.

Low dose male rats had an increased incidence of fatty metmorphosis in the liver (control, 8/50; low dose, 16/50; high dose, 7/50). Although dose-related increases were not seen in this 2-year study, the increase seen in the low dose group could be considered related to the exposure to oxytetracycline hydrochloride, since fatty metamorphosis was observed in male rats receiving this compound in the diet in the 13-week study and in Wistar rats injected intramuscularly with 300 mg/kg (De Jonge, 1973). This effect appears to be species specific, since only rats were affected.

Pheochromocytomas of the adrenal gland occurred with a positive trend in male rats (control, 10/50; low dose, 18/50; high dose, 24/50), and the incidence in the high dose group was greater than that in the controls (see Table 10). The incidence of malignant pheochromocytomas decreased slightly (2/50; 1/50; 0/50). Pheochromocytomas or malignant pheochromocytomas (combined) were observed in male rats with a positive trend by the incidental tumor test, and the incidence in the high dose group was greater than that in the controls. However, neither the trend nor the high dose incidence was statistically significant by logistic regression analysis ($P=0.061$ and 0.053, respectively), a procedure for incidental tumor analysis that does not require time intervals (Dinse and Lagakos, 1983). The increased incidence of pheochromocytomas in high dose male rats appears to be due in part to the improved survival in this group relative to controls. Since the incidence in the high dose

group was also greater than the control rate in NTP studies (358/1,702, 21%; range, 3/50-21/49, 6%-44%; Appendix F, Table F1), this increase may have been associated with exposure to oxytetracycline hydrochloride. Adrenal gland medullary hyperplasia was elevated slightly but not significantly in dosed male rats (7/50; 14/50; 9/50).

Adenomas or adenocarcinomas (combined) in the pituitary gland of female rats were observed with a positive trend ($P<0.05$), and the incidence was greater ($P<0.05$) in the high dose group than in the control group. The incidences were as follows: control, 20/50; low dose, 24/50; high dose, 32/50. Since the incidence in the high dose group was also greater than the control rate in NTP studies (805/1,704, 47%; range, 9/39-33/47, 23%-70%; Table F2), these tumors may have been related to exposure to this antibiotic. The incidence of hyperplasia of the pituitary gland was lower in dosed female rats than in controls (16/50; 10/50; 11/50).

Oxytetracycline hydrochloride (1,000 ppm) and nitrite (1,000 ppm) given in drinking water increased the incidence of liver tumors in Sprague-Dawley rats (Taylor and Lijinsky, 1975). The incidence of liver tumors was not increased in rats receiving oxytetracycline hydrochloride in the present studies, suggesting that nitrosation is essential for induction of liver tumors by this compound.

In male and female mice, no nonneoplastic or neoplastic lesions were considered related to the administration of oxytetracycline hydrochloride.

Oxytetracycline hydrochloride was not mutagenic in Salmonella strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation (Appendix G, Table G1) and did not induce chromosomal aberrations in Chinese hamster ovary cells either with or without metabolic activation (Table G5). The two highest doses of oxytetracycline hydrochloride tested in L5178Y/TK$^{+/-}$ mouse lymphoma cells induced forward mutations only in the presence of Aroclor 1254-induced male F344 rat liver S9, but the highest dose (200 µg/ml) was highly toxic and the second highest (100 µg/ml) was slightly toxic (Table G3). An increase in the frequency of sister-chromatid exchanges in Chinese hamster ovary cells was observed for all doses of oxytetracycline hydrochloride tested in the presence of S9, and the response increased with increasing dose (Table G4). However, the positive response in the absence of S9 was marginal, and control values, both in the presence and absence of S9, were high. Although studies by Blitek et al. (1983) and Andrews et al. (1980) indicate that oxytetracycline hydrochloride may be nitrosated to a genetically active agent, the mutagenicity of oxytetracycline hydrochloride is considered limited because the relative increase in SCEs was minimal and positive response in the mouse lymphoma assay was observed only at nearly toxic dose levels.

Conclusions: Under the conditions of these 2-year feed studies of oxytetracycline hydrochloride, there was *equivocal evidence of carcinogenicity** for male F344/N rats, as indicated by increased incidences of pheochromocytomas of the adrenal gland. There was *equivocal evidence of carcinogenicity* for female F344/N rats fed diets containing oxytetracycline hydrochloride, as indicated by increased incidences of adenomas of the pituitary gland. There was *no evidence of carcinogenicity* for male or female B6C3F$_1$ mice fed diets containing 6,300 or 12,500 ppm oxytetracycline hydrochloride for 2 years.

*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 13.

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	3 (6%)	1 (2%)
Squamous cell carcinoma	1 (2%)		
Trichoepithelioma		2 (4%)	
Keratoacanthoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	4 (8%)	1 (2%)	2 (4%)
Neurofibroma			1 (2%)
Neurofibrosarcoma		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma	1 (2%)		2 (4%)
Pheochromocytoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type		2 (4%)	
Leukemia, mononuclear cell	22 (44%)	22 (44%)	16 (32%)
#Thymus	(48)	(47)	(50)
Thymoma, benign		1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Neurofibrosarcoma			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Neurofibrosarcoma, invasive			1 (2%)
#Liver	(50)	(50)	(50)
Neoplastic nodule	6 (12%)	5 (10%)	7 (14%)
Hepatocellular carcinoma			2 (4%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(48)
Adenoma, NOS	20 (40%)	27 (54%)	15 (31%)
Adenocarcinoma, NOS	1 (2%)		
#Adrenal	(50)	(50)	(50)
Cortical adenoma	2 (4%)	2 (4%)	3 (6%)
#Adrenal cortex	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	10 (20%)	18 (36%)	24 (48%)
Pheochromocytoma, malignant	2 (4%)	1 (2%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(50)	(50)
C-cell adenoma	2 (4%)	2 (4%)	4 (8%)
C-cell carcinoma	1 (2%)	3 (6%)	3 (6%)
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma	2 (4%)	4 (8%)	7 (14%)
Islet cell carcinoma	4 (8%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS		2 (4%)	
Adenocarcinoma, NOS	1 (2%)	1 (2%)	1 (2%)
#Testis	(50)	(50)	(50)
Interstitial cell tumor	41 (82%)	37 (74%)	40 (80%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
*Ear canal	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		2 (4%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Pelvis	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
*Mesentery	(50)	(50)	(50)
Teratoma, benign			1 (2%)
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		2 (4%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, malignant		1 (2%)	
Foot			
Sarcoma, NOS	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	1	1
Moribund sacrifice	23	21	11
Terminal sacrifice	22	28	38

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	50	50	49
Total primary tumors	126	141	133
Total animals with benign tumors	48	48	48
Total benign tumors	84	100	100
Total animals with malignant tumors	33	29	25
Total malignant tumors	36	34	26
Total animals with secondary tumors##	2		1
Total secondary tumors	2		1
Total animals with tumors uncertain--benign or malignant	6	7	7
Total uncertain tumors	6	7	7

* 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 A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF OXYTETRACYCLINE HYDROCHLORIDE

	CONTROL (UNTR)	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)
Keratoacanthoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
Teratoma, benign	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	13 (26%)	9 (18%)	9 (18%)
#Iliac lymph node	(49)	(50)	(50)
Endometrial stromal sarcoma, metastatic			1 (2%)
#Thymus	(49)	(50)	(50)
Nonchromaffin paraganglioma			1 (2%)
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Neurofibrosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule	5 (10%)	4 (8%)	6 (12%)
#Pancreas	(50)	(50)	(50)
Endometrial stromal sarcoma, metastatic			1 (2%)
#Forestomach	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
#Duodenum	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
#Kidney/pelvis	(50)	(50)	(50)
Transitional cell carcinoma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(50)
Adenoma, NOS	19 (38%)	17 (34%)	30 (60%)
Adenocarcinoma, NOS	2 (4%)	7 (14%)	3 (6%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma	6 (12%)	5 (10%)	1 (2%)
#Adrenal cortex	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	6 (12%)	4 (8%)	3 (6%)
Ganglioneuroma			1 (2%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma	1 (2%)	1 (2%)	1 (2%)
Follicular cell carcinoma		1 (2%)	
C-cell adenoma	6 (12%)	6 (12%)	5 (10%)
C-cell carcinoma	2 (4%)	3 (6%)	2 (4%)
#Parathyroid	(41)	(39)	(34)
Adenoma, NOS			1 (3%)
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		1 (2%)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	2 (4%)
Fibroadenoma	21 (42%)	15 (30%)	15 (30%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	3 (6%)	2 (4%)	2 (4%)
Adenoma, NOS	2 (4%)	5 (10%)	2 (4%)
#Uterus	(50)	(50)	(50)
Endometrial stromal polyp	15 (30%)	10 (20%)	21 (42%)
Endometrial stromal sarcoma		1 (2%)	3 (6%)
#Ovary	(50)	(50)	(50)
Luteoma	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Adenocarcinoma, NOS, invasive	1 (2%)	3 (6%)	
Astrocytoma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
Squamous cell carcinoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Sarcoma, NOS, invasive			1 (2%)
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	3	3
Moribund sacrifice	18	19	13
Terminal sacrifice	30	28	34

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	49	44	49
Total primary tumors	111	96	114
Total animals with benign tumors	43	37	45
Total benign tumors	83	66	82
Total animals with malignant tumors	20	22	22
Total malignant tumors	23	26	26
Total animals with secondary tumors##	1	3	2
Total secondary tumors	1	3	3
Total animals with tumors uncertain--benign or malignant	5	4	6
Total uncertain tumors	5	4	6

* 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 OXYTETRACYCLINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	13 34	10 09	10 01	10 03	13 33	11 10	10 04	10 05	11 13	11 16	14 11	11 19	13 36	15 50	13 32	13 39	14 45	11 15	14 43	12 27	13 35	10 08	11 17	14 46	11 14
WEEKS ON STUDY	08 00	06 01	06 02	06 06	06 06	06 67	07 75	07 75	07 75	07 75	07 76	07 79	07 79	08 81	08 82	08 86	09 90	09 92	09 93	09 95	09 95	09 96	09 97	10 00	10 01
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma										X															
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma				X														X		X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																					X			X	X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS						X	X		X			X			X			X					X	X	X
Adenocarcinoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Cortical adenoma																									
Pheochromocytoma																					X		X	X	X
Pheochromocytoma, malignant							X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	+	+	+	–	–	–	–	–	+	–	+	–	+	–	+	+	+	+	+	+	–	+	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																				X					
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			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
Adenocarcinoma, NOS						X																			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma	X																								
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma							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
Foot, NOS																									
Sarcoma, NOS		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	12 03	10 06	14 07	10 02	10 07	11 11	11 12	11 18	12 20	12 21	12 22	12 24	12 25	12 26	12 28	12 29	13 30	13 31	13 37	13 38	14 40	14 42	14 44	14 48	14 49	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 01	10 02	10 02	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma										X																1
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																	X									4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic				X																						1
Alveolar/bronchiolar adenoma																					X					1
Alveolar/bronchiolar carcinoma							X																			1
Pheochromocytoma, metastatic	X																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule									X										X					X		6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS				X	X		X					X	X	X	X			X		X		X	X			20
Adenocarcinoma, NOS																X										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS											X															1
Cortical adenoma			X															X								2
Pheochromocytoma						X								X				X		X	X		X			10
Pheochromocytoma, malignant	X																									2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma				X				X																		2
C cell carcinoma			X																							1
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma						X						X														2
Islet cell carcinoma				X						X								X								4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	X	X	X	X	X	X	X	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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
Adenocarcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										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		X				X	22
Foot, NOS																										
Sarcoma, NOS																										1

* Animals necropsied

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

ANIMAL NUMBER	036	028	043	008	045	038	031	007	033	010	022	050	021	048	016	032	027	029	039	001	009	002	003	004	005
WEEKS ON STUDY	047	055	061	065	081	084	086	087	087	089	091	093	094	094	095	095	099	099	100	101	103	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma													X												
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma, benign																						X			
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule								X											X						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X		X		X	X		X				X		X	X	X	X					X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																		X							X
Pheochromocytoma													X			X	X		X	X	X		X		
Pheochromocytoma, malignant															X										
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																							X		
C-cell carcinoma																	X		X						
Parathyroid	+	+	+	–	–	–	–	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									X
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X		X		X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									X
Adenocarcinoma, NOS							X																		
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																									
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
Sarcoma, NOS	X																								
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant																					X				
Malignant lymphoma, lymphocytic type			X																X						
Leukemia, mononuclear cell		X			X	X		X	X	X	X			X	X	X	X	X		X	X				

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

ANIMAL NUMBER	0006	0011	0012	0013	0014	0015	0017	0018	0019	0020	0023	0024	0025	0026	0030	0034	0035	0037	0040	0041	0042	0044	0046	0047	0049	TOTAL:
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma										X			X							X						3
Trichoepithelioma																					X		X			2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Neurofibrosarcoma																						X				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma, benign																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule						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
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X	X				X		X			X		X	X	X	X	X		X	X		X	X	X	27
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										2
Pheochromocytoma	X	X	X	X		X		X					X	X	X			X					X			18
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma										X																2
C-cell carcinoma																									X	3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	−	+	−	+	−	+	−	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma		X										X			X											4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																							X			1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X		X	X	X	X	X		X	X		X		X	X	X	X	X	X		X	X		X	37
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
Adenoma, NOS											X															2
Adenocarcinoma, NOS																										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	*50
Carcinoma, NOS	X															X										2
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
Sarcoma, NOS																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS			X										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
Mesothelioma, malignant																										1
Malignant lymphoma, lymphocytic type																										2
Leukemia, mononuclear cell				X	X						X	X							X	X				X	X	22

* Animals necropsied

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

ANIMAL NUMBER	065	051	090	052	069	059	070	061	075	089	095	099	053	054	055	056	057	058	060	062	063	064	066	067	068
WEEKS ON STUDY	077	079	085	087	092	095	097	099	099	099	100	101	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma										X											X				
Neurofibroma																					X				
Neurofibrosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma, invasive					X																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule										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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X				X				X						X		X	X				X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma							X											X							
Pheochromocytoma	X		X	X			X	X	X			X		X	X			X		X		X	X	X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma								X						X											
C-cell carcinoma																								X	
Parathyroid	−	−	+	−	+	−	−	+	+	+	−	+	+	+	−	−	+	+	+	+	+	−	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma											X		X												
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	N	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X		X	X			X	X	X	X	X	X		X	X	X	X	X	X		X		X	
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
Adenocarcinoma, 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
Adenoma, NOS																									
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
Teratoma, benign									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			

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

ANIMAL NUMBER	071	072	073	074	076	077	078	079	080	081	082	083	084	085	086	087	088	091	092	093	094	096	097	098	100	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 papilloma		X																								1
Keratoacanthoma												X														1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										2
Neurofibroma																										1
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma	X																									2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurofibrosarcoma																		X								1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurofibrosarcoma, invasive																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule									X	X		X						X								7
Hepatocellular carcinoma			X				X																			2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
Adenoma, NOS		X	X			X					X			X		X								X	X	15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																		X								3
Pheochromocytoma		X		X	X			X		X	X						X						X	X	X	24
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell adenoma																X								X		4
C cell carcinoma				X									X													3
Parathyroid	+	+	+	+	+	+	+	−	+	+	+	+	−	−	−	+	+	−	+	−	+	−	+	+	+	33
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma	X				X							X												X	X	7
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X		X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	40
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
Adenocarcinoma, 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
Adenoma, NOS		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
Teratoma, benign																										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									16

* Animals necropsied

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

ANIMAL NUMBER	14 41	14 40	11 15	11 17	10 05	14 43	15 50	11 12	13 35	10 08	11 14	12 26	12 21	13 30	11 11	10 02	14 47	11 13	14 48	10 01	10 03	10 04	10 06	10 07	10 09
WEEKS ON STUDY	08 86	08 87	08 88	08 89	09 90	09 90	09 90	09 93	09 95	09 96	09 96	09 96	09 99	09 99	10 00	10 01	10 02	10 03	10 03	10 04	10 04	10 04	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																	X								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma, benign																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X			X				X		X					X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS														X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X			X	X	X		X			X			X		X		X	X		X	X		X
Adenocarcinoma, NOS														X											
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																						X			
Pheochromocytoma								X					X		X										
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma	X																								
C-cell carcinoma																				X					
Parathyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X							
Adenocarcinoma, NOS														X											
Fibroadenoma	X			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																
Adenoma, NOS				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp							X		X					X	X					X	X		X	X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive																									
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		

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

ANIMAL NUMBER	110	116	118	119	120	122	123	124	125	127	128	129	131	132	133	134	136	137	138	139	142	144	145	146	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Teratoma, benign																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurofibrosarcoma																		X								1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										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
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS							X			X			X			X				X			X			19
Adenocarcinoma, NOS																						X				2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma	X				X		X								X										X	6
Pheochromocytoma			X					X																	X	6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma											X															1
C-cell adenoma	X		X				X		X									X								6
C-cell carcinoma																			X							2
Parathyroid	+	−	+	+	+	+	+	+	+	−	−	−	+	+	+	+	−	+	+	−	−	+	+	+	+	41
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma													X			X										2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Fibroadenoma	X		X		X	X	X			X		X						X			X		X		21
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															3
Adenoma, NOS							X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp	X				X			X					X				X		X					X		15
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Luteoma																X										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, invasive																						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
Leukemia, mononuclear cell				X						X						X										13

* Animals necropsied

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

ANIMAL NUMBER	022	041	034	039	010	024	028	044	011	008	027	020	002	009	036	035	049	004	047	012	019	023	001	003	005
WEEKS ON STUDY	055	078	083	083	087	087	089	089	091	093	093	095	096	097	099	100	100	101	101	103	103	103	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule									X								X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X																						
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X	X	X	X		X		
Adenocarcinoma, NOS			X					X			X		X		X							X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Cortical adenoma									X			X								X					
Pheochromocytoma																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																							X		
Follicular cell carcinoma																									
C-cell adenoma													X											X	
C-cell carcinoma															X										
Parathyroid	+	−	−	+	+	−	+	−	−	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																X									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Adenocarcinoma, NOS											X														
Fibroadenoma										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											
Adenoma, NOS							X					X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp								X					X				X	X	X			X			
Endometrial stromal sarcoma				X																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, 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	0006	0007	0013	0014	0015	0016	0017	0018	0021	0025	0026	0029	0030	0031	0032	0033	0037	0038	0040	0042	0043	0045	0046	0048	0050	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	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule				X																				X		4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																			X							1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X		X		X	X		X			X				X				X	X			X	X	X	17
Adenocarcinoma, NOS													X													7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																X										1
Cortical adenoma								X																X		5
Pheochromocytoma					X											X									X	4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Follicular cell carcinoma								X																		1
C-cell adenoma	X						X	X											X							6
C-cell carcinoma					X																			X		3
Parathyroid	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma					X		X				X	X	X					X							X	15
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																2
Adenoma, NOS			X	X			X																			5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp			X										X	X										X		10
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, 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															9

* Animals necropsied

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

ANIMAL NUMBER	0098	0061	0075	0052	0085	0054	0067	0074	0077	1000	0086	0068	0099	0093	0065	0062	0051	0053	0055	0056	0057	0058	0059	0060	0063
WEEKS ON STUDY	057	072	075	081	081	084	086	087	092	093	094	097	097	099	101	102	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma, metastatic		X																							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nonchromaffin paraganglioma																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																X			X						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma, metastatic		X																							
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X			X				X	X		X	X	X		X	X	X			X		X		X	X
Adenocarcinoma, NOS														X							X	X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma															X			X							
Ganglioneuroma							X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma										X															
C-cell adenoma														X		X									
C-cell carcinoma																									
Parathyroid	−	−	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Fibroadenoma					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			
Adenoma, NOS						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp	X				X		X				X	X	X		X						X	X		X	
Endometrial stromal sarcoma		X																				X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																
Squamous cell carcinoma				X																					
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, 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
Leukemia, mononuclear cell			X							X			X			X					X				

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

ANIMAL NUMBER	0064	0066	0069	0070	0071	0072	0073	0076	0078	0079	0080	0081	0082	0083	0084	0087	0088	0089	0090	0091	0092	0094	0095	0096	0097	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
Sarcoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal sarcoma, metasta																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nonchromaffin paraganglioma							X																			1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule													X	X				X	X							6
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
Endometrial stromal sarcoma, metasta																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X			X	X	X		X	X	X		X	X	X		X			X		X	X	X		30
Adenocarcinoma, NOS																										3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma									X																	1
Pheochromocytoma																					X					3
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
C-cell adenoma	X												X			X										5
C-cell carcinoma	X							X																		2
Parathyroid	+	+	+	+	+	+	+	+	–	–	–	+	–	–	+	+	+	–	+	–	+	–	–	+	+	34
Adenoma, NOS																					X					1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS			X																							1
Adenocarcinoma, NOS							X											X								2
Fibroadenoma				X		X	X							X						X				X	X	15
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														2
Adenoma, NOS											X															2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp					X	X					X	X				X	X	X	X			X		X	X	21
Endometrial stromal sarcoma																									X	3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	N	*50
Carcinoma, NOS																										1
Squamous cell carcinoma																										1
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
Sarcoma, NOS, 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
Leukemia, mononuclear cell													X							X	X	X				9

* Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	3 (6%)	1 (2%)	1 (2%)
Fibroma	2 (4%)	4 (8%)	2 (4%)
Fibrosarcoma	8 (16%)	5 (10%)	3 (6%)
Osteosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	8 (16%)	4 (8%)	4 (8%)
Alveolar/bronchiolar carcinoma	2 (4%)	6 (12%)	3 (6%)
Pheochromocytoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		
Malignant lymphoma, lymphocytic type	1 (2%)		1 (2%)
Malignant lymphoma, histiocytic type	2 (4%)		2 (4%)
Malignant lymphoma, mixed type	3 (6%)	1 (2%)	4 (8%)
#Spleen	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
#Small intestine	(48)	(47)	(49)
Malignant lymphoma, mixed type	1 (2%)		
#Kidney	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type			1 (2%)
CIRCULATORY SYSTEM			
*Abdominal cavity	(50)	(50)	(50)
Hemangiosarcoma, metastatic	1 (2%)		
#Spleen	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)		
#Heart/atrium	(50)	(50)	(50)
Hemangioma			1 (2%)
#Liver	(50)	(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma		1 (2%)	
#Testis	(50)	(50)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	7 (14%)	8 (16%)	6 (12%)
Hepatocellular carcinoma	11 (22%)	9 (18%)	11 (22%)
#Duodenum	(48)	(47)	(49)
Adenocarcinoma, NOS		1 (2%)	
URINARY SYSTEM			
None			

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Adrenal	(50)	(49)	(50)
Cortical adenoma		2 (4%)	
#Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma	2 (4%)	5 (10%)	2 (4%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma			2 (4%)
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	4	5
Moribund sacrifice	15	13	12
Terminal sacrifice	29	33	33
TUMOR SUMMARY			
Total animals with primary tumors**	36	32	33
Total primary tumors	58	50	44
Total animals with benign tumors	17	20	15
Total benign tumors	22	24	18
Total animals with malignant tumors	29	21	23
Total malignant tumors	36	26	26
Total animals with secondary tumors##	2		1
Total secondary tumors	2		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 B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF OXYTETRACYCLINE HYDROCHLORIDE

