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TOXICOLOGY AND CARCINOGENESIS STUDIES OF ERYTHROMYCIN STEARATE

(CAS NO. 643-22-1)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF ERYTHROMYCIN STEARATE

(CAS NO. 643-22-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the 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 public peer review.

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

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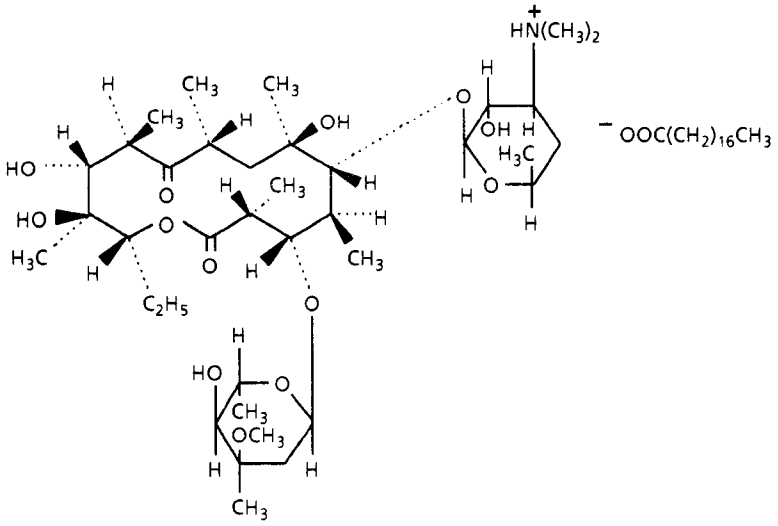

ERYTHROMYCIN STEARATE

CAS No. 643-22-1

$C_{37}H_{67}NO_{13} \cdot C_{18}H_{36}O_2$ Molecular weight 1,018

Synonyms: erythrocin stearate; erythromycin octadecanoate

Trade names: Abbotcine; Bristamycin; Dowmycin E; Eratrex; Erypar; Ethril; Gallimycin; HSDB 4178; OE 7; Pantomicina; Pfizer-E; SK-Erythromycin; Wyamycin S

ABSTRACT

Toxicology and carcinogenesis studies of erythromycin stearate (USP grade, greater than 96% pure) were conducted by administering the antibiotic in feed to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, or 2 years. Erythromycin stearate was studied because of its widespread use in humans as a broad-spectrum macrolide antibiotic and because of the lack of adequate long-term studies for carcinogenicity.

Fourteen-Day and Thirteen-Week Studies: In the 14-day studies, none of the rats (at dietary concentrations up to 50,000 ppm) and 2/5 female mice that received 50,000 ppm died before the end of the studies. Final mean body weights of male rats that received 12,500, 25,000, or 50,000 ppm were 10%, 30%, or 36% lower, respectively, than that of controls; final mean body weights of female rats were 10%, 12%, or 32% lower. None of the dosed mouse groups gained weight. The final mean body weight of male mice that received 50,000 ppm was 10% lower than that of controls.

In the 13-week studies, none of the rats or mice (at dietary concentrations up to 20,000 ppm) died before the end of the studies. Final mean body weights of the 20,000-ppm groups of rats were more than 12% lower than that of the controls for males and 7% lower for females. Final mean body weights of mice that received 10,000 or 20,000 ppm were 15% or 19% lower than that of controls for males and 5% or 14% lower for females.

Multinucleated syncytial hepatocytes were observed in 10/10 male rats that received 20,000 ppm but in 0/10 male rats that received 10,000 ppm. No compound-related gross or microscopic pathologic effects were observed in mice.

Based on these results, 2-year studies of erythromycin stearate were conducted by feeding diets containing 0, 5,000, or 10,000 ppm erythromycin stearate to groups of 50 rats of each sex for 103 weeks. Diets containing 0, 2,500, or 5,000 ppm were fed to groups of 50 mice of each sex for 103 weeks.

Body Weight and Survival in the Two-Year Studies: Mean body weights of high dose male rats were comparable to those of controls throughout the studies. Mean body weights of high dose female rats were 5%-10% lower than those of controls. Mean body weights of dosed and control mice were comparable. The average daily feed consumption was similar for dosed and control male and female rats. For mice, estimated daily feed consumption by low and high dose males was similar to that of the controls and by low and high dose females was 92% that of the controls. The average amount of erythromycin stearate consumed per day was approximately 180 or 370 mg/kg for male rats and 210 or 435 mg/kg for female rats; for mice, the average amounts were 270 or 545 mg/kg for males and 250 or 500 mg/kg for females.

No significant differences in survival were observed between any groups of rats or mice of either sex (final survival--male rats: control, 28/50; low dose, 23/50; high dose, 27/50; female rats: 29/50; 30/50; 38/50; male mice: 34/50; 33/50; 40/50; female mice: 38/50; 34/50; 40/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Granulomas of the liver were observed at increased incidences in high dose rats (male: 1/50; 2/50; 10/50; female: 18/50; 27/50; 43/50). Granulomatous inflammation or granulomas of the spleen were observed in dosed female rats (0/48; 1/49; 3/50). Reticulum cell hyperplasia in the bone marrow occurred at increased incidences in high dose female rats (10/50; 14/50; 25/50).

Squamous cell papillomas of the oral mucosa were observed in 1/50 control, 2/50 low dose, and 3/50 high dose female rats. These tumors were considered to be marginal and not related to exposure. Hyperplasia of the oral mucosa was not observed.

Pheochromocytomas of the adrenal gland in female rats occurred with a positive trend (1/50; 4/49; 5/50). The incidences in the dosed groups are similar to the average historical incidence (9%) of this tumor in untreated control female F344/N rats at the study laboratory. This marginal tumor increase is not considered to be biologically important. No increases in incidences of neoplasms were observed at any site in dosed male rats.

Inflammation in the glandular stomach was observed at increased incidences in dosed male mice (1/49; 4/50; 6/50). Lymphoid hyperplasia in the urinary bladder was observed at increased incidences in dosed female mice (1/50; 9/47; 7/48).

No increases in incidences of neoplasms were observed at any site in dosed male or female mice.

Genetic Toxicology: Erythromycin stearate was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested both with or without exogenous metabolic activation. Erythromycin stearate demonstrated equivocal mutagenicity in the mouse L5178Y lymphoma cell assay in the absence of exogenous metabolic activation (S9); erythromycin stearate was not mutagenic in the presence of S9. Treatment of cultured Chinese hamster ovary cells with erythromycin stearate did not produce an increase in the frequency of sister chromatid exchanges or chromosomal aberrations in either the presence or absence of metabolic activation.

Audit: The data, documents, and pathology materials from the 2-year studies of erythromycin stearate have been audited. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year studies, there was *no evidence of carcinogenic activity** of erythromycin stearate for male or female F344/N rats administered erythromycin stearate in the diet at 5,000 or 10,000 ppm. There was *no evidence of carcinogenic activity* of erythromycin stearate for male or female $B6C3F_1$ mice administered erythromycin stearate in the diet at 2,500 or 5,000 ppm. Dose-related increases in the incidences of granulomas of the liver were observed in male and female rats. The absence of any biologically important chemical-associated effects in mice suggests that higher doses could have been given to male and female mice.

SUMMARY OF THE TWO-YEAR FEED AND GENETIC TOXICOLOGY STUDIES OF ERYTHROMYCIN STEARATE

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Dietary concentrations			
0, 5,000, or 10,000 ppm erythromycin stearate	0, 5,000, or 10,000 ppm erythromycin stearate	0, 2,500, or 5,000 ppm erythromycin stearate	0, 2,500, or 5,000 ppm erythromycin stearate
Survival rates in the 2-year study			
28/50; 23/50; 27/50	29/50; 30/50; 38/50	34/50; 33/50; 40/50	38/50; 34/50; 40/50
Nonneoplastic effects			
Granulomas of the liver	Granulomas of the liver; reticulum cell hyperplasia of the bone marrow	None	None
Neoplastic effects			
None	None	None	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	No evidence	No evidence
Genetic toxicology			
Not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without activation; equivocally mutagenic in the mouse L5178Y lymphoma assay without activation and not mutagenic in the mouse L5178Y lymphoma assay with activation; did not cause sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells with or without activation.			

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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 NTP toxicology and carcinogenesis studies 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 study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans.

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is 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 Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. 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 induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. 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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Erythromycin Stearate is based on the 13-week studies that began in February 1980 and ended in May 1980 and on the 2-year studies that began in December 1980 and ended in December 1982 at Physiological Research Laboratories (Minneapolis, Minnesota).

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The members of the Peer Review Panel who evaluated the draft Technical Report on erythromycin stearate on July 14, 1987, 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 ERYTHROMYCIN STEARATE

On July 14, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of erythromycin stearate 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. J.E. French, NIEHS, introduced the studies by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats; no evidence of carcinogenic activity for male or female mice).

Dr. Sivak, a principal reviewer, agreed with the conclusions. He asked why the doses for the 2-year studies in mice were only half those given to rats, and he emphasized the importance of explaining the rationale for the dose selection for the long-term studies. Dr. French responded that the dose selections were based solely on the observed body weight depression and that mice showed greater body weight differences than did rats during the 13-week studies.

As a second principal reviewer, Dr. Gallo agreed with the conclusions. He commented on the difficulty in evaluating antibiotics by the usual criteria, such as changes in body weight, as some antibiotics lead to increases in body weight. Dr. Gallo speculated that the granulomas or lymphoid hyperplasia reported in liver, spleen, and bladder might be crystalline deposits of the chemical or its metabolites. Dr. French acknowledged that this could be an alternative explanation for the lesions, but he indicated that none was seen on light microscopy.

As a third principal reviewer, Dr. Capen agreed with the conclusions.

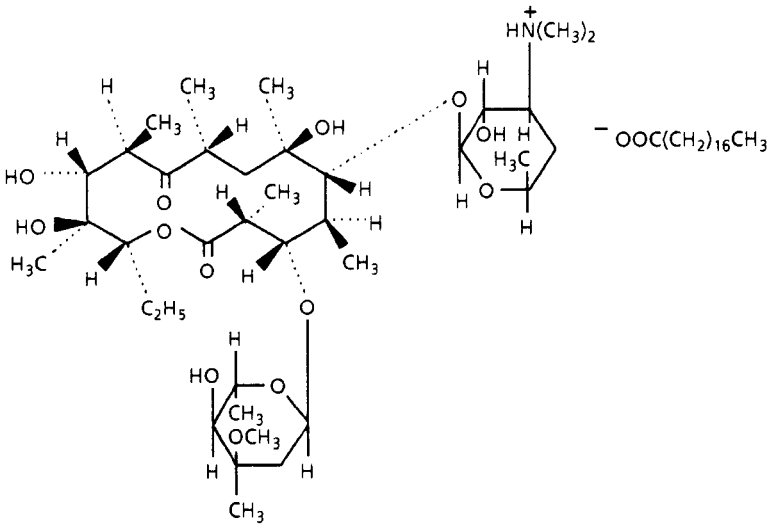
In other discussion, Dr. Ashby commented on the weak positive genotoxic responses to erythromycin stearate in the mammalian cell assay (mouse lymphoma), which may be an artifact resulting from the high doses of the alkaline salt associated with the antibiotic.

Dr. Sivak moved that the Technical Report on erythromycin stearate be accepted with editorial changes discussed and with the conclusions as written for male and female rats and mice, no evidence of carcinogenic activity. Dr. Popp seconded the motion, which was approved unanimously with seven votes.

I. INTRODUCTION

Use, Production, and Exposure
Absorption, Metabolism, and Excretion
Acute Toxicity
Cellular and Subcellular Toxicity
Systemic Toxicity
Reproductive and Developmental Toxicity
Long-Term Toxicity and Carcinogenicity
Genetic Toxicology
Study Rationale

I. INTRODUCTION



ERYTHROMYCIN STEARATE

CAS No. 643-22-1

$C_{37}H_{67}NO_{13} \cdot C_{18}H_{36}O_2$ Molecular weight 1,018

Synonyms: erythrocin stearate; erythromycin octadecanoate

Trade names: Abbotcine; Bristamycin; Dowmycin E; Eratrex; Erypar; Ethril; Gallimycin; HSDB 4178; OE 7; Pantomicina; Pfizer-E; SK-Erythromycin; Wyamycin S

Use, Production, and Exposure

Erythromycin base and various salts are used extensively in the treatment of gram-positive bacterial infections in humans (Sande and Mandell, 1985). Erythromycin belongs to the chemical class of macrolide antibiotics and was discovered by McGuire and colleagues, according to Sande and Mandell (1985). Erythromycin stearate is one of several derivatives used in different formulations. (Other derivatives include erythromycin estolate, erythromycin ethylsuccinate, and erythromycin lactobionate, or erythromycin gluceptate.) Erythromycin base, prepared by fermentation from *Streptomyces erythreus*, is reacted with stearic acid in acetone, and the resulting salt is precipitated with water; USP-grade erythromycin stearate is not less than 55% erythromycin base (Remington's, 1975).

Recent production figures for erythromycin base or stearate salt are not available, but commercial production was reported to the International Trade Commission and U.S. Environmental Protection Agency TSCA inventory, indicating that production was greater than 4.5×10^5 g/year (USITC, 1986; NIOSH, 1987). In 1985, an estimated 33 million prescriptions of erythromycin, in all forms, were filled (Baum et al., 1986). The usual oral dose of erythromycin is 1-2 g per day for adults and 30-50 mg/kg per day for children (4 doses, 6 hours apart, between meals) (Sande and Mandell, 1985).

Absorption, Metabolism, and Excretion

In humans, erythromycin base is absorbed from the upper part of the small intestine, with peak concentrations (0.3-0.5 µg/ml) occurring 4-12 hours after oral administration (Ravagnan et al., 1971; Sande and Mandell, 1985). Various salts of erythromycin have been prepared to improve stability after absorption by different routes. In the gastrointestinal tract, erythromycin base absorption and maximum plasma levels are similar between various salt preparations (Sande and Mandell, 1985). There is a large

intersubject and intrasubject variability between route and erythromycin form used (erythromycin base vs. erythromycin stearate) in humans (Welling, 1977; Welling et al., 1978; Mather et al., 1981).