	CONTROL (UNTR)	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)
Sarcoma, NOS		1 (2%)	
Fibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma	3 (6%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma		2 (4%)	
Adenosquamous carcinoma, metastatic		1 (2%)	
Granulosa cell carcinoma, metastatic		1 (2%)	
Fibrosarcoma, metastatic	1 (2%)		
Osteosarcoma, unclear primary or metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undiffer type	1 (2%)		
Malignant lymphoma, lymphocytic type	3 (6%)	1 (2%)	2 (4%)
Malignant lymphoma, histiocytic type	1 (2%)		2 (4%)
Malignant lymphoma, mixed type	7 (14%)	8 (16%)	8 (16%)
Lymphocytic leukemia	1 (2%)		
#Spleen	(50)	(50)	(50)
Malignant lymphoma, histiocytic type	1 (2%)		
Malignant lymphoma, mixed type	2 (4%)	1 (2%)	1 (2%)
#Mandibular lymph node	(48)	(46)	(49)
Malignant lymphoma, mixed type		1 (2%)	
#Mesenteric lymph node	(48)	(46)	(49)
Malignant lymphoma, histiocytic type			1 (2%)
#Axillary lymph node	(48)	(46)	(49)
Squamous cell carcinoma, metastatic	1 (2%)		
#Duodenum	(50)	(50)	(50)
Malignant lymphoma, mixed type			2 (4%)
#Thymus	(49)	(50)	(50)
Thymoma, benign	1 (2%)		
Malignant lymphoma, lymphocytic type	1 (2%)	1 (2%)	
Malignant lymphoma, mixed type	1 (2%)		
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangioma		1 (2%)	
Hemangiosarcoma		1 (2%)	
Hemangiosarcoma, metastatic	1 (2%)		
#Spleen	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)
#Liver	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)
#Uterus	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	1 (2%)
#Ovary	(44)	(48)	(49)
Hemangioma		1 (2%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	5 (10%)		1 (2%)
Hepatocellular carcinoma	2 (4%)		1 (2%)
#Duodenum	(50)	(50)	(50)
Adenomatous polyp, NOS		1 (2%)	
#Colon	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)		
#Colonic serosa	(50)	(50)	(50)
Sarcoma, NOS, invasive			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma	1 (2%)		1 (2%)
Tubular cell adenocarcinoma	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(50)
Adenoma, NOS	13 (26%)	16 (33%)	10 (20%)
Adenocarcinoma, NOS	3 (6%)		2 (4%)
#Adrenal	(49)	(50)	(50)
Cortical adenoma			1 (2%)
#Adrenal/capsule	(49)	(50)	(50)
Adenoma, NOS	1 (2%)		
#Thyroid	(50)	(50)	(49)
Follicular cell adenoma	2 (4%)	2 (4%)	1 (2%)
Follicular cell carcinoma		1 (2%)	
#Pancreatic islets	(50)	(49)	(50)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	1 (2%)
Adenosquamous carcinoma	1 (2%)	1 (2%)	
Fibroadenoma	1 (2%)	1 (2%)	
#Uterus	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
Endometrial stromal polyp	1 (2%)	2 (4%)	
#Ovary	(44)	(48)	(49)
Cystadenoma, NOS	2 (5%)		1 (2%)
Thecoma			1 (2%)
Granulosa cell carcinoma		1 (2%)	
Sarcoma, NOS			1 (2%)
Teratoma, benign			1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	4 (8%)	3 (6%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Vertebra	(50)	(50)	(50)
Osteosarcoma			1 (2%)
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	5	2
Moribund sacrifice	14	11	12
Terminal sacrifice	31	34	36
TUMOR SUMMARY			
Total animals with primary tumors**	43	34	36
Total primary tumors	64	50	50
Total animals with benign tumors	28	24	17
Total benign tumors	34	28	21
Total animals with malignant tumors	27	21	25
Total malignant tumors	30	22	28
Total animals with secondary tumors##	4	3	1
Total secondary tumors	4	3	1
Total animals with tumors uncertain-- primary or metastatic			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 OXYTETRACYCLINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	13 34	11 17	13 31	11 19	11 18	13 30	12 20	14 48	13 39	10 04	12 23	13 35	12 27	13 33	14 43	11 10	10 07	10 09	12 28	10 01	10 02	10 03	10 05	10 06	10 08
WEEKS ON STUDY	00 07	01 15	04 46	05 55	06 67	08 86	09 91	09 91	09 94	09 95	09 95	09 95	09 96	09 98	09 98	10 00	10 01	10 02	10 02	10 04	10 04	10 04	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS												X		X											
Fibroma																									
Fibrosarcoma						X	X		X		X	X				X	X							X	
Osteosarcoma																									X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X											X					X			
Alveolar/bronchiolar carcinoma																				X					
Pheochromocytoma, metastatic													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Thymus	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X		X								X									
Hepatocellular carcinoma							X					X			X			X	X						
Hemangioma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																			X						
Pheochromocytoma, malignant													X												
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
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
Adenoma, NOS																									
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
Hemangiosarcoma, 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
Malignant lymphoma, NOS																									
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type																X									
Malignant lymphoma, mixed type				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 B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	111	112	113	114	115	116	121	122	124	125	126	129	132	136	137	138	140	141	142	144	145	146	147	149	150	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 papilloma																								X		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS											X															3
Fibroma									X					X												2
Fibrosarcoma																										8
Osteosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X									X		X								X	X	8
Alveolar/bronchiolar carcinoma			X																							2
Pheochromocytoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma											X															2
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X												X			X	X					7
Hepatocellular carcinoma							X							X		X			X			X		X		11
Hemangioma	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Malignant lymphoma, mixed type																									X	1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																					X					2
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	–	–	+	+	+	+	+	–	–	+	+	–	+	–	+	–	+	+	–	+	–	+	+	–	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Adenoma, NOS															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
Hemangiosarcoma, 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
Malignant lymphoma, NOS						X																				1
Malignant lymphoma, lymphocytic type																						X				1
Malignant lymphoma, histiocytic type															X											2
Malignant lymphoma, mixed type							X																			3

* Animals necropsied

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

ANIMAL NUMBER	040	041	036	042	043	004	015	002	030	035	050	049	017	008	031	038	020	001	003	005	006	007	009	010	011
WEEKS ON STUDY	019	021	026	027	031	062	075	076	086	091	092	094	095	096	098	098	099	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																X									
Fibroma																									
Fibrosarcoma						X						X		X										X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X									X		
Alveolar/bronchiolar carcinoma											X								X			X	X		X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS									X																
Lymph nodes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X														X	
Hepatocellular carcinoma							X	X		X					X	X	X		X						
Hemangiosarcoma									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																X									
Pheochromocytoma																					X				
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS								X																	
Malignant lymphoma, mixed type										X															

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

ANIMAL NUMBER	012	013	014	016	018	019	021	022	023	024	025	026	027	028	029	032	033	034	037	039	044	045	046	047	048	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 papilloma																	X									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma					X						X							X					X			4
Fibrosarcoma																						X				5
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X								X											4
Alveolar/bronchiolar carcinoma					X																					6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X		X		X	X		X				X							8
Hepatocellular carcinoma															X	X										9
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma, NOS											X															1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma															X											2
Pheochromocytoma									X		X		X			X										5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	−	−	−	+	+	−	−	−	+	+	+	−	+	+	−	−	−	+	+	+	+	−	−	+	25
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Sarcoma, NOS																										1
Malignant lymphoma, mixed type																										1

* Animals necropsied

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

ANIMAL NUMBER	060	057	071	068	076	073	077	055	052	069	088	075	066	099	089	083	051	053	054	056	058	059	061	062	063
WEEKS ON STUDY	016	023	029	068	069	073	085	090	092	094	094	097	099	100	101	102	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS							X																		
Fibroma																				X					
Fibrosarcoma				X		X						X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic										X															
Alveolar/bronchiolar adenoma																					X	X			
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X														X					X
Hepatocellular carcinoma										X	X								X			X	X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type										X															
Urinary bladder	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
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
Malignant lymphoma, lymphocytic type			X																						
Malignant lymphoma, histiocytic type								X					X												
Malignant lymphoma, mixed type									X								X								

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

ANIMAL NUMBER	0064	0065	0067	0070	0072	0074	0078	0079	0080	0081	0082	0084	0085	0086	0087	0090	0091	0092	0093	0094	0095	0096	0097	0098	0100	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
Sarcoma, NOS																										1
Fibroma				X																						2
Fibrosarcoma																										3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma			X		X																					4
Alveolar/bronchiolar carcinoma											X									X						3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma						X																				1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X		X								X					6
Hepatocellular carcinoma	X						X					X							X			X			X	11
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, lymphocytic type																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma													X							X						2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																X							X			2
Parathyroid	+	+	−	−	−	+	+	+	−	+	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	35
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma			X																							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
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type		X										X														4

* Animals necropsied

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

ANIMAL NUMBER	124	136	142	143	126	127	114	138	139	122	125	106	134	149	121	105	118	123	108	101	102	103	104	107	109
WEEKS ON STUDY	043	053	078	078	082	085	086	091	092	093	094	098	098	098	099	100	100	100	101	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma											X														
Hemangiosarcoma, metastatic					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									
Fibrosarcoma, metastatic											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																		X							
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																			X						
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Thymoma, benign																									
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X						
Hepatocellular carcinoma								X																	
Hemangiosarcoma						X																			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma														X											
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma		X																							
Tubular cell adenocarcinoma		X																							
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																				X		X	X	X	
Adenocarcinoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X																
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	+	+	–	+	+	+	–	–	–	–	+	+	–	+	+	–	+	+	–	+	+	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Adenosquamous carcinoma																			X						
Fibroadenoma													X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+
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	N
Adenoma, NOS																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
Malignant lymphoma, undiffer type																	X								
Malignant lymphoma, lymphocytic type							X								X										
Malignant lymphoma, histiocytic type												X													
Malignant lymphoma, mixed type														X											X
Lymphocytic leukemia			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	110	111	112	113	115	116	117	119	120	128	129	130	131	132	133	135	137	140	141	144	145	146	147	148	150	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
Hemangiosarcoma, metastatic																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic					X																					1
Alveolar/bronchiolar adenoma										X				X					X							3
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Malignant lymphoma, histiocytic type		X																								1
Malignant lymphoma, mixed type						X																				2
Lymph nodes	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma, benign																			X							1
Malignant lymphoma, lymphocytic type					X																					1
Malignant lymphoma, mixed type																			X							1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X					X					X	X										5
Hepatocellular carcinoma					X																					2
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X		X	X	X			X				X						X			X			X		13
Adenocarcinoma, NOS									X				X	X												3
Adrenal	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma								X					X													2
Parathyroid	–	+	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	35
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																									X	1
Adenosquamous carcinoma																										1
Fibroadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp						X																				1
Ovary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	44
Cystadenoma, NOS	X																									2
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
Adenoma, NOS	X																		X							4
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type																						X				3
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type			X				X			X			X							X						7
Lymphocytic leukemia																										1

* Animals necropsied

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

ANIMAL NUMBER	0014	0026	0032	0044	0113	0225	0200	0155	0055	0311	0422	0441	0333	0477	0001	0002	0003	0004	0006	0007	0008	0009	0010	0111	0112
WEEKS ON STUDY	0677	0886	0887	0888	0994	0994	0995	0996	0998	0998	0998	0999	1000	1001	1002	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Hemangioma																									
Hemangiosarcoma																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic								X																	
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Adenosquamous carcinoma, metastatic															X										
Granulosa cell carcinoma, metastatic														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type													X												
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Malignant lymphoma, mixed type																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SY STEM																									
Salivary gland	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X						X	X	X					X	X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
Parathyroid	–	+	+	–	+	+	+	+	–	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																	
Adenosquamous carcinoma															X										
Fibroadenoma												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp							X																X		
Hemangiosarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma														X											
Hemangioma																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
Adenoma, 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
Malignant lymphoma, lymphocytic type									X																
Malignant lymphoma, mixed type				X	X		X																	X	

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

ANIMAL NUMBER	016	017	018	019	021	022	023	024	027	028	029	030	034	035	036	037	038	039	040	043	045	046	048	049	050	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
Sarcoma, NOS																X										1
Hemangioma												X														1
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma										X																1
Alveolar/bronchiolar carcinoma								X															X			2
Adenosquamous carcinoma, metastatic																										1
Granulosa cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	46
Malignant lymphoma, mixed type												X														1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, lymphocytic type															X											1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS									X																	1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Adenoma, NOS			X				X		X				X	X			X				X	X		X		16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma						X				X																2
Follicular cell carcinoma																						X				1
Parathyroid	+	+	+	+	–	–	–	+	+	–	+	+	+	–	+	–	+	–	–	+	+	+	+	+	+	36
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Adenocarcinoma, NOS														X												2
Adenosquamous carcinoma																										1
Fibroadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																										2
Hemangiosarcoma																	X									1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
Granulosa cell carcinoma																										1
Hemangioma																										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
Adenoma, NOS												X							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
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type	X			X					X							X										8

* Animals necropsied

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

ANIMAL NUMBER	060	074	081	100	051	053	080	061	087	085	055	075	095	068	052	054	056	057	058	059	062	063	064	065	066
WEEKS ON STUDY	079	089	091	091	094	094	094	097	097	099	100	100	100	102	104	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X							X																	
Osteosarcoma, unclear primary or metastatic												X													
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular carcinoma										X															
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																X									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, invasive								X																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																								X	
Tubular cell adenocarcinoma														X											
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X			X			X					X				X	
Adenocarcinoma, NOS							X																		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	+	+	–	–	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS			X																						
Hemangiosarcoma													X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																									
Thecoma																									
Sarcoma, NOS								X																	
Teratoma, benign									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS					X																				
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
Osteosarcoma								X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type											X						X								
Malignant lymphoma, histiocytic type	X																								
Malignant lymphoma, mixed type			X	X	X																X				

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

ANIMAL NUMBER	0067	0069	0070	0071	0072	0073	0076	0077	0078	0079	0082	0083	0084	0086	0088	0089	0090	0091	0092	0093	0094	0098	0097	0098	0099	TOTAL:
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	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				3
Osteosarcoma, unclear prim or metasta																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Malignant lymphoma, mixed type					X																					1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, histiocytic type											X															1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Hepatocellular carcinoma																										1
Hemangiosarcoma		X																								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type				X																						2
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, invasive																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X			X									X	X		X									10
Adenocarcinoma, NOS							X																			2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																		X								1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																							X			1
Parathyroid	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	42
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma													X													1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Hemangiosarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma, NOS	X																									1
Thecoma		X																								1
Sarcoma, NOS																										1
Teratoma, benign																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										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
Osteosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type																										2
Malignant lymphoma, histiocytic type								X																		2
Malignant lymphoma, mixed type									X			X					X			X						8

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		1 (2%)
Inflammation, active chronic		1 (2%)	
Calcinosis circumscripta		1 (2%)	
Hyperkeratosis	1 (2%)	1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	
Congestion, NOS	7 (14%)	1 (2%)	2 (4%)
Hemorrhage	3 (6%)	5 (10%)	2 (4%)
Bronchopneumonia, acute	1 (2%)		
Inflammation, chronic	1 (2%)		
Pneumonia, interstitial chronic	7 (14%)	4 (8%)	3 (6%)
Bronchopneumonia, chronic	1 (2%)	1 (2%)	
Cholesterol deposit		1 (2%)	
Hyperplasia, alveolar epithelium		1 (2%)	
Metaplasia, osseous	1 (2%)	4 (8%)	
Histiocytosis	5 (10%)	5 (10%)	4 (8%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(50)
Necrosis, NOS		1 (2%)	
Myelofibrosis	1 (2%)	2 (4%)	1 (2%)
Mastocytosis		1 (2%)	1 (2%)
#Spleen	(50)	(50)	(50)
Hematoma, NOS		1 (2%)	
Fibrosis	6 (12%)	2 (4%)	2 (4%)
Pigmentation, NOS	36 (72%)	33 (66%)	34 (68%)
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis	35 (70%)	27 (54%)	33 (66%)
#Splenic capsule	(50)	(50)	(50)
Fibrosis		1 (2%)	
#Lymph node	(49)	(49)	(49)
Hemosiderosis		1 (2%)	
#Mandibular lymph node	(49)	(49)	(49)
Congestion, NOS	1 (2%)		
Hemosiderosis	3 (6%)	2 (4%)	
Plasmacytosis	3 (6%)	3 (6%)	
Hyperplasia, lymphoid	2 (4%)	1 (2%)	
#Thoracic lymph node	(49)	(49)	(49)
Congestion, NOS	1 (2%)	1 (2%)	
Hemosiderosis	2 (4%)		
#Mesenteric lymph node	(49)	(49)	(49)
Cyst, NOS		1 (2%)	
Congestion, NOS	1 (2%)		
Edema, NOS		1 (2%)	
Pigmentation, NOS		1 (2%)	
Hemosiderosis	3 (6%)	1 (2%)	
Mastocytosis	1 (2%)		
#Salivary gland	(50)	(50)	(50)
Mastocytosis		1 (2%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Liver	(50)	(50)	(50)
Hematopoiesis	1 (2%)		
#Thymus	(48)	(47)	(50)
Embryonal duct cyst	19 (40%)	13 (28%)	19 (38%)
Congestion, NOS	1 (2%)	2 (4%)	
Hemosiderosis	1 (2%)	1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, chronic	41 (82%)	42 (84%)	48 (96%)
Necrosis, coagulative		1 (2%)	
#Heart/atrium	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	1 (2%)
Thrombus, organized	1 (2%)		1 (2%)
#Endocardium/left atrium	(50)	(50)	(50)
Mineralization		1 (2%)	
*Aorta	(50)	(50)	(50)
Mineralization			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization	2 (4%)		
*Testicular artery	(50)	(50)	(50)
Mineralization	1 (2%)		
Thrombus, organized		1 (2%)	
*Pulmonary vein	(50)	(50)	(50)
Mineralization	1 (2%)	3 (6%)	
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Cystic ducts	2 (4%)	3 (6%)	6 (12%)
Inflammation, active chronic		1 (2%)	
Inflammation, chronic	9 (18%)	7 (14%)	7 (14%)
Atrophy, NOS	4 (8%)	3 (6%)	7 (14%)
#Liver	(50)	(50)	(50)
Congenital malformation, NOS	1 (2%)	1 (2%)	2 (4%)
Congestion, NOS	1 (2%)		1 (2%)
Inflammation, acute	2 (4%)		
Granuloma, NOS	2 (4%)	2 (4%)	
Necrosis, NOS	11 (22%)	2 (4%)	5 (10%)
Metamorphosis, fatty	8 (16%)	16 (32%)	7 (14%)
Lipoidosis		1 (2%)	
Cytoplasmic vacuolization	1 (2%)	1 (2%)	
Basophilic cyto change	1 (2%)		3 (6%)
Focal cellular change	31 (62%)	33 (66%)	46 (92%)
Hepatocytomegaly	1 (2%)		
Hypertrophy, focal	1 (2%)		
Angiectasis	1 (2%)		
#Hepatic capsule	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Granuloma, NOS		1 (2%)	
#Liver/periportal	(50)	(50)	(50)
Inflammation, chronic	38 (76%)	27 (54%)	38 (76%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	49 (98%)	44 (88%)	48 (96%)
#Pancreas	(50)	(50)	(50)
Dilatation/ducts			1 (2%)
Fibrosis			1 (2%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(50)	(50)	(50)
Focal cellular change			1 (2%)
Atrophy, NOS	27 (54%)	29 (58%)	33 (66%)
Hyperplasia, NOS		5 (10%)	3 (6%)
#Glandular stomach	(50)	(50)	(50)
Mineralization	1 (2%)		
Degeneration, cystic	32 (64%)	39 (78%)	40 (80%)
#Forestomach	(50)	(50)	(50)
Ulcer, acute		1 (2%)	2 (4%)
Inflammation, active chronic		2 (4%)	1 (2%)
Hyperkeratosis	1 (2%)		1 (2%)
#Colon	(50)	(50)	(50)
Hematoma, NOS		1 (2%)	
Necrosis, ischemic		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis		1 (2%)	
Congestion, NOS	1 (2%)		1 (2%)
Hemorrhage	2 (4%)		
Nephropathy	49 (98%)	49 (98%)	49 (98%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS	4 (8%)		
Infarct, healed			1 (2%)
#Kidney/medulla	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Renal papilla	(50)	(50)	(50)
Necrosis, coagulative		1 (2%)	
#Kidney/tubule	(50)	(50)	(50)
Mineralization	28 (56%)	18 (36%)	30 (60%)
Necrosis, NOS		2 (4%)	
Pigmentation, NOS	42 (84%)	44 (88%)	39 (78%)
#Kidney/pelvis	(50)	(50)	(50)
Hemorrhage	3 (6%)	3 (6%)	3 (6%)
#Urinary bladder	(50)	(50)	(50)
Calculus, gross observation only		1 (2%)	
Calculus, microscopic examination	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		1 (2%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, active chronic	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(48)
Cyst, NOS	2 (4%)	2 (4%)	6 (13%)
Angiectasis		1 (2%)	
#Anterior pituitary	(50)	(50)	(48)
Cyst, NOS	5 (10%)	4 (8%)	5 (10%)
Multiple cysts			1 (2%)
Hemorrhage		1 (2%)	
Hyperplasia, NOS	18 (36%)	14 (28%)	29 (60%)
Angiectasis		1 (2%)	
#Adrenal/capsule	(50)	(50)	(50)
Hyperplasia, NOS			1 (2%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
Metamorphosis, fatty	28 (56%)	22 (44%)	26 (52%)
Pigmentation, NOS	42 (84%)	36 (72%)	41 (82%)
Cytoplasmic vacuolization			1 (2%)
Hyperplasia, NOS	8 (16%)	8 (16%)	11 (22%)
#Adrenal medulla	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Cytoplasmic vacuolization		1 (2%)	
Cytomegaly			1 (2%)
Hyperplasia, NOS	7 (14%)	14 (28%)	9 (18%)
#Thyroid	(50)	(50)	(50)
Embryonal duct cyst	1 (2%)	1 (2%)	
Mineralization		1 (2%)	2 (4%)
Cystic follicles	4 (8%)	5 (10%)	7 (14%)
Inflammation, chronic		1 (2%)	2 (4%)
Pigmentation, NOS	1 (2%)	1 (2%)	6 (12%)
Hyperplasia, C-cell	36 (72%)	31 (62%)	39 (78%)
Hyperplasia, follicular cell	5 (10%)	3 (6%)	7 (14%)
#Pancreatic islets	(50)	(50)	(50)
Hyperplasia, NOS	4 (8%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele		1 (2%)	1 (2%)
Hyperplasia, cystic	20 (40%)	14 (28%)	19 (38%)
*Prepuce	(50)	(50)	(50)
Calculus, microscopic examination		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Hemorrhage	1 (2%)		
Inflammation, suppurative		1 (2%)	
Inflammation, active chronic	3 (6%)	10 (20%)	4 (8%)
Inflammation, chronic		3 (6%)	1 (2%)
Hyperplasia, NOS			1 (2%)
#Prostate	(48)	(50)	(50)
Inflammation, suppurative	5 (10%)	6 (12%)	2 (4%)
Inflammation, active chronic	18 (38%)	21 (42%)	26 (52%)
*Seminal vesicle	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	2 (4%)	
Inflammation, active chronic	3 (6%)	3 (6%)	4 (8%)
Inflammation, chronic		1 (2%)	1 (2%)
#Testis	(50)	(50)	(50)
Necrosis, NOS			1 (2%)
Hyperplasia, interstitial cell	42 (84%)	36 (72%)	45 (90%)
#Testis/tubule	(50)	(50)	(50)
Mineralization	32 (64%)	22 (44%)	23 (46%)
Degeneration, NOS	39 (78%)	37 (74%)	39 (78%)
Oligospermia	6 (12%)	2 (4%)	4 (8%)
*Epididymis	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, active chronic			1 (2%)
*Scrotum	(50)	(50)	(50)
Steatitis	2 (4%)		
Inflammation, active chronic			1 (2%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Hemorrhage		1 (2%)	
#Brain	(50)	(50)	(50)
Hydrocephalus, internal	1 (2%)		
Hemorrhage	5 (10%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		
Malacia		1 (2%)	1 (2%)
Infarct, NOS		1 (2%)	
Corpora amylacea		1 (2%)	
Atrophy, pressure	2 (4%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage			1 (2%)
Retinopathy	2 (4%)	3 (6%)	1 (2%)
Cataract	2 (4%)	1 (2%)	1 (2%)
Phthisis bulbi			1 (2%)
*Eye/sclera	(50)	(50)	(50)
Mineralization		2 (4%)	
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Eye/crystalline lens	(50)	(50)	(50)
Cataract		2 (4%)	
*Ear canal	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
*Joint of lower extremity	(50)	(50)	(50)
Osteoarthritis		1 (2%)	
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Steatitis	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, chronic	6 (12%)	6 (12%)	2 (4%)
Pigmentation, NOS	7 (14%)	5 (10%)	8 (16%)
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 OXYTETRACYCLINE HYDROCHLORIDE