The absorption of erythromycin is affected by the presence or absence of food and the form being administered. Erythromycin is inactivated by gastric juice, and the presence of food delays ultimate absorption (Sande and Mandell, 1985). The form of the derivative and its resistance to acid and/or enzymatic hydrolysis are important variables in absorption and delivery to a target site. In volunteers (age and sex unspecified), ingestion of food delayed the absorption of orally administered erythromycin base, whereas the absorption of the stearate salt was increased in the presence of food (Malmborg, 1979; DiSanto and Chodos, 1981). Other studies in volunteers have reported opposite findings (Rutland et al., 1979; Digranes et al., 1984). In studies that considered both food and water intake (Welling, 1977; Welling et al., 1978), erythromycin stearate absorption was decreased by both food and water intake, independently; in the presence of food and sufficient water intake, erythromycin base and stearate were found to be bioequivalent.

Erythromycin base and erythromycin stearate are inactivated by gastric juices when administered neat and without enteric coatings (Sande and Mandell, 1985). Boggiano and Gleeson (1976) found that under in vitro conditions at a pH of 1.2-3.2, erythromycin stearate dissolved and rapidly lost its biologic activity. Addition of pepsin did not affect the results. Only enteric-coated tablets retained biologic activity.

Absorption of erythromycin may be age-dependent. Eriksson et al. (1981) reported that erythromycin, in suspension, was absorbed the least in infants younger than 1 month of age but was well absorbed in fasting children between 6 months and 6 years of age. Erythromycin stearate absorption was not affected by the presence of food in this study.

Antibiotics in general, including erythromycin, are poorly absorbed or not absorbed at all by patients with celiac or Crohn's disease, possibly because of reduced renal clearance (Parsons et al., 1975, 1976a,b, 1977). However, Iliopoulou et al. (1982) found that the excretion rate of erythromycin was similar for controls and for patients with end-stage renal failure who were being treated by dialysis.

According to Sande and Mandell (1985), 2%-5% of the erythromycin administered orally to humans was excreted in a biologically active form in the urine. The amount excreted increased to 12%-15% after intravenous infusion. Erythromycin is concentrated in the liver and excreted in an active form in the bile. The terminal elimination rate (elimination of 50% of dose, half-life) is 1.6 hours. In pharmacokinetic models based on human exposure, which considered the impact of protein binding and erythromycin affinity for bacterial ribosomes, the half-life was determined to be 1.2 hours (Chun and Seitz, 1977; Wiegand and Chun, 1972). Erythromycin diffuses into intracellular fluids but does not penetrate into brain tissue or cerebrospinal fluid. Erythromycin is stated to penetrate prostatic fluid (resulting in concentrations 40% of those obtained in plasma), traverse the placenta, and attain fetal plasma concentrations of about 5%-20% of those in the maternal circulation (Sande and Mandell, 1985). After oral administration of erythromycin or its stearate to control subjects and to patients with diagnosed infections, erythromycin was detected at therapeutic levels in lung (bronchiolar secretions) (Simon, 1980), saliva (Simon, 1980; Henry et al., 1980), fallopian tubes, peritoneal fluid from the pouch of Douglas (Bergan and Gjonnaess, 1981), vaginal washes (Iliopoulou et al., 1981), and oviduct mucosa (Brihmer, 1986).

Administration of erythromycin or erythromycin stearate to male Sprague Dawley rats (age unspecified) results in the formation of an inactive cytochrome P450-metabolite complex in vivo; a similar complex is formed in vitro after incubation with NADPH and liver microsomes from phenobarbital-induced, but not 3-methylcholanthrene-induced, rats (Larrey et al., 1983). Erythromycin or erythromycin stearate administered to rats induced synthesis of microsomal enzymes and resulted in an inactive erythromycin-P450 complex (Villa et al., 1986). *N*-demethylation of both erythromycin and

aminopyrine was increased. Hydroxylation of aniline was not changed. In dosed rats, *O*-demethylation of 4-nitroanisole and liver glutathione levels were decreased and pentobarbital sleeping time was increased relative to controls.

Acute Toxicity

The following acute toxicity has been reported for the erythromycin base (strains, age and sex for all species unspecified) (NIOSH, 1983):

Rat
Oral LD_{50} = 9,272 mg/kg
Intravenous LD_{50} = 209 mg/kg
Subcutaneous LD_{Lo} = 427 mg/kg

Mouse
Oral LD_{50} = 3,112 mg/kg
Intraperitoneal LD_{50} = 463 mg/kg
Intravenous LD_{50} = 426 mg/kg
Intramuscular LD_{50} = 394 mg/kg

Guinea Pig
Intraperitoneal LD_{50} = 413 mg/kg

No data were reported for erythromycin stearate.

Cellular and Subcellular Toxicity

Sande and Mandell (1985) report that erythromycin and other macrolide antibiotics inhibit bacterial protein synthesis by binding to the 50S ribosomal subunits of sensitive bacteria. Erythromycin competes with chloramphenicol for the same binding site. Binding is reversible and can occur only when the 50S subunit is free from transfer-RNA-bearing nascent peptide chains. Gram-positive bacteria concentrate approximately 100 times more erythromycin than do gram-negative bacteria. At alkaline pH, ionization of the erythromycin molecule is decreased, resulting in increased cellular permeability and antimicrobial activity.

In mouse liver explant cultures from 19- to 21-day-old C3H mice (sex unspecified), toxicity of erythromycin stearate in vitro paralleled toxicity observed in vivo (Dujovne et al., 1970). Erythromycin estolate is toxic to Chang liver cell cultures, as measured by cell viability (lactate dehydrogenase and β-glucuronidase leakage from cells) (Dujovne et al., 1972). In vitro toxicity correlates with in vivo toxicity.

Systemic Toxicity

Adverse reactions to the administration of erythromycin have included toxicity to the liver (Tolman et al., 1974; Alcalay et al., 1986); these reactions may have resulted from immune hypersensitivity. Inman and Rawson (1983) reviewed the use of erythromycin base and its stearate and estolate salts and tetracycline in 12,208 patients. Sixteen reports of jaundice were associated with presumed liver injury. Three of the 16 patients with jaundice had received erythromycin stearate. Jaundice in the other patients was believed to be due to viral hepatitis, gallstones, or cancer. No association could be made between use of erythromycin stearate and jaundice.

An effect of erythromycin on immune function has been suggested. Cooksley and Powell (1977) reported that a 53-year-old woman developed severe cholestatic hepatitis after administration of erythromycin estolate. Lymphocytes from the patient incubated with erythromycin base, the stearate, or the estolate were blastogenic only in response to the estolate salt. A 60-year-old man with severe respiratory distress was determined to be hypersensitive to erythromycin stearate (Abramov et al., 1978). Erythromycin has been shown to have an immunomodulatory effect. Anderson et al. (1982, 1983, 1984) found that a single oral dose of erythromycin stearate (500 mg) administered to volunteers transiently increased neutrophil chemotaxis and neutrophil antistaphylococcidial activity without affecting phagocytosis and inhibited prostaglandin E_2 release but did not affect mononuclear cell chemotaxis or blast transformation. Administration of erythromycin stearate to mice challenged with *Candida albicans* resulted in increased mean survival times. Neutrophils from patients with immune defects (abnormal chemotaxis and a history of recurrent infections) who had received erythromycin stearate orally, and neutrophils incubated in vitro with erythromycin stearate, demonstrated normal in vitro chemotaxis to

endotoxin-activated serum factors (Ras and Anderson, 1986). Oral administration of erythromycin to patients with chronic bronchopneumonia or to control subjects increased phagocytosis, superoxide anion free radical formation, and natural killer cell activity 4-6 hours after treatment (Fraschini et al., 1986).

Administration of erythromycin has been associated with changes in bacterial flora in humans, which could result in systemic effects. Administration of erythromycin stearate has been found to alter the flora of the oral cavity, throat, and colon (Heimdahl and Nord, 1982; Heimdahl et al., 1984). Colonization of these sites by erythromycin-resistant aerobic and anaerobic bacteria and yeast occurred after 7 days of treatment. Nord et al. (1985) also found that oral administration of erythromycin stearate decreased the presence of *Streptococcus salivarius* in the oropharynx, but after treatment was discontinued, normal flora repopulation occurred. In healthy volunteers with no erythromycin-resistant oral streptococci, administration of erythromycin on two separate occasions with a 1-week interval resulted in the presence of erythromycin-resistant bacterial strains that persisted for some time (Harrison et al., 1985).

Reproductive and Developmental Toxicity

Reproductive toxicity has been reported for the erythromycin base but not for erythromycin stearate (rat, 10-15 d pregnant, oral $TD_{Lo} = 6$ g/kg; rat, 6-10 d pregnant, subcutaneous = 50 mg/kg; mouse, 8-13 d pregnant, oral = 12 g/kg) (NIOSH, 1983).

Long-Term Toxicity and Carcinogenicity

No long-term toxicity and carcinogenicity data were available in the literature.

Genetic Toxicology

No mutagenicity data for erythromycin stearate other than from NTP experiments were available in the literature; on the basis of the NTP test results, the chemical appears to be a nonmutagen. Erythromycin stearate was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in a preincubation protocol with or without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Mortelmans et al., 1986; Appendix E, Table E1). Erythromycin stearate demonstrated equivocal mutagenicity in the mouse L5178Y lymphoma cell assay because, in the absence of S9, increases in forward mutations were observed only at concentrations at or just below those that caused precipitation (Table E2). No increases in mutations occurred in the presence of Aroclor 1254-induced F344 rat liver S9 at concentrations that did not cause precipitation. The positive responses reported for erythromycin stearate at higher concentrations (above the level that caused precipitation) in the presence of S9 were not considered in judging mutagenicity according to NTP quality control criteria. Treatment of cultured Chinese hamster ovary cells with erythromycin stearate did not produce an increase in the frequency of sister chromatid exchanges or chromosomal aberrations in either the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Tables E3 and E4).

Study Rationale

Erythromycin stearate was nominated by the National Cancer Institute for study because it is the most widely used macrolide antibiotic and because of the lack of adequate carcinogenicity studies. Administration of erythromycin stearate in feed was chosen to obtain exposure by the oral route, the primary route for administration of the drug in humans.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF ERYTHROMYCIN STEARATE

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 ERYTHROMYCIN STEARATE

Certified USP-grade erythromycin stearate was obtained in one lot (lot no. 287 FM) from Upjohn Company (Kalamazoo, Michigan). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on analyses performed in support of the erythromycin studies are on file at NIEHS.

Lot no. 287 FM was obtained as a fluffy, colorless powder. Its melting point was determined to be 100°-104° C, although this may be the temperature at which the chemical dissolves in stearic acid. The identity of erythromycin stearate was confirmed by spectroscopy. The infrared spectrum (Figure 1) was consistent with that in the literature (Sadtler Pharmaceutical Spectra). The ultraviolet/visible spectrum and nuclear magnetic resonance spectrum (Figure 2) were consistent with those expected for the structure of erythromycin stearate.

The purity of erythromycin stearate was determined by elemental analysis, water analysis, titration of the amino group, thin-layer chromatography, and high-performance liquid chromatography. Cumulative data indicated that lot no. 287 FM had a minimum purity of approximately 96% as erythromycin stearate. Results of elemental analysis for carbon were low; results for hydrogen and nitrogen agreed with the theoretical values. Water content by Karl Fischer titration was 2.49%. Nonaqueous potentiometric titration of the tertiary amino group with 0.5 N perchloric acid indicated an erythromycin stearate content of 96% corresponding to 69% erythromycin (693 µg erythromycin/mg erythromycin stearate) which exceeds the USP minimum purity of 55% erythromycin. Thin-layer chromatography on silica gel plates with an *n*-butanol:acetic acid:water (3:1:1) solvent system detected a single spot by both iodine and phosphomolybdic acid visualization; a major spot and one minor impurity were detected by an ethyl acetate:methanol (9:1) solvent system. High-performance liquid chromatography on a µBondapak C_{18} column with detection at 230 nm and a water:methanol solvent system at a flow rate of 1 ml/minute detected four impurities with a total peak area of 15.0% that of the major peak when operated in an isocratic mode (12:88 solvent ratio) and three impurities with a total relative area of 14.9% when used with a solvent program (70%-100% methanol in 8 minutes). Gas chromatography of a silyl ester derivative of the study chemical with a 3% OV-17 column, a nitrogen carrier at a flow rate of 60 ml/minute, and flame ionization detection indicated four impurities, each with a relative area of 1%-10% of the major peak area (exact values were not reported due to the semiquantitative nature of the derivatization procedure). The impurities detected chromatographically were probably other erythromycins (B or C) or isomers of erythromycin.

A stability study, in which stability was monitored by titration of the tertiary amino group with 0.1 N perchloric acid, indicated that erythromycin stearate was stable when stored for 2 weeks at temperatures up to 60° C. Further confirmation of the stability of the bulk chemical during the toxicity studies (storage at 25° C in the dark) was obtained by titration with 0.1 N perchloric acid and gas chromatography of a silyl ester derivative of the sample with an OV-17 or SP-2250 column and flame ionization detection. No degradation of the bulk chemical was observed throughout the studies. The identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

The formulated diets were prepared by adding a dry premix of feed and erythromycin stearate to the appropriate amount of feed (Table 1). The mixture was blended for 15 minutes. The homogeneity of diet mixtures formulated at the analytical chemistry and study laboratories was confirmed by extracting feed samples (taken from three points of the blender) with an acetonitrile:water (85:15) solution, preparing silyl derivatives of the extracts, and performing gas chromatographic analysis with an OV-17 column and flame ionization detection. At the analytical chemistry laboratory, values ranged from