	CONTROL (UNTR)	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, active chronic	1 (2%)		
Inflammation, chronic		1 (2%)	
Hyperkeratosis	1 (2%)	1 (2%)	1 (2%)
Acanthosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Mineralization	1 (2%)		1 (2%)
Congestion, NOS	2 (4%)		1 (2%)
Hemorrhage	2 (4%)	5 (10%)	3 (6%)
Bronchopneumonia, acute		1 (2%)	
Pneumonia, interstitial chronic	9 (18%)	9 (18%)	4 (8%)
Bronchopneumonia, chronic			1 (2%)
Cholesterol deposit		1 (2%)	
Hyperplasia, alveolar epithelium	3 (6%)		2 (4%)
Histiocytosis	12 (24%)	9 (18%)	6 (12%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(49)
Inflammation, active chronic		1 (2%)	
Hyperplasia, granulocytic			1 (2%)
Hyperplasia, reticulum cell	1 (2%)	1 (2%)	
Hyperplasia, megakaryocytic	1 (2%)		
#Spleen	(50)	(50)	(50)
Hematoma, NOS		2 (4%)	
Fibrosis			1 (2%)
Infarct, NOS			1 (2%)
Pigmentation, NOS	43 (86%)	45 (90%)	36 (72%)
Hyperplasia, reticulum cell	1 (2%)		
Hematopoiesis	42 (84%)	40 (80%)	43 (86%)
#Splenic capsule	(50)	(50)	(50)
Fibrosis	1 (2%)		
#Splenic follicles	(50)	(50)	(50)
Atrophy, NOS	1 (2%)	2 (4%)	3 (6%)
#Lymph node	(49)	(50)	(50)
Congestion, NOS	1 (2%)		
Hemosiderosis	1 (2%)		
#Mandibular lymph node	(49)	(50)	(50)
Cyst, NOS		1 (2%)	
Hemosiderosis	6 (12%)	6 (12%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)		
#Thoracic lymph node	(49)	(50)	(50)
Hemosiderosis	1 (2%)	1 (2%)	
#Mesenteric lymph node	(49)	(50)	(50)
Edema, NOS	1 (2%)		
Hemosiderosis	1 (2%)	1 (2%)	
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Liver	(50)	(50)	(50)
Hematopoiesis	3 (6%)	2 (4%)	3 (6%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(49)	(50)	(50)
Embryonal duct cyst	23 (47%)	14 (28%)	22 (44%)
Congestion, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Inflammation, chronic	43 (86%)	47 (94%)	41 (82%)
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization	1 (2%)		
*Pulmonary vein	(50)	(50)	(50)
Mineralization		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Cystic ducts	7 (14%)	3 (6%)	1 (2%)
Inflammation, acute		2 (4%)	
Inflammation, active chronic		2 (4%)	
Inflammation, chronic	7 (14%)	6 (12%)	8 (16%)
Atrophy, NOS	11 (22%)	9 (18%)	4 (8%)
Hyperplasia, NOS		1 (2%)	2 (4%)
#Liver	(50)	(50)	(50)
Accessory structure	2 (4%)	7 (14%)	9 (18%)
Bile stasis		1 (2%)	
Cyst, NOS		1 (2%)	
Congestion, NOS			1 (2%)
Granuloma, NOS	21 (42%)	16 (32%)	10 (20%)
Necrosis, NOS	6 (12%)	1 (2%)	5 (10%)
Metamorphosis, fatty	10 (20%)	8 (16%)	7 (14%)
Nuclear alteration	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change	42 (84%)	46 (92%)	48 (96%)
Eosinophilic cyto change			1 (2%)
Hepatocytomegaly	2 (4%)	1 (2%)	
Regeneration, NOS	1 (2%)	1 (2%)	
#Liver/centrilobular	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Liver/periportal	(50)	(50)	(50)
Inflammation, chronic	37 (74%)	40 (80%)	37 (74%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	43 (86%)	36 (72%)	38 (76%)
#Pancreas	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
#Pancreatic acinus	(50)	(50)	(50)
Focal cellular change		1 (2%)	
Atrophy, NOS	33 (66%)	24 (48%)	27 (54%)
Hyperplasia, NOS	5 (10%)	2 (4%)	3 (6%)
#Glandular stomach	(50)	(50)	(50)
Mineralization	1 (2%)		1 (2%)
Degeneration, cystic	39 (78%)	40 (80%)	40 (80%)
Hyperplasia, epithelial		1 (2%)	
#Forestomach	(50)	(50)	(50)
Ulcer, chronic	1 (2%)		
Hyperkeratosis			1 (2%)
#Gastric fundus	(50)	(50)	(50)
Hyperkeratosis	1 (2%)		
#Colon	(50)	(50)	(50)
Abscess, chronic	1 (2%)		

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Hemorrhage		1 (2%)	
Abscess, NOS			1 (2%)
Nephropathy	49 (98%)	49 (98%)	49 (98%)
Infarct, healed			5 (10%)
#Kidney/tubule	(50)	(50)	(50)
Mineralization	34 (68%)	35 (70%)	41 (82%)
Necrosis, NOS	1 (2%)		
Pigmentation, NOS	43 (86%)	48 (96%)	42 (84%)
#Kidney/pelvis	(50)	(50)	(50)
Calculus, microscopic examination	1 (2%)		
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute		1 (2%)	
#Urinary bladder	(50)	(50)	(50)
Calculus, microscopic examination		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
#Anterior pituitary	(50)	(50)	(50)
Cyst, NOS	32 (64%)	16 (32%)	20 (40%)
Multiple cysts	3 (6%)	6 (12%)	2 (4%)
Hemorrhagic cyst	1 (2%)		
Granuloma, NOS	1 (2%)		
Hyperplasia, NOS	16 (32%)	10 (20%)	11 (22%)
Angiectasis	1 (2%)	1 (2%)	8 (16%)
#Adrenal	(50)	(50)	(50)
Mineralization			1 (2%)
#Adrenal/capsule	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
#Adrenal cortex	(50)	(50)	(50)
Cyst, NOS	2 (4%)		
Hemorrhage	1 (2%)		
Metamorphosis, fatty	24 (48%)	16 (32%)	20 (40%)
Pigmentation, NOS	43 (86%)	47 (94%)	40 (80%)
Hypertrophy, NOS		1 (2%)	
Hypertrophy, focal		1 (2%)	1 (2%)
Hyperplasia, NOS	18 (36%)	21 (42%)	22 (44%)
Angiectasis			1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, NOS	8 (16%)	12 (24%)	6 (12%)
#Thyroid	(50)	(50)	(50)
Embryonal duct cyst			2 (4%)
Mineralization	1 (2%)	1 (2%)	1 (2%)
Cystic follicles	6 (12%)	6 (12%)	4 (8%)
Hyperplasia, C-cell	42 (84%)	37 (74%)	37 (74%)
Hyperplasia, follicular cell		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Mineralization		1 (2%)	
Galactocele		1 (2%)	
Inflammation, acute		1 (2%)	1 (2%)
Hyperplasia, cystic	44 (88%)	43 (86%)	44 (88%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
*Clitoral gland	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, active chronic	2 (4%)	10 (20%)	4 (8%)
Inflammation, chronic		1 (2%)	
Hyperplasia, NOS		1 (2%)	
#Uterus	(50)	(50)	(50)
Dilatation, NOS	3 (6%)	1 (2%)	4 (8%)
Hydrometra	1 (2%)	1 (2%)	
Cyst, NOS		1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Decidual alteration, NOS			1 (2%)
#Uterus/endometrium	(50)	(50)	(50)
Hyperplasia, cystic	10 (20%)	5 (10%)	7 (14%)
#Ovary	(50)	(50)	(50)
Follicular cyst, NOS		1 (2%)	
Parovarian cyst	4 (8%)		1 (2%)
Angiectasis			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hydrocephalus, internal		1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		
Malacia	3 (6%)		1 (2%)
Atrophy, pressure	5 (10%)	2 (4%)	1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Retinopathy	4 (8%)	1 (2%)	4 (8%)
Cataract	4 (8%)	1 (2%)	4 (8%)
*Eye/sclera	(50)	(50)	(50)
Mineralization	1 (2%)		
*Eye/cornea	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)
Inflammation, chronic			1 (2%)
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Fibrous osteodystrophy			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Steatitis		1 (2%)	
*Mesentery	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Steatitis	5 (10%)	3 (6%)	3 (6%)
Necrosis, fat		1 (2%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic	6 (12%)	1 (2%)	5 (10%)
Pigmentation, NOS	6 (12%)	2 (4%)	7 (14%)
Hyperplasia, NOS	2 (4%)	1 (2%)	2 (4%)
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 OXYTETRACYCLINE HYDROCHLORIDE

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

	CONTROL (UNTR)	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%)	
Epidermal inclusion cyst		1 (2%)	
Inflammation, acute	1 (2%)		
Ulcer, acute	1 (2%)		
Abscess, NOS	3 (6%)		1 (2%)
Inflammation, chronic	1 (2%)	3 (6%)	1 (2%)
Ulcer, chronic	2 (4%)	1 (2%)	
Granulation tissue	1 (2%)		1 (2%)
Hyperkeratosis	2 (4%)	1 (2%)	
Metaplasia, osseous			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Cyst, NOS	2 (4%)		
Steatitis	5 (10%)	4 (8%)	2 (4%)
Inflammation, chronic		1 (2%)	3 (6%)
Metaplasia, osseous		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Mineralization		1 (2%)	
Atelectasis	1 (2%)		
Congestion, NOS	3 (6%)	5 (10%)	8 (16%)
Hemorrhage	7 (14%)	6 (12%)	8 (16%)
Bronchopneumonia, NOS		2 (4%)	
Inflammation, acute focal	1 (2%)		
Inflammation, chronic	1 (2%)		
Pneumonia, interstitial chronic	3 (6%)	7 (14%)	2 (4%)
Bronchopneumonia, chronic	9 (18%)	3 (6%)	5 (10%)
Cholesterol deposit	3 (6%)	2 (4%)	2 (4%)
Hyperplasia, alveolar epithelium	13 (26%)	4 (8%)	8 (16%)
Histiocytosis	6 (12%)	8 (16%)	10 (20%)
HEMATOPOIETIC SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Lymphocytosis	1 (2%)	1 (2%)	
#Bone marrow	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Hyperplasia, granulocytic	37 (74%)	30 (60%)	36 (72%)
#Spleen	(50)	(50)	(50)
Hematoma, NOS		1 (2%)	
Inflammation, acute	1 (2%)		1 (2%)
Pigmentation, NOS	39 (78%)	39 (78%)	28 (56%)
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, lymphoid	3 (6%)	6 (12%)	4 (8%)
Hematopoiesis	46 (92%)	47 (94%)	47 (94%)
#Splenic capsule	(50)	(50)	(50)
Fibrosis, focal	1 (2%)		
#Lymph node	(48)	(49)	(50)
Inflammation, acute	1 (2%)		
Inflammation, active chronic			1 (2%)
Hemosiderosis	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)		

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(48)	(49)	(50)
Inflammation, chronic			1 (2%)
Hemosiderosis	13 (27%)	12 (24%)	16 (32%)
Hyperplasia, lymphoid	1 (2%)		
#Mesenteric lymph node	(48)	(49)	(50)
Inflammation, acute	2 (4%)		
Hemosiderosis		1 (2%)	
Angiectasis		1 (2%)	
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	
#Inguinal lymph node	(48)	(49)	(50)
Mineralization			1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Liver	(50)	(50)	(50)
Hematopoiesis	7 (14%)	3 (6%)	10 (20%)
#Thyroid	(50)	(50)	(50)
Lymphocytosis		1 (2%)	
#Thymus	(47)	(47)	(49)
Cyst, NOS	9 (19%)	5 (11%)	6 (12%)
Hemorrhage			1 (2%)
Necrosis, NOS		1 (2%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)	
CIRCULATORY SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Periarteritis	1 (2%)		
*Vertebra	(50)	(50)	(50)
Periarteritis	1 (2%)		
#Heart	(50)	(50)	(50)
Mineralization			1 (2%)
Inflammation, chronic	3 (6%)	4 (8%)	3 (6%)
*Mesenteric artery	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
Thrombus, canalized	1 (2%)		
*Mesentery	(50)	(50)	(50)
Periarteritis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic	24 (48%)	25 (50%)	26 (52%)
Atrophy, NOS	2 (4%)	2 (4%)	
#Liver	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
Inflammation, acute	2 (4%)		3 (6%)
Inflammation, chronic	5 (10%)	4 (8%)	5 (10%)
Necrosis, coagulative	4 (8%)		5 (10%)
Infarct, focal	1 (2%)		
Metamorphosis, fatty		1 (2%)	2 (4%)
Cytoplasmic vacuolization	1 (2%)	2 (4%)	5 (10%)
Focal cellular change		2 (4%)	
Regeneration, NOS			2 (4%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS	2 (4%)		
#Pancreas	(50)	(49)	(50)
Cystic ducts		1 (2%)	
Inflammation, chronic	2 (4%)	4 (8%)	2 (4%)
Focal cellular change		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDE.. OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF OXYTETRACYCLINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(50)	(49)	(50)
Cytoplasmic vacuolization	34 (68%)	35 (71%)	34 (68%)
Atrophy, NOS	2 (4%)	3 (6%)	
Hyperplasia, NOS	2 (4%)		4 (8%)
#Glandular stomach	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	
Cyst, NOS	3 (6%)	1 (2%)	2 (4%)
Inflammation, acute	3 (6%)	1 (2%)	2 (4%)
Inflammation, active chronic	1 (2%)		
Degeneration, cystic	4 (8%)	4 (8%)	4 (8%)
Hyperplasia, epithelial	3 (6%)	1 (2%)	2 (4%)
Metaplasia, squamous	2 (4%)		1 (2%)
#Forestomach	(50)	(50)	(50)
Inflammation, acute	1 (2%)		1 (2%)
Ulcer, chronic		1 (2%)	
Erosion			1 (2%)
Hyperplasia, epithelial	1 (2%)		
Hyperkeratosis	1 (2%)		
Acanthosis	1 (2%)		
#Duodenum	(48)	(47)	(49)
Necrosis, coagulative		1 (2%)	
#Colon	(50)	(50)	(49)
Inflammation, chronic			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis		1 (2%)	
Congestion, NOS			1 (2%)
Hemorrhage	1 (2%)		
Pyelonephritis, acute/chronic	1 (2%)		1 (2%)
Inflammation, chronic	27 (54%)	30 (60%)	29 (58%)
Pyelonephritis, chronic			1 (2%)
Nephropathy	1 (2%)	1 (2%)	1 (2%)
Necrosis, NOS	1 (2%)		
Infarct, focal		1 (2%)	
Metaplasia, osseous		2 (4%)	2 (4%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS	2 (4%)		1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Mineralization	21 (42%)	19 (38%)	16 (32%)
Dilatation, NOS			1 (2%)
Necrosis, NOS	7 (14%)	3 (6%)	4 (8%)
Pigmentation, NOS	1 (2%)		
Regeneration, NOS	34 (68%)	28 (56%)	29 (58%)
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
*Ureter	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Urinary bladder	(50)	(49)	(48)
Calculus, gross observation only	1 (2%)		1 (2%)
Calculus, microscopic examination	2 (4%)	1 (2%)	2 (4%)
Hemorrhage	1 (2%)		
Inflammation, active chronic	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic			2 (4%)
Metaplasia, squamous			1 (2%)
*Urethra	(50)	(50)	(50)
Calculus, microscopic examination	9 (18%)	15 (30%)	6 (12%)
Congestion, NOS		1 (2%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(50)
Cyst, NOS	4 (8%)	2 (4%)	2 (4%)
Hyperplasia, NOS	3 (6%)	2 (4%)	5 (10%)
#Pituitary posterior	(50)	(49)	(50)
Embryonal duct cyst	1 (2%)		
#Adrenal/capsule	(50)	(49)	(50)
Hyperplasia, NOS	43 (86%)	45 (92%)	45 (90%)
#Adrenal cortex	(50)	(49)	(50)
Accessory structure		1 (2%)	
Pigmentation, NOS			1 (2%)
Hyperplasia, NOS	4 (8%)	5 (10%)	6 (12%)
Angiectasis	2 (4%)		1 (2%)
#Adrenal medulla	(50)	(49)	(50)
Cytoplasmic vacuolization	1 (2%)		
Hyperplasia, NOS	3 (6%)	9 (18%)	5 (10%)
Angiectasis	2 (4%)		
#Thyroid	(50)	(50)	(50)
Embryonal duct cyst		1 (2%)	1 (2%)
Cystic follicles	14 (28%)	20 (40%)	16 (32%)
Inflammation, acute	1 (2%)		
Hyperplasia, C-cell	1 (2%)	6 (12%)	5 (10%)
Hyperplasia, follicular cell	5 (10%)	1 (2%)	1 (2%)
#Parathyroid	(29)	(25)	(35)
Cyst, NOS	1 (3%)	2 (8%)	
#Pancreatic islets	(50)	(49)	(50)
Cytoplasmic vacuolization		1 (2%)	
Hyperplasia, NOS	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Calculus, microscopic examination	1 (2%)	1 (2%)	1 (2%)
*Prepuce	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Inflammation, active chronic	1 (2%)		2 (4%)
Ulcer, chronic	1 (2%)		2 (4%)
*Preputial gland	(50)	(50)	(50)
Mineralization		1 (2%)	
Dilatation/ducts	1 (2%)		
Inflammation, suppurative	1 (2%)	3 (6%)	
Inflammation, active chronic	8 (16%)	11 (22%)	10 (20%)
Inflammation, chronic	9 (18%)	9 (18%)	3 (6%)
#Prostate	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	
Inflammation, active chronic	1 (2%)		3 (6%)
Inflammation, chronic		1 (2%)	2 (4%)
*Seminal vesicle	(50)	(50)	(50)
Calculus, microscopic examination	1 (2%)		
Inflammation, suppurative		1 (2%)	
Inflammation, active chronic	2 (4%)		3 (6%)
Inflammation, chronic		1 (2%)	
Atrophy, diffuse	1 (2%)		
#Testis	(50)	(50)	(50)
Hyperplasia, interstitial cell	3 (6%)	3 (6%)	2 (4%)
#Testis/tubule	(50)	(50)	(50)
Mineralization	3 (6%)	7 (14%)	3 (6%)
Cyst, NOS			1 (2%)
Degeneration, NOS	21 (42%)	16 (32%)	21 (42%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
*Epididymis	(50)	(50)	(50)
Granuloma, spermatic			1 (2%)
*Scrotum	(50)	(50)	(50)
Necrosis, fat		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
#Brain	(50)	(50)	(50)
Mineralization	31 (62%)	32 (64%)	23 (46%)
Hemorrhage	1 (2%)		2 (4%)
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
*Tarsal joint	(50)	(50)	(50)
Osteoarthritis	2 (4%)		
*Skeletal muscle	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Steatitis	2 (4%)		2 (4%)
Necrosis, fat			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, chronic	13 (26%)	12 (24%)	11 (22%)
Amyloidosis	1 (2%)		
Hyperplasia, NOS			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		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 OXYTETRACYCLINE HYDROCHLORIDE