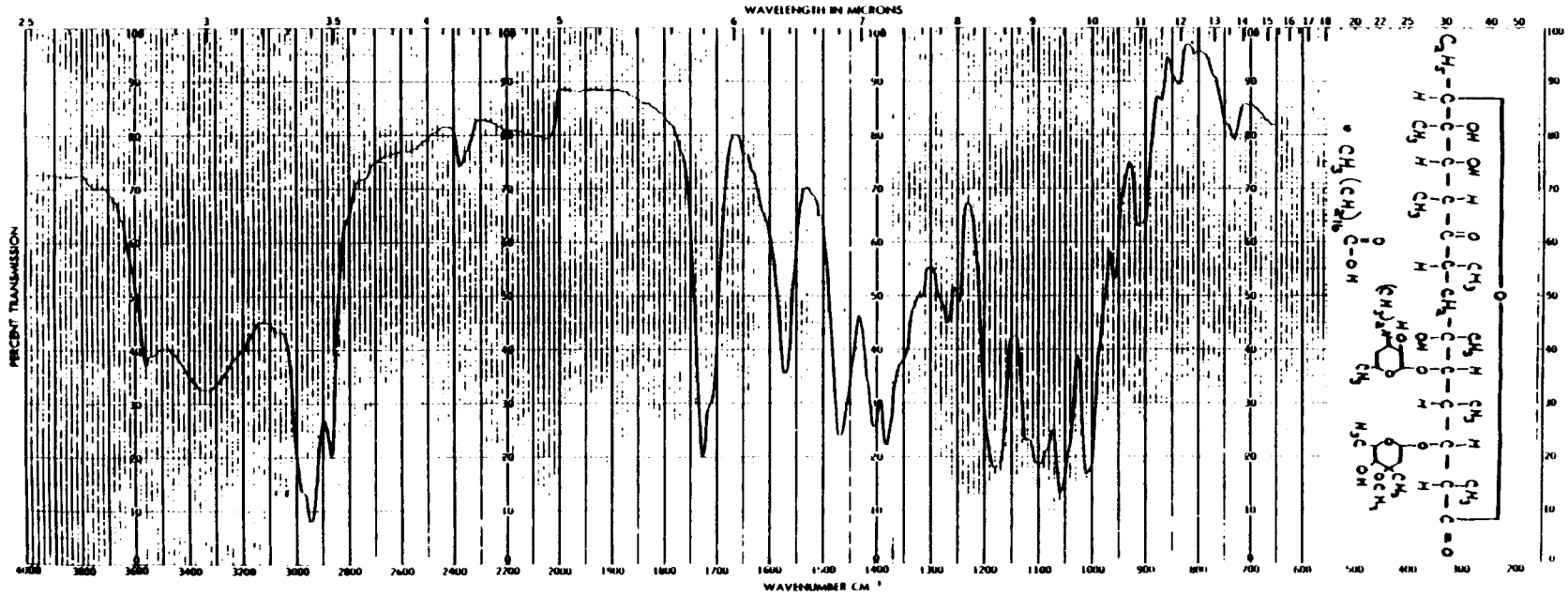


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF ERYTHROMYCIN STEARATE (LOT NO. 287 FM)

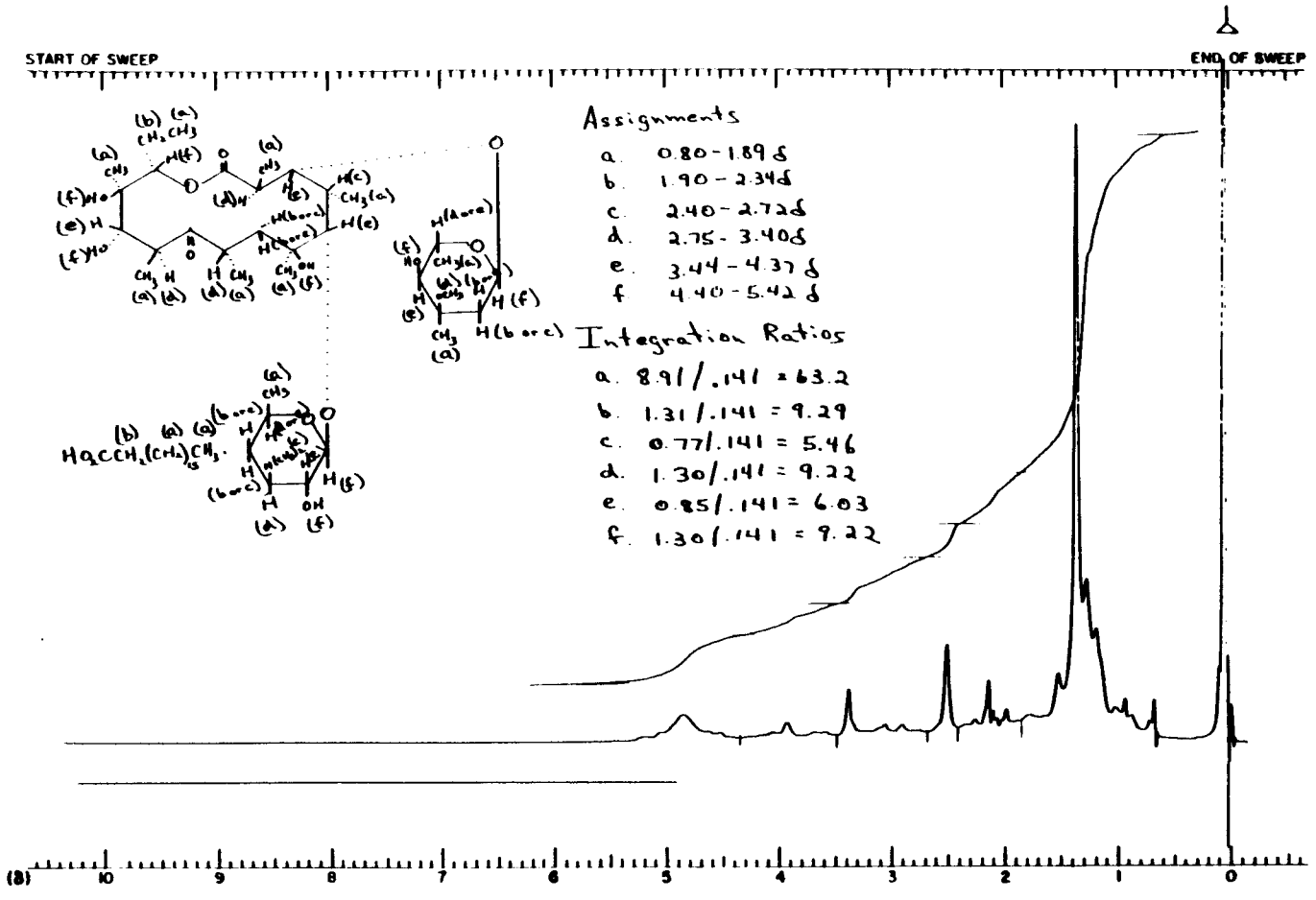


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF ERYTHROMYCIN STEARATE (LOT NO. 287 FM)

TABLE 1. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF ERYTHROMYCIN STEARATE

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Premix mixed with bulk feed in a Patterson-Kelly 8-qt twin-shell® blender for 5 min with intensifier bar on and 10 min without intensifier bar	Same as 14-d studies	Premix prepared in beaker and mixed with spatula. Bulk mixing done in a 1-ft^3 Patterson-Kelly twin-shell® stainless steel blender for 5 min with intensifier bar on and 10 min without intensifier bar
Maximum Storage Time		
14 d	14 d	14 d
Storage Conditions		
5° C	≤5° C	5° C

96.1% to 97.8% of the target value at a concentration of 10,000 ppm. At the study laboratory, homogeneous mixing of the formulated feed blends was a problem, as indicated by the results of a homogeneity study which showed a spread of 100%-115% of the target value at a concentration of 20,000 ppm. Further studies at the same analytical laboratory with the same analytical method showed that erythromycin stearate at 10,000 ppm was stable in feed when stored for 2 weeks at 5° C; additional studies detected no notable decrease in concentration of erythromycin stearate in samples stored either in sealed glass bottles in the dark or in feeders kept under normal animal room conditions. Formulated diets were stored at 5° C for no longer than 14 days.

Periodic analyses for erythromycin stearate in feed mixtures were conducted by the study and analytical chemistry laboratories to determine if the formulated diets contained the correct concentrations of erythromycin stearate. Samples were analyzed as described above except that methanol was used as the extracting solvent and, during the first half of the 2-year studies, extracts were passed through Sep Pac® cartridges before silylation at the study laboratory. Formulated diets were analyzed once, at the beginning of the 13-week studies. The results ranged from 88% to 104% of the target concentration (Table 2). During the 2-year studies, the feed mixtures were analyzed approximately every 1-2 months. Concentrations varied from 14% to 109.6% of the target concentration; the second lowest concentration observed was 90.8% of the target concentration (Table 3). Because 41/42 formulated diets analyzed were within 10% of the target concentrations, it is estimated that the formulated diets were prepared within specifications 98% of the time. Referee analyses were performed periodically by an independent laboratory. Initially, variable agreement was found between laboratories (Table 4). An adjustment in the analytical procedure used by the referee laboratory improved the agreement between laboratories for the last two sets of referee samples.

TABLE 2. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF ERYTHROMYCIN STEARATE (a)

Target Concentration (ppm)	Determined Concentration (ppm) (b)	Determined as a Percent of Target
1,250	1,290	103
2,500	2,600	104
5,000	4,400	88
10,000	9,400	94
20,000	19,300	96.5

(a) Mix date: 1/29/80
(b) Results of duplicate analysis

TABLE 3. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF ERYTHROMYCIN STEARATE (a)

Date Mixed	Concentration of Erythromycin Stearate in Feed for Target Concentration (ppm)		
	2,500	5,000	10,000
12/03/80	2,400	5,250	(b) 1,400
12/08/80	--	--	(c) 10,300
12/24/80	2,510	4,780	10,900
02/05/81	2,510	5,440	10,100
04/09/81	2,740	5,220	10,300
	(d) 2,440	(d) 4,640	(d) 10,800
07/09/81	2,590	5,200	9,900
08/13/81	2,460	4,910	10,000
10/08/81	2,340	4,800	9,470
12/24/81	2,270	4,810	9,700
01/28/82	2,510	4,760	10,700
03/11/82	2,490	5,030	10,300
05/13/82	2,390	5,150	10,400
06/17/82	2,560	4,670	10,600
09/02/82	2,340	5,050	9,530
10/07/82	2,380	4,920	9,390
Mean (ppm)	2,464	4,999	9,478
Standard deviation	121.9	228.0	2,371.7
Coefficient of variation (percent)	4.9	4.6	25.0
Range (ppm)	2,270-2,740	4,640-5,440	1,400-10,900
Number of samples	14	14	14

(a) Results of duplicate analysis
(b) Out of specifications; not used in the studies. If this value is excluded, the mean and standard deviation are 10,099 and 487.8.
(c) Remix; not included in the mean.
(d) Analysis performed by Capsule Laboratories

TABLE 4. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF ERYTHROMYCIN STEARATE

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
04/09/81	2,500	2,740	(c,d) 3,140
10/08/81	10,000	9,470	(d) 8,100
05/13/82	2,500	2,390	2,360
09/02/82	5,000	5,050	4,990

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) A value of 2,440 ppm was found by Capsule Laboratories.
(d) Out of specifications

FOURTEEN-DAY STUDIES

Five- to six-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held for approximately 3 weeks before the studies began. Groups of five rats and five mice of each sex were fed diets containing 0, 3,125, 6,250, 12,500, 25,000, or 50,000 ppm erythromycin stearate for 14 consecutive days. Rats and mice were observed twice per day and were weighed once per week. Further details of animal maintenance are given in Table 5.

THIRTEEN-WEEK STUDIES

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

Four- to five-week-old male and female F344/N rats and 5- to 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 16 days, distributed to weight classes, and then assigned to cages according to a table of random numbers. Cages were assigned to dosed and control groups according to another table of random numbers.

Groups of 10 rats and 10 mice of each sex were given diets containing 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm erythromycin stearate for 13 weeks. Control diets consisted of NIH 07 Rat and Mouse Ration. Formulated diets, control diets, and water were available ad libitum. Further experimental details are summarized in Table 5.

Animals were checked two times per day; moribund animals were killed. Feed consumption was measured by cage once per week. Individual animal weights were recorded once per week. The following hematologic analyses were conducted on blood from the brachial vessels of the controls and the 20,000-ppm groups: hemoglobin concentration, erythrocyte count, leukocyte count, differential leukocyte count, hematocrit value, nucleated erythrocyte count, and platelet determination.

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 5.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 5,000, or 10,000 ppm erythromycin stearate were fed to groups of 50 rats of each sex for 103 weeks. Diets containing 0, 2,500, or 5,000 ppm were fed to groups of 50 mice of each sex for 103 weeks.

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF ERYTHROMYCIN STEARATE

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, 3,125, 6,250, 12,500, 25,000, or 50,000 ppm erythromycin stearate in feed	0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm erythromycin stearate in feed	Rats--0, 5,000, or 10,000 ppm erythromycin stearate in feed; mice-- 0, 2,500, or 5,000 ppm
Date of First Dose		
6/12/79	2/1/80	Rats--12/9/80; mice--12/23/80
Date of Last Dose		
6/25/79	5/2/80	Rats--11/29/82; mice--12/13/82
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 measured 1 × wk	Same as 14-d studies	Observed 2 × d; weighed initially, 1 × wk for 13 wk, and 1 × mo thereafter; palpated 1 × mo at weighing, starting at wk 41; feed consumption estimated 1 × mo
Necropsy and Histologic Examination		
Necropsy performed on all animals; 6,250-, 12,500-, and 25,000-ppm groups examined histologically	Necropsy performed on all animals; histologic exams performed on animals that died before the end of the studies and on all control and high dose animals that had gross lesions; hematologic exam performed on control and high dose groups	Necropsy and histologic examination performed on all animals
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		
Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Portage, MI [rats], or Kingston, NY [mice])	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory		
Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
Method of Animal Identification		
Rats--tail mark; mice--ear punch	Toe clip	Ear notch, toe clip
Time Held Before Study		
20 d	16 d	14 d
Age When Placed on Study		
8-9 wk	Rats--6-7 wk; mice--7-8 wk	Same as 13-wk studies
Age When Killed		
11 wk	Rats--20-21 wk; mice--21-22 wk	Rats--110-111 wk; mice--111-112 wk
Necropsy Dates		
Rats--6/28/79; mice--6/27/79	Rats--5/5/80-5/8/80; mice--5/6/80-5/9/80	Rats--12/7/82-12/14/82; mice--12/21/82-12/28/82