	CONTROL (UNTR)	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%)		
Ulcer, acute			1 (2%)
Inflammation, chronic	1 (2%)		
Erosion			1 (2%)
Hyperkeratosis		2 (4%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sebaceous cyst	2 (4%)		
Hemorrhage	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Congestion, NOS	2 (4%)	3 (6%)	2 (4%)
Hemorrhage	3 (6%)	6 (12%)	
Pneumonia, interstitial chronic		4 (8%)	2 (4%)
Bronchopneumonia, chronic	6 (12%)	8 (16%)	5 (10%)
Cholesterol deposit	2 (4%)	1 (2%)	3 (6%)
Hyperplasia, alveolar epithelium	8 (16%)	9 (18%)	5 (10%)
Histiocytosis	8 (16%)	10 (20%)	6 (12%)
HEMATOPOIETIC SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Lymphocytosis	1 (2%)	2 (4%)	1 (2%)
#Brain	(50)	(50)	(50)
Lymphocytosis		1 (2%)	
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
*Skin	(50)	(50)	(50)
Mastocytosis		1 (2%)	
#Bone marrow	(50)	(50)	(50)
Fibrosis	4 (8%)	6 (12%)	7 (14%)
Hyperplasia, granulocytic	30 (60%)	28 (56%)	29 (58%)
#Spleen	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Infarct, acute		1 (2%)	
Pigmentation, NOS	46 (92%)	46 (92%)	49 (98%)
Angiectasis		1 (2%)	
Hyperplasia, lymphoid	10 (20%)	19 (38%)	15 (30%)
Hematopoiesis	46 (92%)	47 (94%)	49 (98%)
#Lymph node	(48)	(46)	(49)
Hemosiderosis			1 (2%)
Hyperplasia, lymphoid		1 (2%)	
#Mandibular lymph node	(48)	(46)	(49)
Hemosiderosis	17 (35%)	20 (43%)	20 (41%)
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid	4 (8%)	1 (2%)	4 (8%)
Mastocytosis	1 (2%)		1 (2%)
#Thoracic lymph node	(48)	(46)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Mediastinal lymph node	(48)	(46)	(49)
Hyperplasia, lymphoid			1 (2%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(48)	(46)	(49)
Hematoma, NOS			1 (2%)
Hemosiderosis			1 (2%)
Hyperplasia, reticulum cell		1 (2%)	
Hyperplasia, lymphoid			2 (4%)
#Inguinal lymph node	(48)	(46)	(49)
Hyperplasia, reticulum cell			1 (2%)
#Liver	(50)	(50)	(50)
Hematopoiesis	27 (54%)	31 (62%)	26 (52%)
#Liver/periportal	(50)	(50)	(50)
Hematopoiesis	1 (2%)		
#Peyer's patch	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(49)	(50)	(50)
Embryonal duct cyst	1 (2%)	4 (8%)	4 (8%)
Cyst, NOS	5 (10%)	2 (4%)	5 (10%)
Congestion, NOS			1 (2%)
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, lymphoid		3 (6%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, active chronic	1 (2%)		1 (2%)
Inflammation, chronic	5 (10%)	3 (6%)	1 (2%)
Periarteritis	2 (4%)		
*Pulmonary artery	(50)	(50)	(50)
Mineralization	1 (2%)		
*Pulmonary vein	(50)	(50)	(50)
Mineralization			1 (2%)
*Ovarian vein	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(48)	(49)
Inflammation, chronic	7 (14%)	17 (35%)	14 (29%)
Hemosiderosis	1 (2%)		
Atrophy, NOS	1 (2%)	1 (2%)	1 (2%)
#Liver	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Inflammation, acute		1 (2%)	
Inflammation, active chronic	1 (2%)		3 (6%)
Inflammation, chronic	10 (20%)	17 (34%)	17 (34%)
Peliosis hepatis	1 (2%)		
Necrosis, NOS	4 (8%)	3 (6%)	2 (4%)
Infarct, healed	1 (2%)		
Metamorphosis, fatty	2 (4%)	3 (6%)	3 (6%)
Focal cellular change	1 (2%)		1 (2%)
Hepatocytomegaly			1 (2%)
Metaplasia, osseous	1 (2%)		
Regeneration, NOS		2 (4%)	1 (2%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS	1 (2%)		3 (6%)
#Pancreas	(50)	(49)	(50)
Cystic ducts	1 (2%)	1 (2%)	
Inflammation, chronic	4 (8%)	6 (12%)	3 (6%)
Atrophy, NOS		2 (4%)	2 (4%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(50)	(49)	(50)
Cytoplasmic vacuolization	31 (62%)	35 (71%)	39 (78%)
Hyperplasia, NOS		1 (2%)	3 (6%)
#Glandular stomach	(49)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
Cyst, NOS	3 (6%)	4 (8%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, active chronic	1 (2%)	1 (2%)	
Inflammation, chronic			1 (2%)
Degeneration, cystic	3 (6%)	2 (4%)	5 (10%)
Hyperplasia, epithelial			1 (2%)
Metaplasia, squamous		2 (4%)	2 (4%)
#Forestomach	(49)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
Hyperkeratosis	1 (2%)	2 (4%)	1 (2%)
#Peyer's patch	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
#Duodenum	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Hematoma, NOS		1 (2%)	
Pyelonephritis, acute/chronic		1 (2%)	1 (2%)
Inflammation, chronic	19 (38%)	26 (52%)	23 (46%)
Infarct, healed	1 (2%)		
#Kidney/cortex	(50)	(50)	(50)
Infarct, healed		1 (2%)	
Metaplasia, osseous	3 (6%)		1 (2%)
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis			1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Mineralization			2 (4%)
Necrosis, NOS	7 (14%)	11 (22%)	10 (20%)
Metamorphosis, fatty		1 (2%)	
Regeneration, NOS	25 (50%)	23 (46%)	32 (64%)
#Kidney/pelvis	(50)	(50)	(50)
Calculus, microscopic examination	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		1 (2%)	
#Urinary bladder	(48)	(49)	(49)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Metaplasia, squamous		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(50)
Cyst, NOS	3 (6%)	2 (4%)	1 (2%)
Hyperplasia, NOS	11 (22%)	4 (8%)	14 (28%)
Hyperplasia, focal	2 (4%)	1 (2%)	
Angiectasis		3 (6%)	1 (2%)
#Adrenal/capsule	(49)	(50)	(50)
Pigmentation, NOS		1 (2%)	
Hyperplasia, NOS	49 (100%)	50 (100%)	50 (100%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(49)	(50)	(50)
Cyst, NOS		1 (2%)	
Congestion, NOS		1 (2%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)
Metamorphosis, fatty	2 (4%)	3 (6%)	1 (2%)
Pigmentation, NOS	36 (73%)	30 (60%)	41 (82%)
Cytoplasmic vacuolization			1 (2%)
Hyperplasia, NOS	3 (6%)	1 (2%)	5 (10%)
Angiectasis		1 (2%)	
#Adrenal medulla	(49)	(50)	(50)
Hyperplasia, NOS	2 (4%)	3 (6%)	
#Thyroid	(50)	(50)	(49)
Embryonal duct cyst	2 (4%)	1 (2%)	1 (2%)
Cystic follicles	22 (44%)	20 (40%)	15 (31%)
Inflammation, active chronic	1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)		1 (2%)
Hyperplasia, C-cell	9 (18%)	9 (18%)	13 (27%)
Hyperplasia, follicular cell	7 (14%)	16 (32%)	10 (20%)
#Thyroid follicle	(50)	(50)	(49)
Atrophy, NOS	1 (2%)		
#Parathyroid	(35)	(36)	(42)
Cyst, NOS	1 (3%)	1 (3%)	
Hyperplasia, NOS	1 (3%)		1 (2%)
#Pancreatic islets	(50)	(49)	(50)
Hyperplasia, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Hyperplasia, cystic	12 (24%)	10 (20%)	6 (12%)
#Uterus	(50)	(50)	(50)
Hydrometra	1 (2%)	3 (6%)	4 (8%)
Hemorrhage	1 (2%)		
Hematoma, organized		1 (2%)	
Inflammation, acute	6 (12%)	9 (18%)	6 (12%)
Abscess, NOS	1 (2%)		
Metaplasia, squamous	1 (2%)	1 (2%)	2 (4%)
#Uterus/endometrium	(50)	(50)	(50)
Hyperplasia, cystic	47 (94%)	46 (92%)	48 (96%)
#Fallopian tube	(50)	(50)	(50)
Inflammation chronic suppurative		1 (2%)	
#Ovary	(44)	(48)	(49)
Follicular cyst, NOS	3 (7%)	2 (4%)	6 (12%)
Parovarian cyst	9 (20%)	11 (23%)	4 (8%)
Congestion, NOS			1 (2%)
Hemorrhagic cyst	1 (2%)		
Abscess, NOS	1 (2%)	1 (2%)	2 (4%)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	
Hyperplasia, epithelial			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Mineralization	27 (54%)	25 (50%)	30 (60%)
Atrophy, pressure	1 (2%)	1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)
*Spinal cord	(50)	(50)	(50)
Degeneration, Wallerian		2 (4%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*Ear	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Abdominal muscle	(50)	(50)	(50)
Inflammation chronic suppurative		1 (2%)	
Abscess, chronic			1 (2%)
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Abscess, chronic		1 (2%)	
*Mesentery	(50)	(50)	(50)
Steatitis	3 (6%)	3 (6%)	
Inflammation, acute		2 (4%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, chronic	25 (50%)	19 (38%)	20 (40%)
Adipose tissue			
Mineralization	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 E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

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

	Control	25,000 ppm	50,000 ppm
Skin: Squamous Cell Papilloma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	4.5%	10.3%	2.6%
Terminal Rates (c)	1/22 (5%)	3/29 (10%)	1/38 (3%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.410N	P=0.407	P=0.635N
Incidental Tumor Tests (d)	P=0.410N	P=0.407	P=0.635N
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	6.7%	10.3%	2.6%
Terminal Rates (c)	1/22 (5%)	3/29 (10%)	1/38 (3%)
Week of First Observation	75	104	104
Life Table Tests (d)	P=0.228N	P=0.604	P=0.361N
Incidental Tumor Tests (d)	P=0.346N	P=0.496	P=0.581N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	(e) 2/50 (4%)
Adjusted Rates (b)	12.3%	2.6%	4.9%
Terminal Rates (c)	1/22 (5%)	0/29 (0%)	1/38 (3%)
Week of First Observation	66	94	99
Life Table Tests (d)	P=0.132N	P=0.142N	P=0.185N
Incidental Tumor Tests (d)	P=0.363N	P=0.231N	P=0.487N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.181N	P=0.339N
Subcutaneous Tissue: Fibroma or Neurofibrosarcoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	12.3%	6.0%	7.0%
Terminal Rates (c)	1/22 (5%)	1/29 (3%)	1/38 (3%)
Week of First Observation	66	94	92
Life Table Tests (d)	P=0.243N	P=0.265N	P=0.306N
Incidental Tumor Tests (d)	P=0.552N	P=0.382N	P=0.632
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.339N	P=0.500N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	22/50 (44%)	22/50 (44%)	16/50 (32%)
Adjusted Rates (b)	57.7%	50.2%	34.0%
Terminal Rates (c)	7/22 (32%)	8/29 (28%)	8/38 (21%)
Week of First Observation	62	55	77
Life Table Tests (d)	P=0.010N	P=0.283N	P=0.013N
Incidental Tumor Tests (d)	P=0.318N	P=0.569	P=0.349N
Cochran-Armitage Trend Test (d)	P=0.131N		
Fisher Exact Test (d)		P=0.580N	P=0.152N
Liver: Neoplastic Nodule			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	22.6%	15.2%	17.7%
Terminal Rates (c)	3/22 (14%)	3/29 (10%)	6/38 (16%)
Week of First Observation	95	87	99
Life Table Tests (d)	P=0.330N	P=0.345N	P=0.358N
Incidental Tumor Tests (d)	P=0.508N	P=0.396N	P=0.538N
Cochran-Armitage Trend Test (d)	P=0.439		
Fisher Exact Test (d)		P=0.500N	P=0.500

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

	Control	25,000 ppm	50,000 ppm
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	9/50 (18%)
Adjusted Rates (b)	22.6%	15.2%	22.9%
Terminal Rates (c)	3/22 (14%)	3/29 (10%)	8/38 (21%)
Week of First Observation	95	87	99
Life Table Tests (d)	P=0.524N	P=0.345N	P=0.530N
Incidental Tumor Tests (d)	P=0.415	P=0.396N	P=0.527
Cochran-Armitage Trend Test (d)	P=0.231		
Fisher Exact Test (d)		P=0.500N	P=0.288
Pituitary Gland: Adenoma			
Overall Rates (a)	20/50 (40%)	27/50 (54%)	15/48 (31%)
Adjusted Rates (b)	61.7%	68.1%	36.7%
Terminal Rates (c)	11/22 (50%)	17/29 (59%)	12/37 (32%)
Week of First Observation	67	61	77
Life Table Tests (d)	P=0.006N	P=0.454	P=0.010N
Incidental Tumor Tests (d)	P=0.137N	P=0.180	P=0.171N
Cochran-Armitage Trend Test (d)	P=0.227N		
Fisher Exact Test (d)		P=0.115	P=0.244N
Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	21/50 (42%)	27/50 (54%)	15/48 (31%)
Adjusted Rates (b)	65.2%	68.1%	36.7%
Terminal Rates (c)	12/22 (55%)	17/29 (59%)	12/37 (32%)
Week of First Observation	67	61	77
Life Table Tests (d)	P=0.003N	P=0.535	P=0.005N
Incidental Tumor Tests (d)	P=0.089N	P=0.247	P=0.110N
Cochran-Armitage Trend Test (d)	P=0.171N		
Fisher Exact Test (d)		P=0.158	P=0.186N
Adrenal Cortex: Cortical Adenoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	8.5%	6.3%	7.4%
Terminal Rates (c)	1/22 (5%)	1/29 (3%)	2/38 (5%)
Week of First Observation	102	99	97
Life Table Tests (d)	P=0.561N	P=0.600N	P=0.637N
Incidental Tumor Tests (d)	P=0.478	P=0.645N	P=0.583
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.691	P=0.500
Adrenal Cortex: Adenocarcinoma or Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	12.9%	6.3%	7.4%
Terminal Rates (c)	2/22 (9%)	1/29 (3%)	2/38 (5%)
Week of First Observation	102	99	97
Life Table Tests (d)	P=0.351N	P=0.386N	P=0.413N
Incidental Tumor Tests (d)	P=0.488N	P=0.425N	P=0.549N
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.500N	P=0.661
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	10/50 (20%)	18/50 (36%)	24/50 (48%)
Adjusted Rates (b)	37.2%	51.2%	52.9%
Terminal Rates (c)	6/22 (27%)	12/29 (41%)	17/38 (45%)
Week of First Observation	95	94	77
Life Table Tests (d)	P=0.161	P=0.221	P=0.166
Incidental Tumor Tests (d)	P=0.014	P=0.135	P=0.015
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		P=0.059	P=0.003

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

	Control	25,000 ppm	50,000 ppm
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	12/50 (24%)	19/50 (38%)	24/50 (48%)
Adjusted Rates (b)	41.0%	52.6%	52.9%
Terminal Rates (c)	6/22 (27%)	12/29 (41%)	17/38 (45%)
Week of First Observation	75	94	77
Life Table Tests (d)	P=0.305	P=0.314	P=0.312
Incidental Tumor Tests (d)	P=0.026	P=0.163	P=0.026
Cochran-Armitage Trend Test (d)	P=0.009		
Fisher Exact Test (d)		P=0.097	P=0.011
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	9.1%	6.9%	10.0%
Terminal Rates (c)	2/22 (9%)	2/29 (7%)	3/38 (8%)
Week of First Observation	104	104	99
Life Table Tests (d)	P=0.484	P=0.593N	P=0.597
Incidental Tumor Tests (d)	P=0.436	P=0.593N	P=0.527
Cochran-Armitage Trend Test (d)	P=0.252		
Fisher Exact Test (d)		P=0.691	P=0.339
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	4.2%	9.2%	7.9%
Terminal Rates (c)	0/22 (0%)	1/29 (3%)	3/38 (8%)
Week of First Observation	102	99	104
Life Table Tests (d)	P=0.435	P=0.391	P=0.505
Incidental Tumor Tests (d)	P=0.293	P=0.326	P=0.422
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.309	P=0.309
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	12.9%	15.7%	17.7%
Terminal Rates (c)	2/22 (9%)	3/29 (10%)	6/38 (16%)
Week of First Observation	102	99	99
Life Table Tests (d)	P=0.377	P=0.500	P=0.444
Incidental Tumor Tests (d)	P=0.249	P=0.453	P=0.337
Cochran-Armitage Trend Test (d)	P=0.122		
Fisher Exact Test (d)		P=0.357	P=0.159
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	9.1%	13.8%	17.9%
Terminal Rates (c)	2/22 (9%)	4/29 (14%)	6/38 (16%)
Week of First Observation	104	104	100
Life Table Tests (d)	P=0.208	P=0.469	P=0.271
Incidental Tumor Tests (d)	P=0.183	P=0.469	P=0.228
Cochran-Armitage Trend Test (d)	P=0.055		
Fisher Exact Test (d)		P=0.339	P=0.080
Pancreatic Islets: Islet Cell Carcinoma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	16.4%	0.0%	0.0%
Terminal Rates (c)	3/22 (14%)	0/29 (0%)	0/38 (0%)
Week of First Observation	95		
Life Table Tests (d)	P=0.005N	P=0.037N	P=0.019N
Incidental Tumor Tests (d)	P=0.006N	P=0.041N	P=0.029N
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.059N	P=0.059N

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

	Control	25,000 ppm	50,000 ppm
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	25.2%	13.8%	17.9%
Terminal Rates (c)	5/22 (23%)	4/29 (14%)	6/38 (16%)
Week of First Observation	95	104	100
Life Table Tests (d)	P=0.318N	P=0.213N	P=0.342N
Incidental Tumor Tests (d)	P=0.375N	P=0.221N	P=0.428N
Cochran-Armitage Trend Test (d)	P=0.437		
Fisher Exact Test (d)		P=0.370N	P=0.500
Testis: Interstitial Cell Tumor			
Overall Rates (a)	41/50 (82%)	37/50 (74%)	40/50 (80%)
Adjusted Rates (b)	100.0%	85.9%	86.9%
Terminal Rates (c)	22/22 (100%)	23/29 (79%)	32/38 (84%)
Week of First Observation	62	65	79
Life Table Tests (d)	P<0.001N	P=0.027N	P<0.001N
Incidental Tumor Tests (d)	P=0.079N	P=0.085N	P=0.073N
Cochran-Armitage Trend Test (d)	P=0.451N		
Fisher Exact Test (d)		P=0.235N	P=0.500N
Preputial Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	2.2%	9.0%	2.6%
Terminal Rates (c)	0/22 (0%)	2/29 (7%)	1/38 (3%)
Week of First Observation	67	86	104
Life Table Tests (d)	P=0.462N	P=0.381	P=0.688N
Incidental Tumor Tests (d)	P=0.549	P=0.247	P=0.652
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753
All Sites: Mesothelioma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	10.0%	0.0%
Terminal Rates (c)	0/22 (0%)	2/29 (7%)	0/38 (0%)
Week of First Observation		103	
Life Table Tests (d)	P=0.489N	P=0.178	(f)
Incidental Tumor Tests (d)	P=0.573N	P=0.156	(f)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(f)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) A neurofibroma was also observed in one of these animals.
(f) No P value is reported because no tumors were observed in the 50,000-ppm and control groups.

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

	Control	25,000 ppm	50,000 ppm
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	13/50 (26%)	9/50 (18%)	9/50 (18%)
Adjusted Rates (b)	30.8%	22.2%	22.9%
Terminal Rates (c)	4/31 (13%)	2/28 (7%)	5/34 (15%)
Week of First Observation	87	55	75
Life Table Tests (d)	P=0.209N	P=0.311N	P=0.241N
Incidental Tumor Tests (d)	P=0.179N	P=0.093N	P=0.333N
Cochran-Armitage Trend Test (d)	P=0.194N		
Fisher Exact Test (d)		P=0.235N	P=0.235N
Liver: Neoplastic Nodule			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	12.5%	11.9%	17.1%
Terminal Rates (c)	1/31 (3%)	2/28 (7%)	5/34 (15%)
Week of First Observation	90	91	102
Life Table Tests (d)	P=0.461	P=0.540N	P=0.524
Incidental Tumor Tests (d)	P=0.353	P=0.499N	P=0.392
Cochran-Armitage Trend Test (d)	P=0.434		
Fisher Exact Test (d)		P=0.500N	P=0.500
Pituitary Gland: Adenoma			
Overall Rates (a)	19/50 (38%)	17/50 (34%)	30/50 (60%)
Adjusted Rates (b)	44.9%	52.9%	69.5%
Terminal Rates (c)	9/31 (29%)	13/28 (46%)	21/34 (62%)
Week of First Observation	86	101	57
Life Table Tests (d)	P=0.050	P=0.544N	P=0.066
Incidental Tumor Tests (d)	P=0.012	P=0.477N	P=0.013
Cochran-Armitage Trend Test (d)	P=0.017		
Fisher Exact Test (d)		P=0.418N	P=0.022
Pituitary Gland: Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	3/50 (6%)
Adjusted Rates (b)	5.8%	17.5%	8.4%
Terminal Rates (c)	1/31 (3%)	1/28 (4%)	2/34 (6%)
Week of First Observation	99	83	99
Life Table Tests (d)	P=0.431	P=0.075	P=0.520
Incidental Tumor Tests (d)	P=0.294	P=0.083	P=0.429
Cochran-Armitage Trend Test (d)	P=0.427		
Fisher Exact Test (d)		P=0.080	P=0.500
Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	20/50 (40%)	24/50 (48%)	32/50 (64%)
Adjusted Rates (b)	47.4%	62.5%	72.6%
Terminal Rates (c)	10/31 (32%)	14/28 (50%)	22/34 (65%)
Week of First Observation	86	83	57
Life Table Tests (d)	P=0.044	P=0.202	P=0.051
Incidental Tumor Tests (d)	P=0.004	P=0.230	P=0.007
Cochran-Armitage Trend Test (d)	P=0.011		
Fisher Exact Test (d)		P=0.273	P=0.014
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	19.4%	14.5%	2.9%
Terminal Rates (c)	6/31 (19%)	2/28 (7%)	1/34 (3%)
Week of First Observation	104	91	104
Life Table Tests (d)	P=0.044N	P=0.561N	P=0.043N
Incidental Tumor Tests (d)	P=0.053N	P=0.541N	P=0.043N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test (d)		P=0.500N	P=0.056N

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

	Control	25,000 ppm	50,000 ppm
Adrenal Gland: Adenocarcinoma or Cortical Adenoma			
Overall Rates (a)	6/50 (12%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	19.4%	17.8%	2.9%
Terminal Rates (c)	6/31 (19%)	3/28 (11%)	1/34 (3%)
Week of First Observation	104	91	104
Life Table Tests (d)	P=0.048N	P=0.556	P=0.043N
Incidental Tumor Tests (d)	P=0.058N	P=0.576	P=0.043N
Cochran-Armitage Trend Test (d)	P=0.055N		
Fisher Exact Test (d)		P=0.620	P=0.056N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	16.5%	14.3%	8.5%
Terminal Rates (c)	3/31 (10%)	4/28 (14%)	2/34 (6%)
Week of First Observation	93	104	101
Life Table Tests (d)	P=0.170N	P=0.425N	P=0.227N
Incidental Tumor Tests (d)	P=0.219N	P=0.400N	P=0.336N
Cochran-Armitage Trend Test (d)	P=0.187N		
Fisher Exact Test (d)		P=0.370N	P=0.243N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/50 (12%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (b)	17.8%	20.0%	13.8%
Terminal Rates (c)	5/31 (16%)	5/28 (18%)	3/34 (9%)
Week of First Observation	86	96	99
Life Table Tests (d)	P=0.396N	P=0.551	P=0.462N
Incidental Tumor Tests (d)	P=0.450N	P=0.565	P=0.530N
Cochran-Armitage Trend Test (d)	P=0.437N		
Fisher Exact Test (d)		P=0.620	P=0.500N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	6.5%	9.7%	5.9%
Terminal Rates (c)	2/31 (6%)	2/28 (7%)	2/34 (6%)
Week of First Observation	104	99	104
Life Table Tests (d)	P=0.558N	P=0.458	P=0.662N
Incidental Tumor Tests (d)	P=0.586N	P=0.470	P=0.662N
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.500	P=0.691
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	9/50 (18%)	6/50 (12%)
Adjusted Rates (b)	24.1%	29.0%	16.6%
Terminal Rates (c)	7/31 (23%)	7/28 (25%)	4/34 (12%)
Week of First Observation	86	96	99
Life Table Tests (d)	P=0.293N	P=0.413	P=0.340N
Incidental Tumor Tests (d)	P=0.348N	P=0.432	P=0.397N
Cochran-Armitage Trend Test (d)	P=0.339N		
Fisher Exact Test (d)		P=0.500	P=0.387N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	21/50 (42%)	15/50 (30%)	15/50 (30%)
Adjusted Rates (b)	52.2%	44.3%	37.5%
Terminal Rates (c)	13/31 (42%)	10/28 (36%)	10/34 (29%)
Week of First Observation	86	93	81
Life Table Tests (d)	P=0.112N	P=0.254N	P=0.141N
Incidental Tumor Tests (d)	P=0.171N	P=0.193N	P=0.203N
Cochran-Armitage Trend Test (d)	P=0.123N		
Fisher Exact Test (d)		P=0.149N	P=0.149N