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF ERYTHROMYCIN STEARATE (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMAL MAINTENANCE (Continued)		
Method of Animal Distribution Distributed to weight classes, then assigned to cages by a table of random numbers; cages assigned to dosed and control groups by another table of random numbers.	Same as 14-d studies	Same as 14-d studies
Feed Rodent Laboratory Chow 5001® meal (Ralston Purina Co., St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding Aspen wood chips	Same as 14-d studies	Aspen wood shavings, heat-treated (Minnesota Sawdust and Shavings Co., Anoka, MN)
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies; water softened through sodium zeolite to <1 grain/gal and then filtered
Cages Polycarbonate (Lab Products, Inc.)	Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 13-wk studies
Cage Filters		Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--20.0°-23.3° C; hum--33%-46%; light 12 h/d; 120 room air changes/h	Temp--17.2°-26.6° C; hum--22%-50%; light 12 h/d; 120 room air changes/h	Temp--22.2°-26.7° C; hum--30%-74%; fluorescent light 12 h/d; 15 room air changes/h

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 facility for 2 weeks. 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 6-7 weeks of age and the mice, at 7-8 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 F).

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/6N 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/6N colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage; cages were not rotated during the studies. Water and feed were available ad libitum. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. 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 5.

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 to be missing or dead from other than natural causes; 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: life table tests, incidental tumor analysis, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of high dose and low dose groups with controls and tests for overall dose-response trends. For studies in which administration of the test compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

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 (1959) 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 recently developed 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.

Fisher Exact/Cochran-Armitage Trend Analyses--In addition to survival-adjusted methods, 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 appendixes containing the analyses of 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

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III. RESULTS: RATS

FOURTEEN-DAY STUDIES

None of the rats died before the end of the studies (Table 6). Feed consumption of rats that received 25,000 or 50,000 ppm was notably lower than that of controls. Final mean body weights of male rats that received 12,500, 25,000, or 50,000 ppm were 10%, 30%, or 36% lower, respectively, than that of controls. Final mean body weights of female rats that received 12,500, 25,000, or 50,000 ppm were 10%, 12%, or 32% lower, respectively, than that of controls. Lethargy and rough coats were observed at 12,500 ppm and above; diarrhea was observed at 50,000 ppm. Two male rats that received 25,000 ppm had hyperemic intestines.

THIRTEEN-WEEK STUDIES

None of the rats died before the end of the studies (Table 7). Final mean body weights of the 20,000-ppm groups were 12% lower than that of the controls for males and 7% lower for females. Feed consumption by dosed and control groups was comparable (except for males at 20,000 ppm). All dosed rats except the 1,250-ppm group of males were lethargic. Males that received 5,000-20,000 ppm and females that received 10,000 or 20,000 ppm had rough coats. Multinucleated syncytial hepatocytes were observed in all males that received 20,000 ppm.

Dose Selection Rationale: Because of lower weight gain at higher concentrations, dietary concentrations of erythromycin stearate selected for rats for the 2-year studies were 5,000 and 10,000 ppm.

TABLE 6. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF ERYTHROMYCIN STEARATE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	110 ± 5	174 ± 12	+64 ± 7	--	15.1	15.9
3,125	5/5	103 ± 5	155 ± 11	+52 ± 6	89	13.7	14.8
6,250	5/5	110 ± 5	169 ± 10	+59 ± 5	97	14.4	15.5
12,500	5/5	110 ± 8	156 ± 14	+46 ± 6	90	12.1	14.3
25,000	5/5	108 ± 5	121 ± 8	+13 ± 4	70	7.9	11.1
50,000	5/5	117 ± 8	111 ± 6	−6 ± 2	64	4.9	6.3
FEMALE							
0	5/5	92 ± 5	120 ± 7	+28 ± 3	--	10.9	10.4
3,125	5/5	101 ± 4	121 ± 4	+20 ± 2	101	12.3	11.0
6,250	5/5	94 ± 3	112 ± 6	+18 ± 3	93	11.2	10.7
12,500	5/5	93 ± 6	108 ± 7	+15 ± 2	90	9.1	10.9
25,000	5/5	99 ± 1	105 ± 2	+6 ± 1	88	6.4	8.5
50,000	5/5	88 ± 3	82 ± 2	−6 ± 2	68	3.1	4.4

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams of feed consumed per animal per day; not corrected for scatter.

TABLE 7. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF ERYTHROMYCIN STEARATE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 4	Week 12
MALE							
0	10/10	135 ± 1	305 ± 5	+170 ± 6	--	14.5	11.5
1,250	10/10	135 ± 1	305 ± 2	+170 ± 2	100	13.4	11.5
2,500	10/10	127 ± 1	291 ± 10	+164 ± 10	95	13.2	11.1
5,000	10/10	137 ± 1	312 ± 3	+175 ± 3	102	13.9	11.8
10,000	10/10	130 ± 1	285 ± 3	+155 ± 3	93	13.4	11.0
20,000	10/10	138 ± 1	269 ± 2	+131 ± 3	88	12.2	11.3
FEMALE							
0	10/10	101 ± 1	168 ± 2	+67 ± 2	--	8.2	7.5
1,250	10/10	101 ± 1	168 ± 6	+67 ± 6	100	8.7	8.0
2,500	10/10	105 ± 1	176 ± 2	+71 ± 2	105	8.5	8.2
5,000	10/10	105 ± 2	179 ± 2	+74 ± 2	107	8.5	8.0
10,000	10/10	104 ± 1	164 ± 2	+60 ± 1	98	8.5	7.9
20,000	10/10	104 ± 1	156 ± 2	+52 ± 3	93	7.9	8.0

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean weight change of the group ± standard error of the mean
(d) Grams of feed consumed per animal per day; not corrected for scatter.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of high dose male rats were within 6% of those of controls throughout the studies (Table 8 and Figure 3). Mean body weights of high dose female rats were 5%-10% lower than those of controls from week 35 to the end of the studies. Mean body weights of low dose male and female rats were comparable to those of controls throughout the studies. The average daily feed consumption per rat by low dose and high dose rats was 99% and 98% that by controls for males (Appendix G, Table G1) and 103% and 99% for females (Table G2). The average amount of erythromycin stearate consumed per day was approximately 180 or 370 mg/kg by low dose or high dose male rats and 210 or 435 mg/kg by low dose or high dose female rats. No compound-related clinical signs were observed.