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

	Control	25,000 ppm	50,000 ppm
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	22/50 (44%)	15/50 (30%)	16/50 (32%)
Adjusted Rates (b)	53.6%	44.3%	40.1%
Terminal Rates (c)	13/31 (42%)	10/28 (36%)	11/34 (32%)
Week of First Observation	86	93	81
Life Table Tests (d)	P=0.114N	P=0.202N	P=0.144N
Incidental Tumor Tests (d)	P=0.180N	P=0.141N	P=0.219N
Cochran-Armitage Trend Test (d)	P=0.125N		
Fisher Exact Test (d)		P=0.107N	P=0.151N
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	5.6%	2.4%	8.8%
Terminal Rates (c)	0/31 (0%)	0/28 (0%)	3/34 (9%)
Week of First Observation	99	93	104
Life Table Tests (d)	P=0.418	P=0.519N	P=0.525
Incidental Tumor Tests (d)	P=0.324	P=0.471N	P=0.429
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.500N	P=0.500
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	22/50 (44%)	16/50 (32%)	17/50 (34%)
Adjusted Rates (b)	53.6%	45.7%	42.7%
Terminal Rates (c)	13/31 (42%)	10/28 (36%)	12/34 (35%)
Week of First Observation	86	93	81
Life Table Tests (d)	P=0.158N	P=0.265N	P=0.188N
Incidental Tumor Tests (d)	P=0.249N	P=0.190N	P=0.283N
Cochran-Armitage Trend Test (d)	P=0.175N		
Fisher Exact Test (d)		P=0.151N	P=0.206N
Clitoral Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	5.3%	15.0%	5.1%
Terminal Rates (c)	1/31 (3%)	3/28 (11%)	1/34 (3%)
Week of First Observation	89	89	84
Life Table Tests (d)	P=0.577N	P=0.187	P=0.689
Incidental Tumor Tests (d)	P=0.559	P=0.200	P=0.685
Cochran-Armitage Trend Test (d)	P=0.583		
Fisher Exact Test (d)		P=0.218	P=0.691
Clitoral Gland: Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	8.7%	6.2%	5.9%
Terminal Rates (c)	2/31 (6%)	1/28 (4%)	2/34 (6%)
Week of First Observation	95	97	104
Life Table Tests (d)	P=0.383N	P=0.537N	P=0.473N
Incidental Tumor Tests (d)	P=0.434N	P=0.513N	P=0.514N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	13.7%	20.6%	10.8%
Terminal Rates (c)	3/31 (10%)	4/28 (14%)	3/34 (9%)
Week of First Observation	89	89	84
Life Table Tests (d)	P=0.417N	P=0.326	P=0.482N
Incidental Tumor Tests (d)	P=0.474N	P=0.354	P=0.519N
Cochran-Armitage Trend Test (d)	P=0.436N		
Fisher Exact Test (d)		P=0.380	P=0.500N

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

	Control	25,000 ppm	50,000 ppm
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	15/50 (30%)	10/50 (20%)	21/50 (42%)
Adjusted Rates (b)	41.7%	28.0%	50.4%
Terminal Rates (c)	11/31 (35%)	4/28 (14%)	14/34 (41%)
Week of First Observation	90	89	57
Life Table Tests (d)	P=0.176	P=0.262N	P=0.218
Incidental Tumor Tests (d)	P=0.093	P=0.206N	P=0.149
Cochran-Armitage Trend Test (d)	P=0.116		
Fisher Exact Test (d)		P=0.178N	P=0.149
Uterus: Endometrial Stromal Sarcoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.1%	7.8%
Terminal Rates (c)	0/31 (0%)	0/28 (0%)	2/34 (6%)
Week of First Observation		83	72
Life Table Tests (d)	P=0.066	P=0.492	P=0.133
Incidental Tumor Tests (d)	P=0.105	P=0.500	P=0.259
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	15/50 (30%)	11/50 (22%)	22/50 (44%)
Adjusted Rates (b)	41.7%	29.5%	51.4%
Terminal Rates (c)	11/31 (35%)	4/28 (14%)	14/34 (41%)
Week of First Observation	90	83	57
Life Table Tests (d)	P=0.134	P=0.342N	P=0.169
Incidental Tumor Tests (d)	P=0.080	P=0.281N	P=0.149
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.247N	P=0.107

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher 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 OXYTETRACYCLINE HYDROCHLORIDE

	Control	6,300 ppm	12,500 ppm
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	6.5%	12.1%	5.9%
Terminal Rates (c)	2/31 (6%)	4/33 (12%)	2/34 (6%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.548N	P=0.365	P=0.662N
Incidental Tumor Tests (d)	P=0.548N	P=0.365	P=0.662N
Cochran-Armitage Trend Test (d)	P=0.587		
Fisher Exact Test (d)		P=0.339	P=0.691
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	19.0%	12.9%	6.8%
Terminal Rates (c)	1/31 (3%)	2/33 (6%)	0/34 (0%)
Week of First Observation	86	62	68
Life Table Tests (d)	P=0.080N	P=0.307N	P=0.111N
Incidental Tumor Tests (d)	P=0.106N	P=0.470N	P=0.137N
Cochran-Armitage Trend Test (d)	P=0.073N		
Fisher Exact Test (d)		P=0.277N	P=0.100N
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	8.1%	2.8%	2.3%
Terminal Rates (c)	1/31 (3%)	0/33 (0%)	0/34 (0%)
Week of First Observation	95	98	85
Life Table Tests (d)	P=0.203N	P=0.314N	P=0.304N
Incidental Tumor Tests (d)	P=0.286N	P=0.468N	P=0.379N
Cochran-Armitage Trend Test (d)	P=0.201N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	23.9%	15.3%	8.9%
Terminal Rates (c)	2/31 (6%)	2/33 (6%)	0/34 (0%)
Week of First Observation	86	62	68
Life Table Tests (d)	P=0.062N	P=0.239N	P=0.086N
Incidental Tumor Tests (d)	P=0.083N	P=0.417N	P=0.101N
Cochran-Armitage Trend Test (d)	P=0.053N		
Fisher Exact Test (d)		P=0.207N	P=0.074N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (b)	24.4%	24.2%	12.2%
Terminal Rates (c)	3/31 (10%)	6/33 (18%)	2/34 (6%)
Week of First Observation	86	62	68
Life Table Tests (d)	P=0.109N	P=0.501N	P=0.135N
Incidental Tumor Tests (d)	P=0.142N	P=0.544	P=0.168N
Cochran-Armitage Trend Test (d)	P=0.110N		
Fisher Exact Test (d)		P=0.500N	P=0.131N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	12/50 (24%)	10/50 (20%)	6/50 (12%)
Adjusted Rates (b)	29.1%	26.3%	14.2%
Terminal Rates (c)	4/31 (13%)	6/33 (18%)	2/34 (6%)
Week of First Observation	86	62	68
Life Table Tests (d)	P=0.082N	P=0.413N	P=0.104N
Incidental Tumor Tests (d)	P=0.113N	P=0.588	P=0.127N
Cochran-Armitage Trend Test (d)	P=0.079N		
Fisher Exact Test (d)		P=0.405N	P=0.096N

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

	Control	6,300 ppm	12,500 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	8/50 (16%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	23.5%	11.5%	11.8%
Terminal Rates (c)	6/31 (19%)	3/33 (9%)	4/34 (12%)
Week of First Observation	86	96	104
Life Table Tests (d)	P=0.103N	P=0.164N	P=0.143N
Incidental Tumor Tests (d)	P=0.125N	P=0.204N	P=0.159N
Cochran-Armitage Trend Test (d)	P=0.128N		
Fisher Exact Test (d)		P=0.178N	P=0.178N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	6.5%	17.3%	8.8%
Terminal Rates (c)	2/31 (6%)	5/33 (15%)	3/34 (9%)
Week of First Observation	104	92	104
Life Table Tests (d)	P=0.468	P=0.150	P=0.542
Incidental Tumor Tests (d)	P=0.468	P=0.152	P=0.542
Cochran-Armitage Trend Test (d)	P=0.422		
Fisher Exact Test (d)		P=0.134	P=0.500
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	9/50 (18%)	6/50 (12%)
Adjusted Rates (b)	29.6%	25.3%	17.6%
Terminal Rates (c)	8/31 (26%)	7/33 (21%)	6/34 (18%)
Week of First Observation	86	92	104
Life Table Tests (d)	P=0.132N	P=0.462N	P=0.157N
Incidental Tumor Tests (d)	P=0.151N	P=0.512N	P=0.172N
Cochran-Armitage Trend Test (d)	P=0.174N		
Fisher Exact Test (d)		P=0.500N	P=0.207N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	10.5%	2.4%	11.0%
Terminal Rates (c)	2/31 (6%)	0/33 (0%)	3/34 (9%)
Week of First Observation	55	91	92
Life Table Tests (d)	P=0.560N	P=0.188N	P=0.613N
Incidental Tumor Tests (d)	P=0.536N	P=0.144N	P=0.584N
Cochran-Armitage Trend Test (d)	P=0.581N		
Fisher Exact Test (d)		P=0.181N	P=0.643N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	8/50 (16%)	1/50 (2%)	8/50 (16%)
Adjusted Rates (b)	22.1%	2.4%	19.1%
Terminal Rates (c)	5/31 (16%)	0/33 (0%)	3/34 (9%)
Week of First Observation	55	91	29
Life Table Tests (d)	P=0.527N	P=0.020N	P=0.562N
Incidental Tumor Tests (d)	P=0.552	P=0.017N	P=0.597
Cochran-Armitage Trend Test (d)	P=0.559N		
Fisher Exact Test (d)		P=0.016N	P=0.607N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	8.7%	2.4%	5.9%
Terminal Rates (c)	2/31 (6%)	0/33 (0%)	2/34 (6%)
Week of First Observation	95	86	104
Life Table Tests (d)	P=0.382N	P=0.309N	P=0.471N
Incidental Tumor Tests (d)	P=0.409N	P=0.348N	P=0.507N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.309N	P=0.500N

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

	Control	6,300 ppm	12,500 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	7/50 (14%)	8/50 (16%)	6/50 (12%)
Adjusted Rates (b)	19.2%	23.1%	16.6%
Terminal Rates (c)	4/31 (13%)	7/33 (21%)	5/34 (15%)
Week of First Observation	86	91	73
Life Table Tests (d)	P=0.393N	P=0.523	P=0.454N
Incidental Tumor Tests (d)	P=0.393N	P=0.506	P=0.454N
Cochran-Armitage Trend Test (d)	P=0.444N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	11/50 (22%)	9/50 (18%)	11/50 (22%)
Adjusted Rates (b)	29.7%	22.4%	30.1%
Terminal Rates (c)	6/31 (19%)	3/33 (9%)	9/34 (26%)
Week of First Observation	91	75	94
Life Table Tests (d)	P=0.493N	P=0.401N	P=0.528N
Incidental Tumor Tests (d)	P=0.481	P=0.539N	P=0.535
Cochran-Armitage Trend Test (d)	P=0.548N		
Fisher Exact Test (d)		P=0.402N	P=0.595N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	18/50 (36%)	15/50 (30%)	17/50 (34%)
Adjusted Rates (b)	45.2%	37.9%	45.3%
Terminal Rates (c)	10/31 (32%)	9/33 (27%)	14/34 (41%)
Week of First Observation	86	75	73
Life Table Tests (d)	P=0.383N	P=0.330N	P=0.416N
Incidental Tumor Tests (d)	P=0.481N	P=0.444N	P=0.521N
Cochran-Armitage Trend Test (d)	P=0.457N		
Fisher Exact Test (d)		P=0.336N	P=0.500N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	5/49 (10%)	2/50 (4%)
Adjusted Rates (b)	6.2%	15.2%	5.9%
Terminal Rates (c)	1/31 (3%)	5/33 (15%)	2/34 (6%)
Week of First Observation	102	104	104
Life Table Tests (d)	P=0.543N	P=0.239	P=0.663N
Incidental Tumor Tests (d)	P=0.574N	P=0.203	P=0.680
Cochran-Armitage Trend Test (d)	P=0.581		
Fisher Exact Test (d)		P=0.210	P=0.691
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	5/49 (10%)	2/50 (4%)
Adjusted Rates (b)	8.6%	15.2%	5.9%
Terminal Rates (c)	1/31 (3%)	5/33 (15%)	2/34 (6%)
Week of First Observation	96	104	104
Life Table Tests (d)	P=0.381N	P=0.382	P=0.467N
Incidental Tumor Tests (d)	P=0.438N	P=0.301	P=0.556N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test (d)		P=0.346	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparison 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 E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF OXYTETRACYCLINE HYDROCHLORIDE

	Control	6,300 ppm	12,500 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	9.7%	2.9%	6.9%
Terminal Rates (c)	3/31 (10%)	1/35 (3%)	1/36 (3%)
Week of First Observation	104	104	79
Life Table Tests (d)	P=0.535N	P=0.262N	P=0.600N
Incidental Tumor Tests (d)	P=0.562N	P=0.262N	P=0.632N
Cochran-Armitage Trend Test (d)	P=0.592N		
Fisher Exact Test (d)		P=0.309N	P=0.661
Lung: Alveolar/Bronchiolar Adenoma Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	9.7%	8.6%	6.9%
Terminal Rates (c)	3/31 (10%)	3/35 (9%)	1/36 (3%)
Week of First Observation	104	104	79
Life Table Tests (d)	P=0.517N	P=0.607N	P=0.600N
Incidental Tumor Tests (d)	P=0.541N	P=0.607N	P=0.632N
Cochran-Armitage Trend Test (d)	P=0.584		
Fisher Exact Test (d)		P=0.661	P=0.661
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	17/50 (34%)	12/50 (24%)	16/50 (32%)
Adjusted Rates (b)	45.2%	28.9%	37.8%
Terminal Rates (c)	11/31 (35%)	7/35 (20%)	11/36 (31%)
Week of First Observation	86	88	79
Life Table Tests (d)	P=0.304N	P=0.127N	P=0.330N
Incidental Tumor Tests (d)	P=0.369N	P=0.132N	P=0.400N
Cochran-Armitage Trend Test (d)	P=0.455N		
Fisher Exact Test (d)		P=0.189N	P=0.500N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	11.1%	5.2%	5.2%
Terminal Rates (c)	2/31 (6%)	1/35 (3%)	1/36 (3%)
Week of First Observation	86	98	100
Life Table Tests (d)	P=0.210N	P=0.294N	P=0.281N
Incidental Tumor Tests (d)	P=0.237N	P=0.334N	P=0.322N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test (d)		P=0.339N	P=0.339N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	5.7%	0.0%	7.4%
Terminal Rates (c)	1/31 (3%)	0/35 (0%)	2/36 (6%)
Week of First Observation	98		79
Life Table Tests (d)	P=0.436	P=0.219N	P=0.552
Incidental Tumor Tests (d)	P=0.409	P=0.216N	P=0.520
Cochran-Armitage Trend Test (d)	P=0.394		
Fisher Exact Test (d)		P=0.248N	P=0.500
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	10/50 (20%)	10/50 (20%)	11/50 (22%)
Adjusted Rates (b)	29.8%	24.5%	27.1%
Terminal Rates (c)	8/31 (26%)	6/35 (17%)	8/36 (22%)
Week of First Observation	98	88	91
Life Table Tests (d)	P=0.507N	P=0.486N	P=0.551N
Incidental Tumor Tests (d)	P=0.533	P=0.516N	P=0.594
Cochran-Armitage Trend Test (d)	P=0.452		
Fisher Exact Test (d)		P=0.599N	P=0.500

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

	Control	6,300 ppm	12,500 ppm
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	18/50 (36%)	12/50 (24%)	16/50 (32%)
Adjusted Rates (b)	46.3%	28.9%	37.8%
Terminal Rates (c)	11/31 (35%)	7/35 (20%)	11/36 (31%)
Week of First Observation	78	88	79
Life Table Tests (d)	P=0.239N	P=0.094N	P=0.265N
Incidental Tumor Tests (d)	P=0.349N	P=0.114N	P=0.400N
Cochran-Armitage Trend Test (d)	P=0.371N		
Fisher Exact Test (d)		P=0.138N	P=0.417N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	4.3%	5.7%	7.9%
Terminal Rates (c)	0/31 (0%)	2/35 (6%)	2/36 (6%)
Week of First Observation	82	104	100
Life Table Tests (d)	P=0.462	P=0.657N	P=0.552
Incidental Tumor Tests (d)	P=0.414	P=0.629	P=0.487
Cochran-Armitage Trend Test (d)	P=0.408		
Fisher Exact Test (d)		P=0.691N	P=0.500
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	4.3%	11.4%	7.9%
Terminal Rates (c)	0/31 (0%)	4/35 (11%)	2/36 (6%)
Week of First Observation	82	104	100
Life Table Tests (d)	P=0.481	P=0.388	P=0.552
Incidental Tumor Tests (d)	P=0.437	P=0.294	P=0.487
Cochran-Armitage Trend Test (d)	P=0.416		
Fisher Exact Test (d)		P=0.339	P=0.500
Liver: Hepatocellular Adenoma			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	15.6%	0.0%	2.8%
Terminal Rates (c)	4/31 (13%)	0/35 (0%)	1/36 (3%)
Week of First Observation	101		104
Life Table Tests (d)	P=0.025N	P=0.024N	P=0.074N
Incidental Tumor Tests (d)	P=0.027N	P=0.025N	P=0.078N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.028N	P=0.102N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (b)	17.6%	0.0%	5.1%
Terminal Rates (c)	4/31 (13%)	0/35 (0%)	1/36 (3%)
Week of First Observation	91		99
Life Table Tests (d)	P=0.043N	P=0.013N	P=0.099N
Incidental Tumor Tests (d)	P=0.052N	P=0.018N	P=0.118N
Cochran-Armitage Trend Test (d)	P=0.059N		
Fisher Exact Test (d)		P=0.013N	P=0.134N
Pituitary Gland: Adenoma			
Overall Rates (a)	13/50 (26%)	16/49 (33%)	10/50 (20%)
Adjusted Rates (b)	41.9%	42.9%	25.9%
Terminal Rates (c)	13/31 (42%)	13/34 (38%)	8/36 (22%)
Week of First Observation	104	96	97
Life Table Tests (d)	P=0.154N	P=0.445	P=0.183N
Incidental Tumor Tests (d)	P=0.163N	P=0.439	P=0.190N
Cochran-Armitage Trend Test (d)	P=0.287N		
Fisher Exact Test (d)		P=0.306	P=0.318N

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

	Control	6,300 ppm	12,500 ppm
Pituitary Gland: Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	0/49 (0%)	2/50 (4%)
Adjusted Rates (b)	9.7%	0.0%	4.9%
Terminal Rates (c)	3/31 (10%)	0/34 (0%)	1/36 (3%)
Week of First Observation	104		94
Life Table Tests (d)	P=0.337N	P=0.105N	P=0.433N
Incidental Tumor Tests (d)	P=0.346N	P=0.105N	P=0.446N
Cochran-Armitage Trend Test (d)	P=0.389N		
Fisher Exact Test (d)		P=0.125N	P=0.500N
Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	16/50 (32%)	16/49 (33%)	12/50 (24%)
Adjusted Rates (b)	51.6%	42.9%	30.1%
Terminal Rates (c)	16/31 (52%)	13/34 (38%)	9/36 (25%)
Week of First Observation	104	96	94
Life Table Tests (d)	P=0.103N	P=0.452N	P=0.122N
Incidental Tumor Tests (d)	P=0.109N	P=0.456N	P=0.129N
Cochran-Armitage Trend Test (d)	P=0.223N		
Fisher Exact Test (d)		P=0.558	P=0.252N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	6.5%	8.6%	2.8%
Terminal Rates (c)	2/31 (6%)	3/35 (9%)	1/36 (3%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.343N	P=0.556	P=0.448N
Incidental Tumor Tests (d)	P=0.343N	P=0.556	P=0.448N
Cochran-Armitage Trend Test (d)	P=0.409N		
Fisher Exact Test (d)		P=0.500	P=0.508N
Mammary Gland: Adenocarcinoma or Adenosquamous Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	6.3%	7.8%	2.8%
Terminal Rates (c)	1/31 (3%)	1/35 (3%)	1/36 (3%)
Week of First Observation	101	96	104
Life Table Tests (d)	P=0.347N	P=0.557	P=0.449N
Incidental Tumor Tests (d)	P=0.371N	P=0.549	P=0.465N
Cochran-Armitage Trend Test (d)	P=0.402N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Mammary Gland: Fibroadenoma, Adenocarcinoma, or Adenosquamous Carcinoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	8.7%	10.1%	2.8%
Terminal Rates (c)	1/31 (3%)	1/35 (3%)	1/36 (3%)
Week of First Observation	98	96	104
Life Table Tests (d)	P=0.211N	P=0.559	P=0.265N
Incidental Tumor Tests (d)	P=0.226N	P=0.559	P=0.279N
Cochran-Armitage Trend Test (d)	P=0.254N		
Fisher Exact Test (d)		P=0.500	P=0.309N
Harderian Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	11.8%	7.8%	0.0%
Terminal Rates (c)	2/31 (6%)	2/35 (6%)	0/36 (0%)
Week of First Observation	100	94	
Life Table Tests (d)	P=0.036N	P=0.440N	P=0.049N
Incidental Tumor Tests (d)	P=0.038N	P=0.440N	P=0.054N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test (d)		P=0.500N	P=0.059N

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

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher 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 RECEIVING NO TREATMENT

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

	Incidence in Controls		
	Pheochromocytoma	Pheochromocytoma, Malignant	Pheochromocytoma or Pheochromocytoma, Malignant
No 2-year studies by Physiological Research Laboratories 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 F2. 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 by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 743/1,704 (43.6%)	(c) 62/1,704 (3.6%)	(b,c) 805/1,704 (47.2%)
SD (d)	11.71%	4.24%	11.01%
Range (e)			
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) Includes 593 adenomas, NOS, and 150 chromophobe adenomas. No other benign tumors were observed.
(c) Includes 51 carcinomas, NOS, and 11 chromophobe carcinomas. No other malignant tumors were observed.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

GENETIC TOXICOLOGY OF

OXYTETRACYCLINE HYDROCHLORIDE

TABLE G1. MUTAGENICITY OF OXYTETRACYCLINE HYDROCHLORIDE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (μg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0.000	106 ± 7.2	129 ± 0.6	122 ± 7.8
	0.003	142 ± 8.5	128 ± 2.5	99 ± 3.3
	0.010	122 ± 10.7	130 ± 8.4	120 ± 9.7
	0.030	102 ± 13.1	124 ± 5.1	134 ± 2.1
	0.100	113 ± 6.8	103 ± 10.5	134 ± 2.7
	0.300	105 ± 4.0	128 ± 11.0	122 ± 7.2
	1.000	61 ± 1.7	78 ± 4.4	74 ± 1.7
TA1535	0.000	17 ± 3.5	10 ± 2.8	12 ± 1.8
	0.003	15 ± 2.1	12 ± 3.9	10 ± 3.1
	0.010	15 ± 2.6	8 ± 1.5	7 ± 1.7
	0.030	15 ± 2.3	12 ± 0.6	10 ± 1.7
	0.100	15 ± 2.8	10 ± 1.2	9 ± 0.9
	0.300	13 ± 1.5	9 ± 0.7	7 ± 0.7
	1.000	14 ± 3.5	7 ± 0.9	8 ± 0.9
TA1537	0.000	5 ± 1.0	6 ± 0.9	12 ± 3.0
	0.003	5 ± 1.5	6 ± 1.2	6 ± 1.8
	0.010	7 ± 1.0	7 ± 2.2	8 ± 0.6
	0.030	6 ± 0.9	6 ± 0.7	8 ± 2.3
	0.100	3 ± 0.9	4 ± 0.0	4 ± 0.9
	0.300	7 ± 1.2	6 ± 1.2	6 ± 0.7
	1.000	4 ± 0.6	7 ± 1.2	7 ± 0.9
TA98	0.000	15 ± 2.6	28 ± 0.7	20 ± 3.5
	0.003	14 ± 3.1	25 ± 1.5	18 ± 2.2
	0.010	15 ± 1.5	20 ± 1.8	26 ± 1.5
	0.030	15 ± 1.5	22 ± 1.7	27 ± 6.1
	0.100	14 ± 2.2	21 ± 5.5	25 ± 6.4
	0.300	10 ± 3.1	18 ± 3.8	21 ± 3.2
	1.000	10 ± 1.5	14 ± 3.2	17 ± 4.4

(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 (DMSO) 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 OXYTETRACYCLINE HYDROCHLORIDE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Concentration (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Distilled water				
	116	72.3	98	53
	122	59.7	101	68
Ethyl methanesulfonate				
200.0	433	71.8	73	201
	547	84.5	78	216
Oxytetracycline hydrochloride				
12.5	116	66.2	102	58
	124	69.3	112	60
25.0	113	51.5	95	73
	121	65.8	106	61
50.0	89	52.2	93	57
	90	84.7	141	35
100.0	100	82.2	90	41
	87	51.3	64	56
200.0	108	51.8	65	69
	82	74.0	84	37
400.0	100	54.0	43	62
	95	60.0	34	53
800.0	Toxic			

(a) Experiments were performed twice, and all doses were tested in duplicate or 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.

TABLE G3. MUTAGENICITY OF OXYTETRACYCLINE HYDROCHLORIDE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE PRESENCE OF S9 (a)

Concentration (µg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Distilled water				
	152	54.2	101	94
	176	64.5	84	91
	181	76.2	94	79
	166	69.8	117	79
Methylcholanthrene				
2.5	712	57.7	40	412
	663	37.8	33	584
Oxytetracycline hydrochloride				
25.0	189	73.3	98	86
	204	69.0	102	99
50.0	201	73.0	66	92
	179	62.2	85	96
100.0	307	71.0	29	144
	238	45.5	34	174
200.0	920	(b) 3.8	(b) 1	8,000
	1,351	(b) 13.0	4	3,464
400.0	Toxic			

(a) Experiments were performed twice, and all doses were tested in duplicate except the solvent control (distilled water), which was tested in quadruplicate. 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. S9 was prepared from the liver of Aroclor 1254-induced male F344 rats.
(b) Extreme toxicity

TABLE G4. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY OXYTETRACYCLINE HYDROCHLORIDE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	SCE/Cell (d)	Dose (μg/ml)	SCE/Cell (d)
Water (pH 2.86)	10.9	Water (pH 2.86)	13.6
Oxytetracycline hydrochloride		Oxytetracycline hydrochloride	
60	12.9	400	16.0
70	13.5	500	16.6
80	12.7	700	17.6
Mitomycin C		Cyclophosphamide	
0.001	17.7	0.350	18.4
0.010	56.4	2.000	34.4

(a) SCE = sister-chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent at 37° C; 2 hours after initiation of treatment, 10 μM BrdU was added, and incubation was continued for an additional 22-24 hours. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 μg/ml) present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).
(d) Cells were collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air-dried (Galloway et al., 1985).

TABLE G5. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY OXTETRACYCLINE HYDROCHLORIDE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	Abs/100 Cells (percent cells with abs)	Dose (μg/ml)	Abs/100 Cells (percent cells with abs)
Water (pH 2.86)	6 (6)	Water (pH 2.86)	4 (3)
Oxytetracycline hydrochloride		Oxytetracycline hydrochloride	
80	4 (3)	700	5 (5)
90	5 (4)	800	4 (4)
100	5 (4)	900	3 (3)
Mitomycin C		Cyclophosphamide	
0.050	112 (52)	15.000	38 (58)

(a) Abs = aberrations
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 μg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa (Galloway et al., 1985).
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, fresh medium was added, and incubation was continued for 8-10 hours. Colcemid (0.1 μg/ml) was added for the last 2-3 hours of incubation; then cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

APPENDIX H

CHEMICAL CHARACTERIZATION OF OXYTETRACYCLINE HYDROCHLORIDE

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Oxytetracycline Hydrochloride Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Lot no. 304-G-004		
1. Physical properties		
a. Appearance:	Yellow, fluffy solid	Yellow platelets (Merck Index, 1976)
b. Melting point:	180° C (decomposes); (visual, capillary, Büchi 510)	181°-182° C (decomposes) (Merck Index, 1976)
c. Specific rotation:	$[a]_D^{26}$: −202.5° ± 2.0° (solvent: 0.1 N hydrochloric acid)	$[a]_D^{25}$: −196.6° (Merck Index, 1976) (solvent: 0.1 N hydrochloric acid)
	$[a]_D^{26}$: −196.6° ± 1.2° (USP standard) (solvent: 0.1 N hydrochloric acid)	
2. Spectral data		
a. Infrared		
Instrument:	Beckman IR-12	
Phase:	1% in potassium bromide pellet	
Results:	See Figure 5	Consistent with literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	0.1 N hydrochloric acid	0.1 N sulfuric acid

Results:

λ max (nm)	ε × 10^{-4}	λ max (nm)	ε × 10^{-4}
218	1.44 ± 0.02		
268	1.91 ± 0.01	269	1.99
353	1.39 ± 0.01	352	1.35
		(Clarke, 1969)	
218	1.33 ± 0.01		
268	1.76 ± 0.01		
353	1.29 ± 0.01		
(USP standard)			

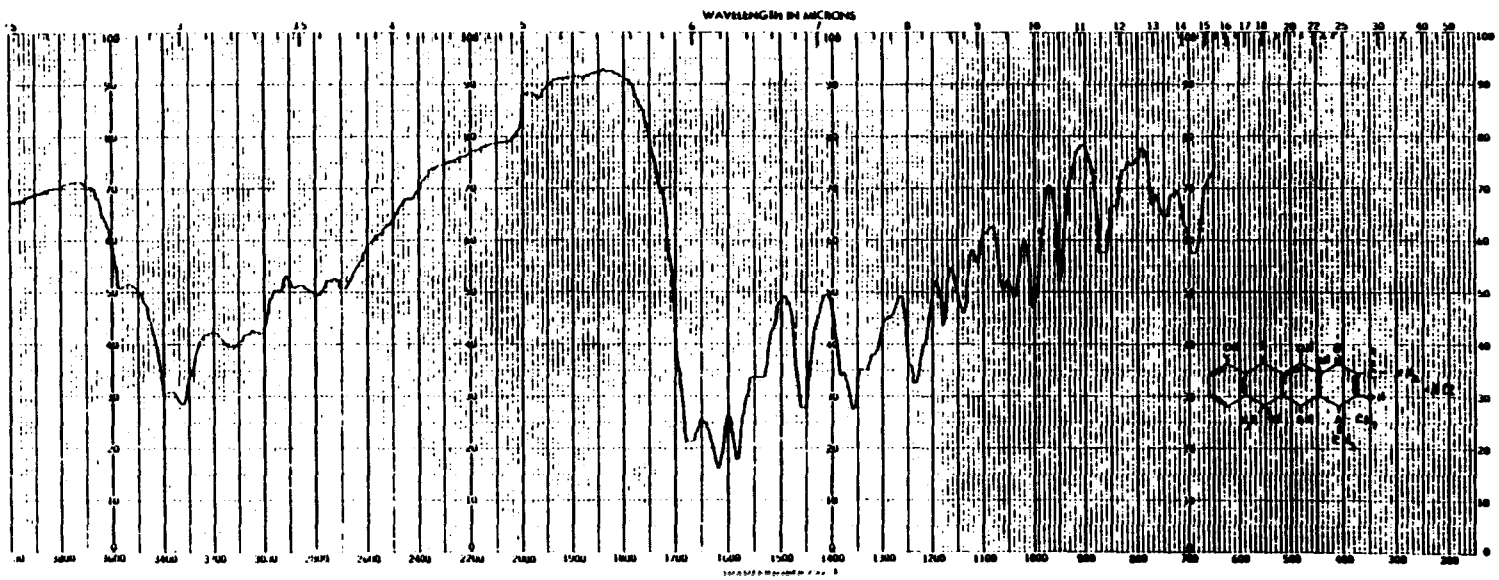

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF OXYTETRACYCLINE HYDROCHLORIDE (LOT NO. 304-G-004)

	Determined	Literature Values
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Dimethyl sulfoxide, d_6 with tetramethylsilane internal standard	
Assignments:	See Figure 6	No literature reference found. Spectrum consistent with structure.
Chemical shift (δ):	a 1.72 b 2.63-3.17 c 3.33-5.00 d 4.68 e 6.74-7.77 f 9.10 g 9.59 h 11.67 i 15.09 j 2.38-2.62 (DMSO)	
Integration ratios:	a 3.6 b 9.4 c, d } 3.9 e 4.4 f 0.9 g 1.0 h 0.9 i 0.9	

3. **Titration**

   a. **Acidic functional group:** Titration of three acidic protons with 0.1 N sodium methoxide. The compound was dissolved in dimethylformamide (Regosz, 1975).

   A purity of 97.5% ± 0.2(δ)% was indicated.

   b. **Amine group:** Titration of one basic proton with 0.1 N perchloric acid in glacial acetic acid. The compound was dissolved in anhydrous formic acid:glacial acetic acid:1,4-dioxane (1:2:2) (Hansen, 1973).

   A purity of 97.8% ± 0.2(δ)% was indicated.

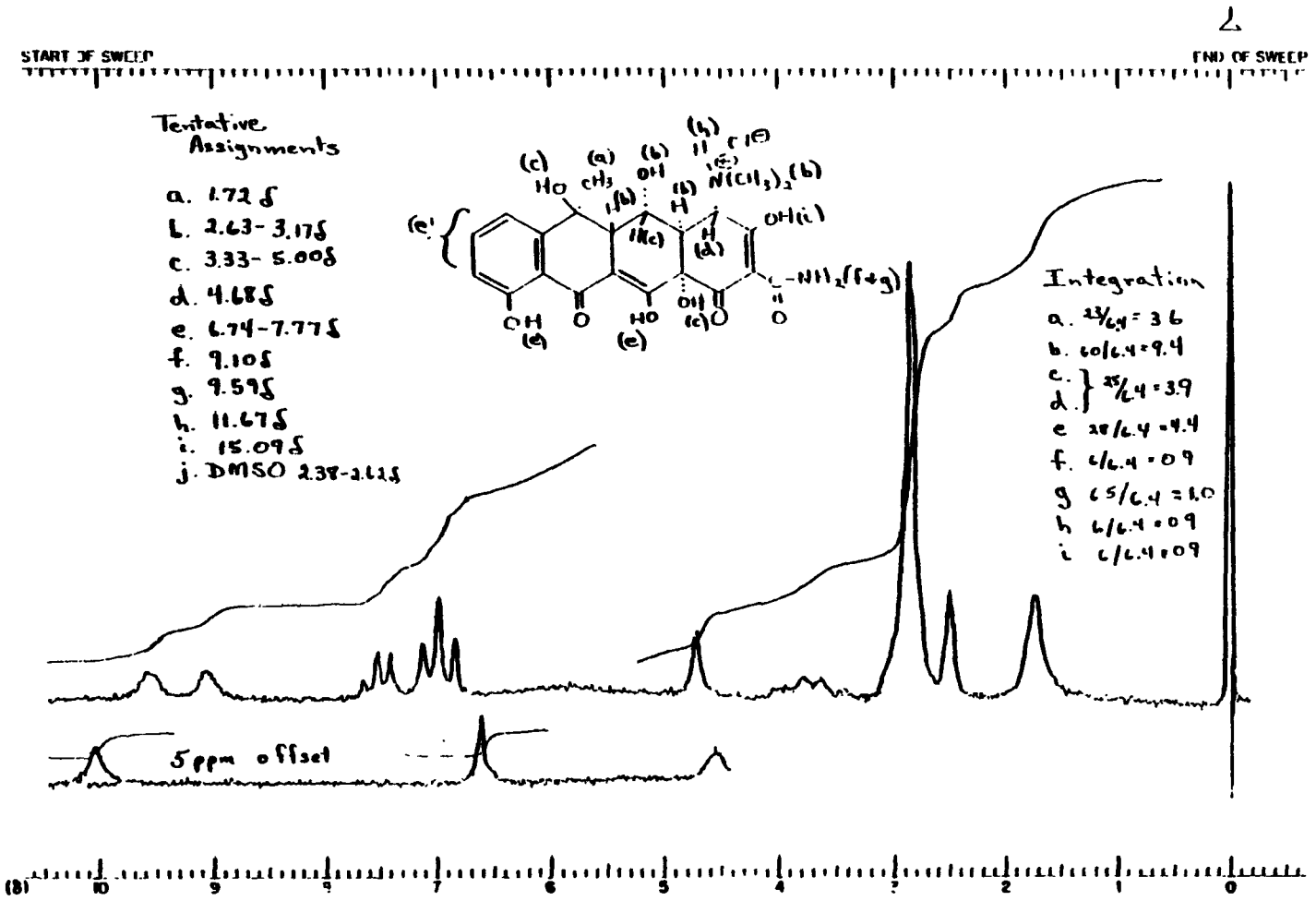

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF OXYTETRACYCLINE HYDROCHLORIDE (LOT NO. 304-G-004)

4. **Potency by chemical assay:** Reaction of the compound with ferric chloride solution, measurement of the absorbance produced at 490 nm, and direct comparison with a USP standard of known potency treated in the same manner (CFR, 1977).

   A potency of 1,006 ± 3(δ) µg/mg compared with the USP standard quoted at 940 µg/mg.

5. **Water analysis (Karl Fischer):** 0.98% ± 0.08(δ)%

6. **Elemental analysis**

Element	C	H	N	O	Cl
Theory (T)	53.18	5.07	5.64	28.98	7.13
Determined (D)	53.01 53.14	5.33 5.24	5.62 5.61	28.34 28.47	7.15 7.09
Percent D/T	99.80	104.24	99.56	98.02	99.86

7. **Chromatographic analysis**

   a. **Thin-layer chromatography**

   Reference standard: 4-Hydroxyacetanilide
   Amount spotted: 5, 40, and 120 µg of compound and 20 µg of reference standard
   Visualization: Ultraviolet at 254 and 356 nm; spray of a solution of boric acid (1 g/100 ml) in concentrated sulfuric acid:water (7:3) (Gyanchandi et al., 1970)

   System 1
   Plates: Silanized Silica Gel 60, F-254, 0.25-mm layer thickness, sprayed with 0.1 M aqueous disodium ethylenediamine tetraacetic acid and air dried overnight before use
   Solvent: *n*-Butanol saturated with water. Manually programmed multiple development.

   System 2
   Plates: Cellulose F, 0.1 mm-layer thickness, sprayed with 0.1 M aqueous disodium ethylenediamine tetraacetic acid and air dried overnight before use
   Solvent: Isopropanol:0.1 M disodium ethylenediamine tetraacetic acid (1:1) with precipitate filtered before use. Manually programmed multiple development.

System 1			System 2		
Spot Intensity	R_f	R_{st}	Spot Intensity	R_f	R_{st}
Major	0.58	0.72	Major	0.83	0.98
Trace	0.69	0.85	Reference	0.85	1.00
Trace	0.38	0.47			
Reference	0.81	1.00			

b. High-performance liquid chromatography

Instrument system
Pump: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Column: μBondapak C_{18}, 300 × 3.9 mm ID
Detection: Ultraviolet, 254 nm
Guard column: CO:PELL ODS, 72 × 2.3 mm ID
Flow rate: 1 ml/min
Solvent system
(A) 1.5 mM tetraammonium ethylenediamine tetraacetic acid in water containing 5% acetic acid (v/v)
(B) Tetrahydrofuran

System 1

Solvent program: 5% (B), isocratic
Samples injected: 20 μl of a 0.6 mg/ml methanolic solution of the compound and 20 μl of a 0.7 mg/ml methanolic solution of the USP standard

Results: The compound exhibited a major peak preceded by one minor impurity (shoulder). Three trace (relative area <0.1%) impurities, one preceding and two following the major peak, were also detected. The USP standard exhibited the same minor impurity and the one trace impurity preceding the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1 (shoulder)	7.5	0.89	0.30
2	8.4	1.00	100.0

System 2

Solvent program: 10% (B), isocratic (for quantitation against a USP standard)
Samples injected: 25 μl of methanolic solutions of the compound and the USP standard containing acetophenone as an internal standard

Results: The results indicated a purity of 105.4% ± 1.6(δ)% relative to the USP standard by comparison of the areas of the major peaks (normalized with the internal standard area).

8. **Conclusions:** The results of the elemental analysis for carbon, hydrogen, nitrogen, and chlorine agreed with theoretical values, but the oxygen value was slightly low. The water content was 0.98% ± 0.08(δ)% by Karl Fischer titrimetry. Titrations of acidic functional groups indicated a purity of 97.5% ± 0.2(δ)%. An amino group titration indicated a purity of 97.8% ± 0.2(δ)%. The results of a chemical assay for potency indicated a value of 1,006 ± 3(δ) µg/mg compared with a USP standard quoted as 940 µg/mg. Thin-layer chromatography detected a major spot and two trace impurities in one system, and only a major spot in the second. A high-performance liquid chromatographic system detected one minor shoulder, relative area of 0.3%, preceding the major peak, and three trace (relative area < 0.1%) impurities in addition to the major peak in the sample. A purity profile of a USP standard material indicated only the minor and trace impurity preceding the major peak. Quantitation by high-performance liquid chromatography (HPLC) indicated a purity of 105.4% ± 1.6(δ)% relative to the USP standard. The optical activity was consistent with a literature value. The infrared and ultraviolet/visible spectra were also consistent with the literature. The ε_{max} values measured for the material were an average of 8% greater than the ε_{max} values for the USP standard material. The nuclear magnetic resonance spectrum was consistent with the structure.

	Determined	Literature Values
B. Lot no. 69150380		
1. Physical properties		
a. Appearance:	Yellow, fluffy, microcrystalline powder	
b. Specific rotation:	$[\alpha]_D^{28°}$: $-202.2° \pm 0.7°$ (solvent: 0.1 N hydrochloric acid)	$[\alpha]_D^{25°}$: $-196.6°$ (Merck Index, 1976) (solvent: 0.1 N hydrochloric acid)
2. Spectral data		
a. Infrared		
Instrument:	Perkin-Elmer 283	
Phase:	1% in potassium bromide pellet	
Results:	See Figure 7	Consistent with structure and literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 219	
Solvent:	0.1 N hydrochloric acid	0.1 N sulfuric acid
Results:	λ max (nm) / ε × 10^{-4}	λ max (nm) / ε × 10^{-4}
	354 / 1.367 ± 0.009 318 / 1.027 ± 0.003 269 / 1.881 ± 0.008 217 / 1.410 ± 0.006	352 / 1.35 269 / 1.99 (Clarke, 1969)
	354 / 1.280 ± 0.008 318 / 0.966 ± 0.008 269 / 1.749 ± 0.009 217 / 1.332 ± 0.023 (USP standard)	353 / 1.496 276 / 1.600 249 / 1.193 (as the free base in phosphate buffer, pH 4.5) (Merck Index, 1976)

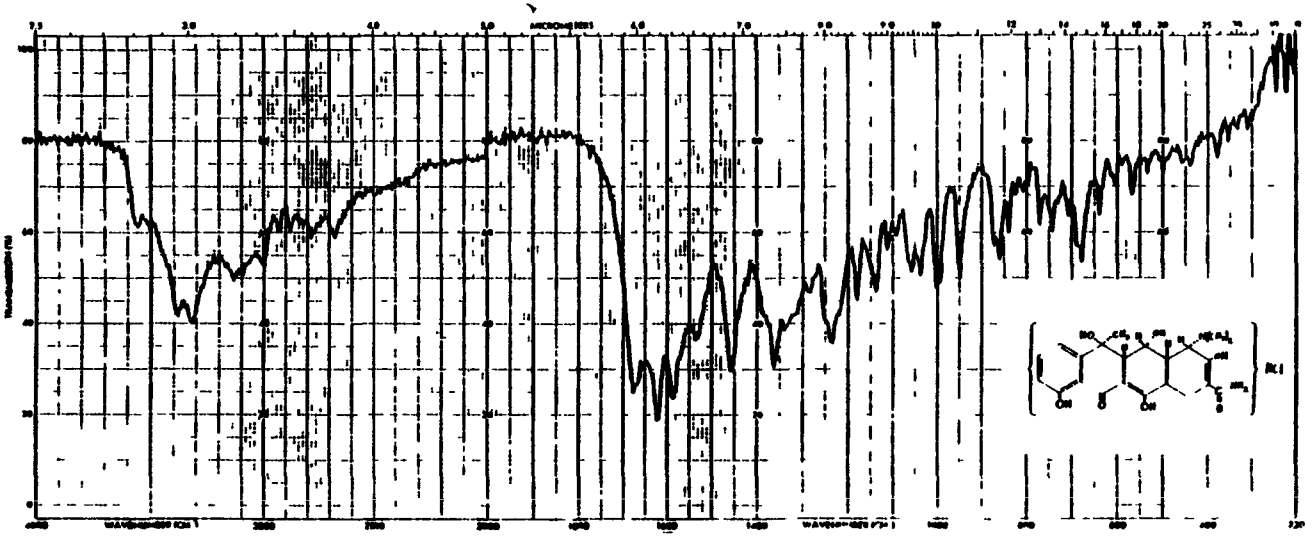

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF OXYTETRACYCLINE HYDROCHLORIDE
(LOT NO. 69150380)

	Determined	Literature Values
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Deuterated dimethyl-sulfoxide, with tetramethyl-silane internal standard	
Assignments:	See Figure 8	Consistent with structure and literature (Asleson et al., 1974; von Wittenau and Blackwood, 1966)

Chemical shift (δ):

a	broad s	1.78	
b	broad s	2.87	
c	broad m	3.5-4.1	
d	broad s	4.76	
e	broad s	5.5-6.8	
f	unresolved d	6.90	$J_{f\text{-}h} = J_{g\text{-}h} = 8$Hz
g	unresolved d	7.05	
h	t	7.53	
i	broad s	9.08	
j	broad s	9.60	
k	s	11.61	
l	s	15.02	
m	unobserved		
n	impurity	1.00	
o	impurity	1.10	
p	impurity	2.08*	

* This impurity peak is a singlet with a chemical shift consistent with that of acetone. If the impurity is acetone, calculations from the integration indicated that it is present at approximately 0.6%.

Integration ratios:

a	3.07
b	7.14
c	0.74
d	0.95
e	0.95
f, g	2.11
h	1.06
i, j	1.06
k	0.95
l	0.95
m	--
n, o	0.1
p	0.4

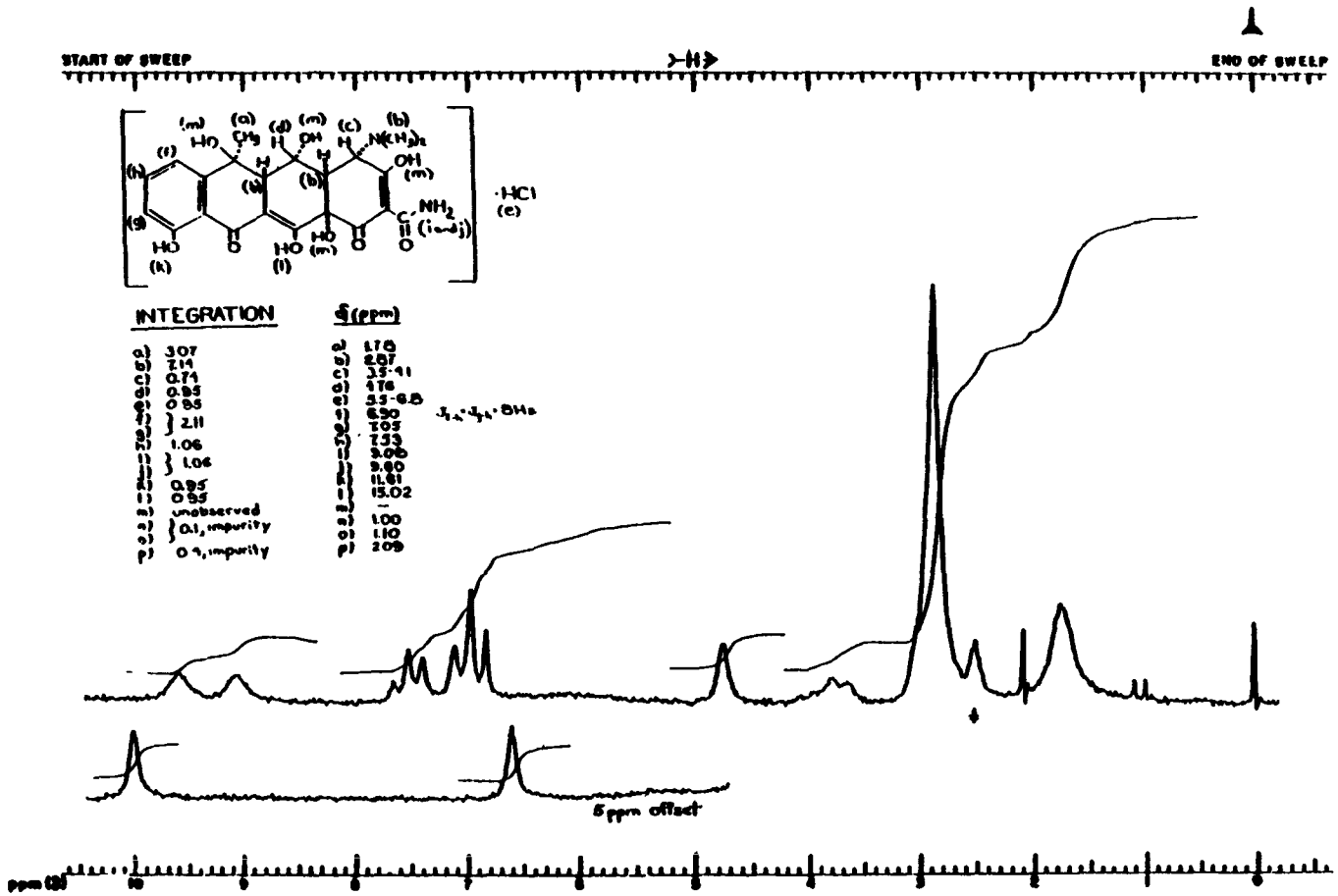

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF OXYTETRACYCLINE HYDROCHLORIDE (LOT NO. 69150380)

3. **Titration**

   a. **Acidic functional group:** The sample was dissolved in dimethylformamide and titrated with 0.1 N sodium methoxide in methanol:toluene (1:4). The titration was monitored potentiometrically with a combination electrode (filled with aqueous 4 M potassium chloride).

      A purity of 98.8% ± 0.3(δ)% (for three equivalents per mole) was indicated.

   b. **Amine group:** The sample was dissolved in formic acid:acetic acid:*p*-dioxane (1:2:2) and titrated with 0.1 N perchloric acid in the presence of mercuric acetate. The titration was monitored potentiometrically with a combination electrode.

      A purity of 99.5% ± 0.2(δ)% was indicated.

4. **Visible spectrophotometric assay:** The sample was dissolved in 0.1 N hydrochloric acid, and the absorptivity was compared with a USP standard, similarly treated, at 354 nm.

   The percent relative absorptivity of the sample (calculated on the dried basis) versus a USP standard was 93.4% ± 0.9(δ)%. The FDA requires the percent relative absorptivity to be 92.5% ± 4.3% of a similarly treated standard, corrected for potency (CFR, 1977).

5. **Potency by chemical assay:** Reaction of the compound with ferric chloride solution, measurement of the absorbance produced at 490 nm, and direct comparison with a USP standard of known potency treated in the same manner (CFR, 1977).

   A potency of 1,003 ± 7(δ) µg/mg of free base compared with the USP standard of 940 µg/mg. The FDA requires a potency of not less than 835 µg of oxytetracycline per milligram, calculated on the dried basis.

6. **Water analysis (Karl Fischer):** 0.39% ± 0.05(δ)%
   The FDA requires moisture content to be equal to or less than 2.0% (CFR, 1977).

7. **Elemental analysis**

Element	C	H	N	Cl
Theory (T)	53.18	5.07	5.64	7.13
Determined (D)	53.13 53.36	5.22 5.25	5.54 5.67	7.17 7.21
Percent D/T	100.1	103.2	99.38	100.8

8. **Chromatographic analysis**

a. **Thin-layer chromatography**

Plates: MN Cellulose, 0.25 mm layer thickness
Reference standard: 10 µl of a 1 mg/ml solution of tryptophan in methanol; oxytetracycline USP reference standard, 30 µl of a 10 mg/ml solution in methanol
Amount spotted: 1, 10, and 30 µl of a 10 mg/ml solution in methanol
Visualization: Ultraviolet at 254 and 366 nm; 0.5% Fast Blue B salt in water/0.1 N sodium hydroxide (Stahl, 1969)

System 1
Solvent: 5% aqueous trisodium citrate saturated with *n*-butanol

System 2
Solvent: 0.1 M aqueous sodium fluoride

	System 1			System 2	
Spot Intensity	R_f	R_{st}	Spot Intensity	R_f	R_{st}
Oxytetracycline					
Slight trace	0.83	1.20	Trace	0.83	1.22
Major	0.75	1.09	Major	0.75	1.10
Minor	0.56	0.81	Minor	0.51	0.75
USP reference					
Slight trace	0.84	1.22	Trace	0.84	1.24
Major	0.75	1.09	Major	0.75	1.10
Tryptophan*	0.69		Tryptophan*	0.68	

* Used for R_{st} calculations

b. **High-performance liquid chromatography**

Detection of impurities

Instrument system
Pump: Waters M6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Column: µBondapak C_{18}, 300 × 3.9 mm ID
Detection: Ultraviolet, 254 nm
Guard column: Whatman CO:PELL ODS, 72 × 2.3 mm ID
Flow rate: 1 ml/min
Solvent system
(A) 1.5 mM tetraammonium ethylenediamine tetraacetic acid in water containing 5% (v/v) acetic acid
(B) Tetrahydrofuran

Solvent ratio: A:B (95:5)
Samples injected: Solution containing 0.786 mg/ml oxytetracycline hydrochloride in methanol filtered into an amber septum vial
Volume injected: 20 µl

Results: The compound exhibited a major peak and one impurity with an area greater than 0.1% of the major peak area. The impurity eluted at 17.2 minutes and had an area equal to 0.42% of the major peak area. A second impurity eluted on the tail of the major peak but was less than 0.1% of the major peak area. In the original analysis, one impurity (0.3% of the major peak area) was observed on the front of the major peak in lot no. 304-G-004 but was not seen this time.

During the solvent ratio search, no additional impurities with areas > 0.1% of the major peak area were observed when injections of a solution of similar concentration to the one used for the analytical system were made at 100, 80, 60, 40, 20, or 10% B.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area* (percent of major peak)
1	9.3	1.00	100.0
2	17.2	1.85	0.42

* Detector response is very dependent upon the absorbance of a substance at the detection wavelength used. The values reported are absolute areas expressed as percentages of the area of the major peak and do not take into account the different ε values of the compound and its impurities. Therefore, the areas reported do not necessarily reflect the actual weight percentages of the impurities in the sample.

Batch comparison by major peak analysis

Samples of the USP standard and both the previous lot, no. 304-G-004, and present lot, no. 69150380, were analyzed by high-performance liquid chromatography. Sample peak heights were compared with internal standard peak heights, and the percent oxytetracycline hydrochloride in each batch was calculated relative to the USP standard. The instrumental parameters listed above for detection of impurities were used with the exceptions noted below.

Solvent ratio: A:B (85:15)
Flow rate: 1.5 ml/min
Samples injected: Solutions containing 0.5 mg/ml accurately weighed oxytetracycline hydrochloride and 0.3 mg/ml acetophenone as internal standard in methanol and filtered into an amber septum vial
Retention times
Oxytetracycline hydrochloride: 4.2 min
Acetophenone (internal standard): 8.0 min

Results

Sample	Percent Oxytetracycline Normalized to USP Reference
USP oxytetracycline	100.0 ± 2.0
Lot no. 304-G-004	100.9 ± 2.0
Lot no. 69150380	100.8 ± 2.0

9. **Conclusions:** The results of the elemental analysis for carbon, hydrogen, nitrogen, and chlorine were in agreement with theoretical values. Thin-layer chromatography, with one system, resolved a major, a minor, and a slight trace spot. The USP reference co-chromatographed with this system exhibited a major spot and a slight trace corresponding to the slight trace observed for the sample. The second thin-layer chromatographic system resolved a major spot and a minor and a trace impurity. The USP reference contained a trace impurity corresponding to the one observed in the sample. High-performance liquid chromatography resolved a major peak and one impurity with a relative area of 0.42%. Major peak comparisons made of the current lot and a USP reference indicated a purity of 100.8% ± 2.0(δ)% relative to the USP reference.

II. Chemical Stability Study Performed by the Analytical Chemistry Laboratory

A. Sample preparation and storage: Samples of oxytetracycline hydrochloride were stored for 2 weeks in amber vials with Teflon®-lined caps at temperatures of −20°, 5°, 25°, or 60° C.

B. Analytical method: Duplicate samples from each storage temperature were prepared by dissolving approximately 20 mg of the material, accurately weighed, in methanol, adding sufficient acetophenone, the internal standard, to produce a final concentration of 0.17 mg/ml, and diluting to 50 ml with methanol. Aliquots (25 µl) of these solutions were injected into the following high-performance liquid chromatographic system.

Instrument system
Pump: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Column: µBondapak C_{18}, 300 × 3.9 mm ID
Detection: Ultraviolet, 254 nm
Guard column: CO:PELL ODS, 72 × 2.3 mm ID
Flow rate: 1 ml/min
Solvent system
(A) 1.5 mM tetraammonium ethylenediamine tetraacetic acid in water containing 5% acetic acid (v/v)
(B) Tetrahydrofuran
Program: 10% B, isocratic (for quantitation against a USP standard)

C. Results

Storage Temperature	Percent Purity (normalized to −20° C sample)
−20° C	100.0
5° C	100.0 ± 1.6(δ)
25° C	97.8 ± 1.6(δ)
60° C	98.7 ± 1.6(δ)

D. Conclusions: Oxytetracycline hydrochloride is stable, within the limits of error of the analysis, when stored for 2 weeks at temperatures up to 60° C. However, because of the relatively large error, the possibility of decomposition at temperatures of 25° C or higher cannot be ruled out.

III. Chemical Stability Study at the Study Laboratory

A. Storage conditions

Bulk chemical: room temperature until 6/1/81, then 5° C
Reference: −20° C

B. Analytical method

1. **Identity determination:** Infrared spectrometry
   Instrument: Perkin-Elmer 283
   Phase: 1% in potassium bromide pellet

2. **Purity determination**

   Ultraviolet spectrometry: A solution of 0.250 mg/ml of ferric chloride hexahydrate was prepared. Twenty milligrams of accurately weighed oxytetracycline hydrochloride was dissolved in 10 ml of 0.1 N hydrochloric acid and diluted to 100 ml. Then 10 ml of the ferric chloride hexahydrate solution was added to 10 ml of the oxytetracycline hydrochloric acid solution, and the mixture was allowed to stand for 15 minutes after which the absorbance was read at 490 nm.

   Nonaqueous titration: Oxytetracycline hydrochloride (200 mg) was accurately weighed into 25 ml of solvent made up of formic acid:1,4-dioxane (purified on an alumina column and distilled):glacial acetic acid (1:2:2). Then 0.86 mg of mercuric acetate was added for each milligram of oxytetracycline hydrochloride, and the resulting solution was titrated with 0.1 N perchloric acid in glacial acetic acid. The potential of the solution was monitored from 0 to 750 mv.

C. Results

1. **Identity:** All bulk infrared spectra were comparable to the reference spectra and to the spectra supplied by the analytical chemistry laboratory.

2. Purity

a. Ultraviolet spectrometry

Date of Analysis	Lot No.	Potency of Bulk Sample (µg/mg)
11/79	304-G-004	(a) 998
02/80	304-G-004	(a) 1,004
06/80	304-G-004	(a) 1,007
10/80	304-G-004	(b) 997
02/81	304-G-004	(c) 1,006
06/81	304-G-004	(b) 1,009
06/81	69150380	(b) 1,020
10/81	69150380	(a) 1,006
02/82	69150380	(a) 991
06/82	69150380	(a) 998
10/82	69150380	(b) 1,024

(a) Result of triplicate analysis
(b) Result of duplicate analysis
(c) Result of quadruplicate analysis

b. Nonaqueous titration

Date of Analysis	Lot No.	Percent Purity (a)	
		Bulk	Reference
02/81	304-G-004	98.9	98.8
06/81	304-G-004	98.0	97.8
06/81	69150380	98.3	--
10/81	69150380	99.9	99.6
02/82	69150380	(b) 100.0	99.6
06/82	69150380	100.5	100.7
10/82	69150380	99.7	98.7

(a) Results of duplicate analysis
(b) Result of triplicate analysis

D. **Conclusion:** No notable degradation occurred during the studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Studies Conducted by the Analytical Chemistry Laboratory

A. Homogeneity Study

1. **Premix:** Oxytetracycline hydrochloride (15.0 g) was transferred to a tared 600-ml beaker and thoroughly mixed by spatula with approximately 15 g of feed. Approximate portions (30-60 g) of additional feed were added and blended in the same manner; then a final portion of feed was incorporated so that the total weight of the premix was 215 g.

2. **Bulk mixing:** A 600-g quantity of feed was layered evenly in the blender; then the 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 briefly and adding it 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 for the first 5 minutes and without it for the next 10 minutes of mixing. During the mixing operation, the blender shells were periodically given a firm tap with a block of wood to knock loose any feed that may have become packed in the corners of the blender.

   At the end of the 15-minute mixing period, approximately 40 g of the feed blend was sampled from the upper left- and right-hand shells and from the bottom discharge port. Triplicate 10.0-g portions of each sample were transferred into 200-ml centrifuge bottles for analysis. The theoretical level of oxytetracycline hydrochloride in the blend was 9.90 mg/g.

3. **Extraction and analysis:** Samples (10 g) were extracted with 100 ml of acidic methanol solution (1 ml hydrochloric acid/liter methanol) by shaking for 15 minutes on a Burrell Wrist-Action® shaker. The extracts were clarified by centrifuging; then 3-ml aliquots were diluted to 200 ml with acidic methanol solution.

   The absorbance of the solutions was measured at 359 nm in 1-cm quartz cells versus acidic methanol on an ultraviolet spectrophotometer. Solutions were protected from light, and all sample readings were corrected before calculating results for the mean absorbance of feed blanks treated as the samples.

4. **Quality control:** All samples and the feed blanks were analyzed in triplicate. Absorbance readings of the samples were corrected for the mean feed blank absorbance before results were calculated. The spiked feed recovery yield was determined in triplicate at the same concentration as the samples and was applied to the analysis results.

   The linearity of the spectrophotometric curve was evaluated with standard solutions of oxytetracycline hydrochloride that were prepared from two separate standard solutions and diluted. All sample results were calculated from the linear regression equation developed from the five standards.

5. **Results**

Sample Location	Oxytetracycline Hydrochloride in Feed (ppm) (a)	Average Percent Recovery (determined/target x 100) (b,c)
Right	9,890	99.9 ± 0.8
Left	9,740	98.4 ± 1.2
Bottom	9,680	97.8 ± 1.1

(a) Corrected for a spiked recovery yield of 95.8% ± 1%
(b) Target concentration of oxytetracycline hydrochloride in feed was 9,900 ppm.
(c) Error values are maximum deviations of individual assay values from the mean.

6. **Conclusion:** Oxtetracycline hydrochloride was blended into rodent feed at a concentration of 9,900 ppm with approximately 1% variation in concentration from the mean blend level at three sampling points in the blender.

B. Stability study

1. **Sample mixing and storage:** Four 8-oz screw-cap bottles were each filled with about 100 g of the formulated diet prepared as described in Section I.A.2. of this appendix and tightly sealed. Single bottles were stored in the dark for 2 weeks at −20°, 5°, 25°, or 45° C.

2. **Extraction and analysis:** Triplicate 10 ± 0.01-g samples of feed from each storage condition were extracted in 200-ml centrifuge bottles with 100 ml of acidic methanol (5 ml concentrated hydrochloric acid/liter methanol). The samples were shaken for 15 minutes on a Burrell Wrist-Action® shaker; then the extracts were clarified by centrifugation for 10 minutes at 2,000 rpm.

   A 5-ml aliquot of each extract was mixed with 6 ml of internal-standard solution (50 mg propiophenone/100 ml methanol). After a thorough mixing, a few milliliters of each solution was filtered through a 0.5-µ Millipore filter and sealed in a 5-ml septum vial. The oxytetracycline hydrochloride content of the solutions was determined by the high-performance liquid chromatographic system described below.

   Instrument: Waters Associates Liquid Chromatograph Model ALC202
   Column: µBondapak C_{18}, 300 mm × 4 mm ID
   Detector: Ultraviolet, 254 nm
   Attenuation: 1.0 AUFS
   Mobile phase: [1.5 mM tetraammonium ethylenediamine tetraacetic acid in water:acetic acid (95:5 v/v)]:[tetrahydrofuran] (88:12)
   Injection volume: 25 µl
   Retention time
   Study chemical: 5.1 min
   Internal standard: 14.0 min

3. **Quality control:** Analyses were performed by making single injections of sample extracts prepared in triplicate. Recovery of the chemicals from feed was determined in triplicate with feed spiked at the same concentrations as the samples. Because the spiked recovery yield was 100.9% ± 1.0%, no correction for recovery was applied to the sample results.

   Results were calculated from relative response factors (RRF) computed from peak heights of the calibration standards using the following equation:

$$RRF = \frac{\text{milligrams per milliliter study chemical} \times \text{peak height of internal standard}}{\text{peak height of study chemical} \times \text{milligrams per millilter of internal standard}}$$

   Then the milligrams per gram of chemical in the vehicle was calculated as

$$\frac{RRF \times \text{sample peak height} \times \text{milligrams per milliliter internal standard} \times DF}{\text{peak height of internal standard} \times \text{grams of sample}}$$

   where DF = dilution factor.

   The linearity of the spectrophotometric curve was evaluated with standard solutions of oxytetracycline hydrochloride that were prepared from a weighed standard solution and diluted. All sample results were calculated from the linear regression equation developed from the four standards.

4. **Results**

Storage Temperature	Oxytetracycline Hydrochloride in Feed (ppm) (a)	Percent Recovered (determined/target × 100) (b)
−20° C	9,920	100.2 ± 2.6
5° C	9,920	100.2 ± 3.5
25° C	10,090	101.9 ± 0.6
45° C	9,760	98.7 ± 2.2

(a) The target concentration of the chemical in feed was 9,900 ppm. The analytical results were not corrected for recovery because the zero-time spiked recovery yield was 100.9% ± 1.0%.
(b) Error values are maximum deviations from the mean and represent the sum of the analytical error plus variations in the composition of the feed blend.

5. **Conclusions:** The recovery of oxytetracycline hydrochloride from feed was influenced to some degree by the acidity of the extracting solvent. The samples from the stability study were extracted with 0.5% hydrochloric acid in methanol and exhibited essentially complete recovery of the chemical, whereas the homogeneity samples extracted with 0.1% hydrochloric acid-methanol showed 95.8% recovery. The weaker acid solution was used for the ultraviolet spectrophotometric method because it was found that the feed blank background in the ultraviolet method was directly related to the level of acid in the extracting solution.

   Oxytetracycline hydrochloride blended into rodent feed at the 1% concentration exhibited no loss of stablity, within the limits of the mean test error (2.2%), after 2 weeks' storage in the dark at temperatures up to 45° C.

II. Homogeneity Study Conducted by the Study Laboratory

A. Preparation: For each concentration, the premix was prepared by weighing a quantity of the bulk chemical, sufficient to prepare a 1-week supply of dosed feed, and quantitatively transferring the weighed chemical to a tared beaker containing approximately 200 g of feed. Another portion of feed was added to adjust the premix weight to 1,000 g. The combined ingredients were thoroughly mixed by spatula.

B. Bulk mixing and sampling: Bulk mixing was performed in a Patterson-Kelly® twin-shell stainless steel blender fitted with an intensifier bar. For each formulation the appropriate amount of undosed feed was accurately weighed and transferred in one-fourth amounts to both sides of the blender. The premix was added in roughly equal amounts to both sides of the blender. The fine residue adhering to the beaker was taken up by using the premix beaker to transfer one or two beakers of remaining feed to the blender and then transferring the remaining feed, in equal amounts, to both sides of the blender. The blender ports were sealed, and mixing was conducted with the intensifier bar for the first 5 minutes and without it for the remaining 10 minutes.

Three samples were taken from each of the 3,100-ppm and 50,000-ppm mixtures. About 50 g of subsurface formulation was taken from the upper left- and right-hand ports and from the discharge port of the twin-shell blender. Analyses were performed on duplicate 10-g samples.

C. Analysis: Samples were extracted with 100 ml of acidified methanol solution (1 ml hydrochloric acid/liter of methanol) by shaking for 15 minutes on a Burrell Wrist-Action® shaker. The extracts were clarified by centrifugation at 2,000 rpm for 10 minutes; then appropriate aliquots were volumetrically diluted with acidified methanol solution to yield final concentrations within the range of the standard curve.

The absorbance of the solutions was measured at 359 nm in 1-cm quartz cells versus acidic methanol on a Cary 219 ultraviolet spectrophotometer. Solutions were protected from light, and all sample readings were corrected before calculating results for the mean absorbance of feed blanks diluted as the samples.

D. Quality assurance measures: All samples and the feed blanks were analyzed in duplicate. Absorbance readings of the samples (0.367-0.572 AU) were corrected for the mean feed blank absorbance of that corresponding dilution before results were calculated. The spiked feed recovery yield (93.61% ± 2.41%) was determined in duplicate at the lowest, median, and highest concentrations of the samples and was applied to the analysis results.

The linearity of the spectrophotometric curve was evaluated with standard solutions of oxytetracycline hydrochloride that were prepared from a weighed standard solution and diluted. All sample results were calculated from the linear regression equation developed from the five standards.

E. Results

Sample Location	Target Concentration (ppm)	Measured Concentration (ppm) (a)	Percent of Target
Upper right	50,000	48,600	97.2
Upper left	50,000	48,600	97.2
Bottom	50,000	49,100	98.2
Batch	50,000	50,100	100.2
Upper right	3,100	3,000	96.8
Upper left	3,100	3,100	100.0
Bottom	3,100	3,000	96.8
Batch	3,100	3,000	96.8

(a) Results of duplicate analysis

F. Conclusion: The determined concentrations were all within ±10% of the target values.

APPENDIX J

METHODS OF ANALYSIS OF FORMULATED DIETS

APPENDIX J. METHODS OF ANALYSIS

I. Study Laboratory

Procedure: A 10-g sample of formulated diet was placed in a 250-ml centrifuge bottle and extracted with 100 ml of acidified methanol (1 ml concentrated hydrochloric acid/liter methanol) by shaking for 15 minutes on a Kraft rotary shaker. The samples were centrifuged at 2,000 rpm for 10 minutes and diluted 1 ml to 100 ml with acidified methanol, and the sample was analyzed at 359 nm on a DMS-90 ultraviolet-visible spectrophotometer.

II. Analytical Chemistry Laboratory

A. Preparation of spiked feed standards: Oxytetracycline hydrochloride is light sensitive. All operations were therefore performed in subdued light with foil-covered or amber glassware.

Two standard solutions of oxytetracycline hydrochloride were prepared independently in extracting solution (1 ml concentrated hydrochloric acid diluted to 1,000 ml with methanol). These solutions were diluted with extracting solution to make four additional standards. Aliquots (10-40 ml) of the six standard solutions were pipetted into individual 200-ml centrifuge bottles containing 5 g of undosed feed to make spiked feed standards bracketing the specified concentration range of the referee sample. One 200-ml centrifuge bottle containing 5 or 10 g of undosed feed was treated with 10-40 ml of extracting solution for use as a blank. The spiked feeds and the feed blank were sealed and allowed to stand overnight at room temperature before being analyzed.

B. Preparation of the referee sample: Triplicate weights of the referee feed sample (approximately 5 or 10 g weighed to the nearest 0.001 g) were transferred to individual 200-ml centrifuge bottles. Extracting solution (10-40 ml) was pipetted into each sample; then the bottles were sealed and allowed to stand overnight at room temperature before analysis by the procedure below.

C. Analysis: Extracting solution (80 ml) was pipetted into each blank, standard, and referee sample bottle, and the bottles were shaken at maximum stroke for 15 minutes on a wrist-action shaker. After being centrifuged for 10 minutes, an aliquot of each extract was diluted with extracting solution. The absorbance of the soutions was measured at 356 or 358 nm versus methanol in 1-cm quartz cells on a Cary 118 or Cary 219 spectrophotometer.

The amount of oxytetracycline hydrochloride in the referee feed samples was determined from the linear regression equation obtained from the standard data, relating the absorbance of each spiked feed standard and blank sample to the amount of chemical in the respective spiked feed standard.

D. Quality assurance measures: The referee feed sample was analyzed in triplicate, and the undosed feed sample was analyzed once. Individually spiked portions of undosed feed (six levels bracketing the specified concentration range of the referee sample) were prepared from two independently weighed standards and were treated as the referee feed samples for obtaining standard curve data.

APPENDIX K

RESULTS OF ANALYSIS OF FORMULATED DIETS

TABLE K1. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE (a)

Date Mixed	6,300 ppm	12,500 ppm	25,500 ppm	50,000 ppm
11/06/80	6,420	12,000	--	--
11/12/80	--	--	25,400	50,000
12/03/80	6,110	12,900	25,900	51,800
12/18/81	6,100	12,500	26,800	50,500
04/01/81	6,320	11,500	24,700	48,100
06/10/81	6,700	12,800	25,100	50,800
07/29/81	6,400	12,300	25,000	50,300
09/23/81	6,500	12,800	25,100	50,200
11/25/81	6,150	12,500	25,400	52,300
12/22/81	6,390	12,400	25,800	52,100
02/24/82	6,170	12,600	24,700	48,700
05/19/82	6,650	12,900	24,600	49,700
07/14/82	6,400	12,900	24,700	50,700
07/28/82	6,800	13,200	24,700	48,100
09/29/82	6,700	12,900	23,400	48,000
Mean (ppm)	6,415	12,586	25,093	50,093
Standard deviation	233	440	784	1,450
Coefficient of variation (percent)	3.6	3.5	3.1	2.9
Range (ppm)	6,100-6,800	11,500-13,200	23,400-26,800	48,000-52,300
Number of samples	14	14	14	14

(a) Results of duplicate analysis

TABLE K2. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF OXYTETRACYCLINE HYDROCHLORIDE

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Analytical Laboratory (b)
12/03/80	6,300	6,100	6,400
06/10/81	25,000	25,050	24,800
12/22/81	50,000	52,100	48,700
05/19/82	12,500	12,950	12,000
07/28/82	6,300	6,750	5,450
09/29/82	6,300	6,690	5,680

(a) Results of duplicate analysis
(b) Results of triplicate analysis

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	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (6 mo)	MHV (mouse hepatitis virus) (12, 18, 24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	

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 OXYTETRACYCLINE HYDROCHLORIDE (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	10/10	RCV
	10/10	Sendai
18	2/9	Sendai
24	5/10	RCV
MICE		
6	--	None positive
12	9/9	Sendai
18	2/10	PVM
	9/10	Sendai
24	5/9	Sendai
	1/10	GDVII

(a) Blood samples were taken from sentinel animals (5/sex) at 6, 12, and 18 months after the start of dosing and from the control animals (5/sex) just before they were killed; samples were sent to Microbiological Associates, Inc. (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 OXYTETRACYCLINE HYDROCHLORIDE

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

Week	Control		25,000 ppm				50,000 ppm			
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
3	17	210	17	215	1.0	1,977	16	202	0.9	3,960
7	18	296	18	292	1.0	1,541	17	278	0.9	3,058
14	15	372	15	358	1.0	1,047	15	343	1.0	2,187
17	16	400	17	387	1.1	1,098	16	369	1.0	2,168
21	15	411	16	394	1.1	1,015	15	379	1.0	1,979
26	16	429	17	417	1.1	1,019	17	401	1.1	2,120
31	17	425	16	415	0.9	964	18	399	1.1	2,256
35	15	430	16	421	1.1	950	16	404	1.1	1,980
39	17	443	15	429	0.9	874	16	418	0.9	1,914
43	16	450	16	440	1.0	909	18	428	1.1	2,103
47	15	453	14	449	0.9	780	16	432	1.1	1,852
51	15	460	16	451	1.1	887	16	441	1.1	1,814
55	14	461	15	452	1.1	830	15	444	1.1	1,689
60	14	472	15	454	1.1	826	15	448	1.1	1,674
64	14	464	15	457	1.1	821	15	447	1.1	1,678
68	14	461	15	455	1.1	824	15	447	1.1	1,678
73	13	454	13	451	1.0	721	14	444	1.1	1,577
77	14	453	15	454	1.1	826	15	450	1.1	1,667
81	14	448	14	446	1.0	785	14	441	1.0	1,587
85	15	449	14	444	0.9	788	14	439	0.9	1,595
89	14	451	14	443	1.0	790	15	439	1.1	1,708
95	13	436	14	438	1.1	799	14	434	1.1	1,613
98	13	430	14	430	1.1	814	14	420	1.1	1,667
102	13	423	14	426	1.1	822	14	421	1.1	1,663
Mean	14.9	424	15.2	417	1.0	946	15.4	407	1.0	1,966
SD (d)	1.4		1.3		0.1	276	1.2		0.1	538
CV (e)	9.4		8.6		10.0	29.2	7.8		10.0	27.4

(a) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of oxytetracycline hydrochloride consumed per day per kilogram of body weight
(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 OXYTETRACYCLINE HYDROCHLORIDE

	Control		25,000 ppm				50,000 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
3	12	146	11	145	0.9	1,897	11	145	0.9	3,793
7	10	183	10	178	1.0	1,404	9	175	0.9	2,571
14	10	213	10	203	1.0	1,232	10	202	1.0	2,475
17	11	224	11	216	1.0	1,273	11	216	1.0	2,546
21	10	224	11	220	1.1	1,250	10	215	1.0	2,326
26	11	233	11	231	1.0	1,190	11	225	1.0	2,444
31	10	236	11	236	1.1	1,165	11	233	1.1	2,361
35	10	239	10	238	1.0	1,050	10	234	1.0	2,137
39	10	243	11	245	1.1	1,122	11	240	1.1	2,292
43	11	247	11	251	1.0	1,096	11	247	1.0	2,227
47	11	257	11	258	1.0	1,066	11	252	1.0	2,183
51	11	268	12	269	1.1	1,115	12	262	1.1	2,290
55	11	275	12	275	1.1	1,091	12	268	1.1	2,239
60	11	289	12	285	1.1	1,053	12	277	1.1	2,166
64	11	299	12	295	1.1	1,017	12	284	1.1	2,113
68	11	304	12	302	1.1	993	12	291	1.1	2,062
73	11	311	12	313	1.1	958	12	300	1.1	2,000
77	11	315	12	318	1.1	943	12	306	1.1	1,961
81	11	319	12	318	1.1	943	12	307	1.1	1,954
85	11	321	12	318	1.1	943	12	306	1.1	1,961
89	11	323	12	319	1.1	940	11	308	1.0	1,786
95	11	328	12	321	1.1	935	12	315	1.1	1,905
98	11	327	12	318	1.1	943	11	311	1.0	1,768
102	10	325	11	314	1.1	876	11	308	1.1	1,786
Mean	10.8	269	11.4	266	1.1	1,104	11.2	259	1.0	2,223
SD (d)	0.5		0.7		0.1	214	0.8		0.1	409
CV (e)	4.6		6.1		9.1	19.4	7.1		10.0	18.4

(a) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of oxytetracycline hydrochloride consumed per day per kilogram of body weight
(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 OXYTETRACYCLINE HYDROCHLORIDE

	Control		6,300 ppm				12,500 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
2	4	26.9	4	27.1	1.0	930	4	26.3	1.0	1,901
6	4	30.4	4	30.0	1.0	840	4	28.8	1.0	1,736
10	3	32.4	3	32.5	1.0	582	3	31.3	1.0	1,198
14	4	33.6	4	33.9	1.0	743	4	33.3	1.0	1,502
17	4	35.4	4	37.2	1.0	677	4	34.8	1.0	1,437
21	4	36.9	4	38.0	1.0	663	4	36.6	1.0	1,366
26	4	37.7	5	38.6	1.3	816	5	36.4	1.3	1,717
31	4	39.2	4	38.6	1.0	653	4	37.0	1.0	1,351
35	4	38.5	4	38.9	1.0	648	4	36.9	1.0	1,355
39	4	39.6	4	39.8	1.0	633	4	37.7	1.0	1,326
44	4	39.5	4	39.8	1.0	633	4	37.8	1.0	1,323
48	4	40.8	4	41.3	1.0	610	4	39.0	1.0	1,282
52	4	41.2	4	41.8	1.0	603	4	39.3	1.0	1,272
56	4	42.5	4	42.8	1.0	589	4	40.1	1.0	1,247
61	4	42.0	4	42.1	1.0	599	4	40.3	1.0	1,241
65	4	41.8	4	41.4	1.0	609	4	39.5	1.0	1,266
69	4	42.3	4	41.4	1.0	609	4	39.4	1.0	1,269
74	4	41.4	4	40.4	1.0	624	4	39.0	1.0	1,282
78	4	41.8	4	41.4	1.0	609	4	39.4	1.0	1,269
82	4	41.0	4	40.3	1.0	625	4	39.0	1.0	1,282
86	4	40.4	4	39.0	1.0	646	4	38.2	1.0	1,309
90	4	40.3	4	38.4	1.0	656	4	37.8	1.0	1,323
96	4	38.9	4	37.9	1.0	665	4	37.3	1.0	1,340
99	4	39.5	4	38.2	1.0	660	4	37.2	1.0	1,344
103	4	40.3	4	38.2	1.0	660	4	37.2	1.0	1,344
Mean	4.0	38.6	4.0	38.4	1.0	663	4.0	36.8	1.0	1,371
SD (d)	0.2		0.3		0.0	84	0.3		0.0	170
CV (e)	5.0		7.5		0.0	12.7	7.5		0.0	12.4

(a) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of oxytetracycline hydrochloride consumed per day per kilogram of body weight
(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 OXYTETRACYCLINE HYDROCHLORIDE

	Control		6,300 ppm				12,500 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
2	3	20.6	3	20.6	1.0	917	3	20.1	1.0	1,866
6	3	22.0	3	22.2	1.0	851	3	21.9	1.0	1,712
10	3	23.2	3	23.7	1.0	797	3	23.3	1.0	1,609
14	3	25.7	3	25.7	1.0	735	3	25.3	1.0	1,482
17	3	28.0	3	28.2	1.0	670	3	26.7	1.0	1,404
21	3	29.0	3	29.4	1.0	643	3	28.2	1.0	1,330
26	4	31.4	3	30.4	0.8	622	4	28.8	1.0	1,736
31	3	31.8	3	31.2	1.0	606	4	29.1	1.3	1,718
35	3	32.3	3	31.1	1.0	608	3	29.5	1.0	1,271
39	4	34.2	4	33.8	1.0	746	4	32.1	1.0	1,558
44	3	34.7	3	33.5	1.0	564	3	32.5	1.0	1,154
48	3	36.3	3	34.7	1.0	545	3	33.9	1.0	1,106
52	4	37.8	4	36.5	1.0	690	4	35.8	1.0	1,397
56	4	39.4	4	38.4	1.0	656	4	37.1	1.0	1,348
61	3	39.3	3	38.7	1.0	488	4	37.2	1.3	1,344
65	3	39.2	3	37.8	1.0	500	3	36.9	1.0	1,016
69	3	40.5	3	39.1	1.0	483	4	38.0	1.3	1,316
74	3	40.3	3	39.0	1.0	485	3	38.0	1.0	987
78	3	39.8	3	39.0	1.0	485	3	38.0	1.0	987
82	4	39.4	4	38.7	1.0	651	4	37.6	1.0	1,330
86	4	39.5	4	38.4	1.0	656	4	37.3	1.0	1,340
90	4	39.6	4	38.3	1.0	658	4	37.4	1.0	1,337
96	4	40.2	4	38.5	1.0	655	4	38.0	1.0	1,316
99	4	40.2	4	38.4	1.0	656	4	37.2	1.0	1,344
103	4	41.3	4	38.8	1.0	649	4	38.1	1.0	1,312
Mean	3.4	34.6	3.4	33.8	1.0	641	3.5	32.7	1.0	1,373
SD (d)	0.5		0.5		0.0	113	0.5		0.1	231
CV (e)	14.7		14.7		0.0	17.6	14.3		10.0	16.8

(a) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of oxytetracycline hydrochloride consumed per day per kilogram of body weight
(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: September 1980 to October 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	No. of Samples
Crude protein (percent by weight)	24.22 ± 1.07	22.6-26.3	24
Crude fat (percent by weight)	5.09 ± 0.46	4.2-6.0	24
Crude fiber (percent by weight)	3.42 ± 0.39	2.4-4.2	24
Ash (percent by weight)	6.63 ± 0.38	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)	11,108 ± 1,093	9,100-14,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	19.0 ± 2.73	16.0-26.0	(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)	1.25 ± 0.15	1.10-1.53	24
Phosphorus (percent)	0.99 ± 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	No. of Samples
Arsenic (ppm)	0.41 ± 0.15	0.13-0.93	24
Cadmium (ppm) (a)	<0.1		24
Lead (ppm)	1.07 ± 0.73	0.27-2.93	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.29 ± 0.07	0.16-0.48	24
Aflatoxins (ppb) (a,b)	<10	<5.0-10.0	24
Nitrate nitrogen (ppm) (c)	9.18 ± 4.33	0.6-18.0	24
Nitrite nitrogen (ppm) (c)	1.99 ± 1.30	0.4-5.3	24
BHA (ppm) (d,e)	5.10 ± 4.19	<0.4-15.0	24
BHT (ppm) (d)	3.05 ± 1.52	1.2-6.0	24
Aerobic plate count (CFU/g)	80,604 ± 48,850	7,000-210,000	24
Coliform (MPN/g) (f)	883 ± 908	<3-2,400	24
E. coli (MPN/g) (g)	8.0 ±7.91	<3-23	23
E. coli (MPN/g) (h)	13.88 ± 30.00	<3-150	24
Total nitrosamines (ppb) (i,j)	6.69 ± 5.60	1.2-18.8	22
Total nitrosamines (ppb) (i,k)	14.55 ± 27.15	1.2-101.6	24
N-Nitrosodimethylamine (ppb) (i,l)	5.25 ± 5.33	0.6-16.8	22
N-Nitrosodimethylamine (ppb) (i,m)	13.02 ± 26.80	0.6-99	24
N-Nitrosopyrrolidine (ppb)	1.21 ± 0.66	<0.3-2.4	24
Pesticides (ppm)			
α-BHC (a,n)	<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 (o)	<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 (p)	<0.05	0.13 (8/25/81); 0.6 (6/29/82)	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 (q)	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) One batch contained less than 0.5 ppm. The value was <0.04, and it was produced on 4/27/81.
(f) MPN = most probable number
(g) Mean, standard deviation, and range exclude one value of 150 produced on 8/26/82.
(h) Mean, standard deviation, and range include the high value given in footnote g.
(i) All values were corrected for percent recovery.
(j) 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.
(k) Mean, standard deviation, and range include the very high values given in footnote j.
(l) Mean, standard deviation, and range exclude two very high values of 97.9 and 99 for batches produced on 1/26/81 and 4/27/81.
(m) Mean, standard deviation, and range include the very high values given in footnote l.
(n) BHC = hexachlorocyclohexane or benzene hexachloride
(o) There was one observation above the detection limit. The value and the date it was obtained are given under the range.
(p) There were two observations above the detection limit. The values and the dates they were obtained are given under the range.
(q) Ten batches contained more than 0.05 ppm.

APPENDIX O

DATA AUDIT SUMMARY

APPENDIX O. DATA AUDIT SUMMARY

The experimental data and laboratory records for the 2-year toxicology and carcinogenesis studies of oxytetracycline hydrochloride in rats and mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice regulations. The animal studies were conducted by Physiological Research Laboratories, Minneapolis, Minnesota, under a subcontract with Tracor Jitco, Inc., from the National Cancer Institute from November 1980 to November 1982 and were initiated prior to NTP's requirement for compliance with Good Laboratory Practice regulations in October 1981. The audit was conducted in June and July 1985 and involved the following personnel from Argus Research Laboratories: Jane E. Goeke, Ph.D.; James J. Hills, B.A.; Alan M. Hoberman, Ph.D.; David M. Willett, B.S.; Diana S. Copeland, D.V.M., D.A.C.V.P.; and Carol L. Veigle, HTL. The audit report was approved by the NTP and is on file at the National Toxicology Program, NIEHS, Research Triangle Park, North Carolina.

For the inlife toxicology portion of the audit, 10% of the study animal records for clinical signs were audited. One hundred percent of the records for animal deaths, moribund and terminal kills, and tissue masses were audited. All records concerning animal receipt, acclimation/quarantine, randomization, identification, body weight, feed consumption, environmental conditions, and sentinel animal data were reviewed. For the analytical chemistry portion of the audit, 100% of the available data was audited. A random 10% sample of the dose calculations was verified. For the pathology portion of this audit, all of the wet tissue bags of both species were counted and all of the control and high dose animals of both species had slides matched with blocks. Wet tissue examinations for untrimmed potential lesions and verification of animal identification were conducted on a random 10% of both rats and mice plus additional animals selected to resolve possible discrepancies between gross observations and microscopic diagnoses. Final pathology tables were correlated with the final report of the laboratory pathologist, corrected pathology tables, Individual Animal Data Records, and Pathology Working Group (PWG) slide review worksheet for a random 10% of the cases.

All data were considered adequate with the following exceptions: dose start and completion dates could not be verified from the available records, and the presence and size of masses were not consistently recorded in the clinical observation and gross necropsy records.

For the analytical chemistry portion of the audit, all data required were present at the archives except the usage dates for formulated diets and the standard curves and ultraviolet absorbance graphs for chemical reanalysis and chemical/vehicle analysis.

All pathology data and materials audited for oxytetracycline hydrochloride were complete and adequate with the following exceptions: the animal identity of 14/56 rats and 19/49 mice could not be verified because some or all of the feet had not been saved with the wet tissue. Tissue alterations suggesting untrimmed potential lesions were found in the residual wet tissues of 24/56 rats and 8/49 mice. In general, these were very minimal tissue alterations that were distributed among dose groups. Histopathologic sampling was judged to be adequate, and these potential lesions were not pursued further. For 14 rats and 6 mice, necropsy observations were made which had no correlating microscopic diagnosis. Lesions were not found on the slides or in the wet tissues. The slide and block match was good. Tissue accountability was poor by NTP standards in one or more of the various dose groups of mice for parathyroid, skin, ovary, gallbladder, and urinary bladder.

In conclusion, the data examined were considered adequate to fulfill the objectives of these studies. Any discrepancies noted were resolved as described or were judged not to affect the conclusions of these studies.

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