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

Weeks on Study	Control		5,000 ppm			10,000 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
1	168	50	167	99	50	164	98	50
2	218	50	217	100	50	207	95	50
3	243	50	242	100	50	232	95	50
4	267	50	262	98	50	254	95	50
5	279	50	276	99	50	265	95	50
6	293	50	292	100	50	278	95	50
7	303	50	305	101	50	289	95	50
8	312	50	317	102	50	298	96	50
9	326	50	329	101	50	309	95	50
10	335	50	336	100	50	316	94	50
11	345	50	347	101	50	326	94	50
12	358	50	360	101	50	339	95	50
13	369	50	369	100	50	350	95	50
17	396	50	393	99	50	375	95	50
21	407	50	406	100	50	390	96	50
27	432	50	426	99	50	410	95	50
31	442	50	439	99	50	424	96	50
35	445	50	445	100	50	430	97	50
40	458	50	458	100	50	443	97	50
44	457	50	451	99	50	438	96	50
48	468	50	462	99	50	453	97	50
52	469	50	469	100	50	455	97	50
57	467	49	471	101	50	455	97	50
61	470	49	472	100	49	457	97	50
65	464	49	466	100	49	454	98	49
70	467	47	452	97	49	449	96	48
75	466	45	464	100	48	448	96	47
79	461	43	452	98	48	440	95	46
83	465	42	453	97	45	445	96	44
87	462	40	449	97	41	436	94	41
91	444	40	445	100	39	425	96	38
96	438	35	460	105	31	421	96	36
100	437	31	427	98	25	416	95	32
103	420	28	410	98	23	410	98	27
FEMALE								
1	126	50	127	101	50	124	98	50
2	146	50	146	100	50	142	97	50
3	155	50	156	101	50	151	97	50
4	166	50	167	101	50	161	97	50
5	168	50	171	102	50	162	96	50
6	179	50	181	101	50	172	96	50
7	184	50	183	99	50	176	96	50
8	189	50	187	99	50	185	98	50
9	193	50	193	100	50	186	96	50
10	196	50	198	101	50	187	95	50
11	200	50	201	101	50	191	96	50
12	202	50	205	101	50	193	96	50
13	205	50	208	101	50	196	96	50
17	219	50	222	101	50	209	95	50
21	220	50	227	103	50	212	96	50
27	233	49	238	102	50	222	95	50
31	238	49	245	103	50	229	96	50
35	255	49	247	97	50	230	90	50
40	249	49	256	103	50	234	94	50
44	256	49	261	102	50	241	94	50
48	263	49	273	104	50	250	95	50
52	273	48	283	104	50	257	94	50
57	289	46	292	101	49	266	92	50
61	293	46	304	104	49	275	94	50
65	302	46	313	104	48	283	94	49
70	313	46	322	103	47	292	93	47
75	317	46	326	103	46	295	93	47
79	321	45	327	102	46	294	92	47
83	323	43	328	102	43	297	92	47
87	326	38	330	101	41	296	91	47
91	316	36	328	104	39	290	92	47
96	330	33	336	102	37	299	91	43
100	329	32	328	100	34	300	91	41
103	328	29	334	102	30	307	94	37

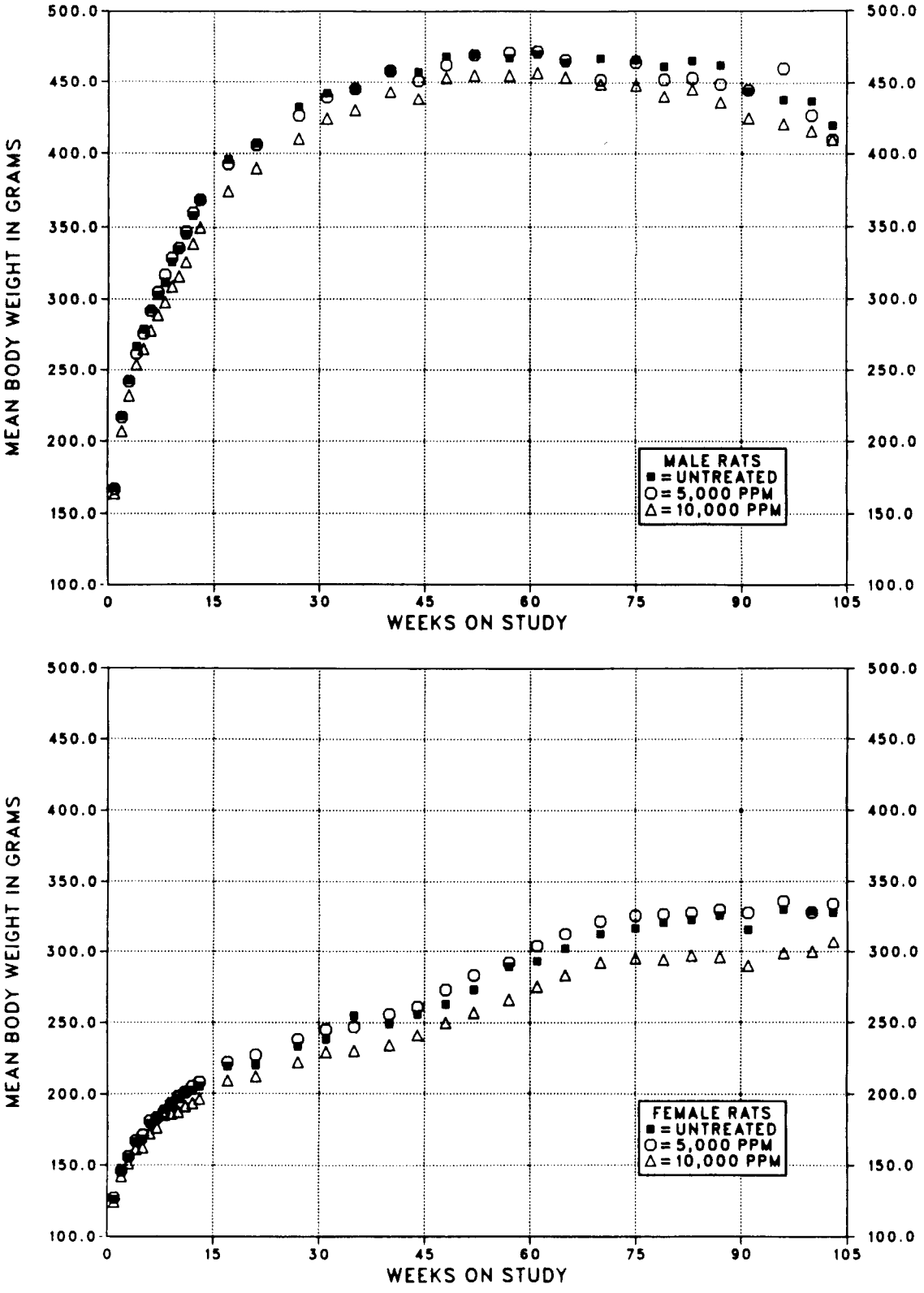

FIGURE 3. GROWTH CURVES FOR RATS FED DIETS CONTAINING ERYTHROMYCIN STEARATE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing erythromycin stearate at the concentrations used in these studies and for controls are shown in Table 9 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the oral cavity, adrenal gland, testis, liver, spleen, bone marrow, Zymbal gland, and eye.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 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 Table A3 (footnotes). Historical incidences of tumors in control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 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 Table B3 (footnotes). Historical incidences of tumors in control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF ERYTHROMYCIN STEARATE

	Control	5,000 ppm	10,000 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	27	23
Killed at termination	28	23	27
Survival P values (c)	0.966	0.454	0.900
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	20	12
Killed at termination	29	30	38
Survival P values (c)	0.050	0.884	0.055

(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.

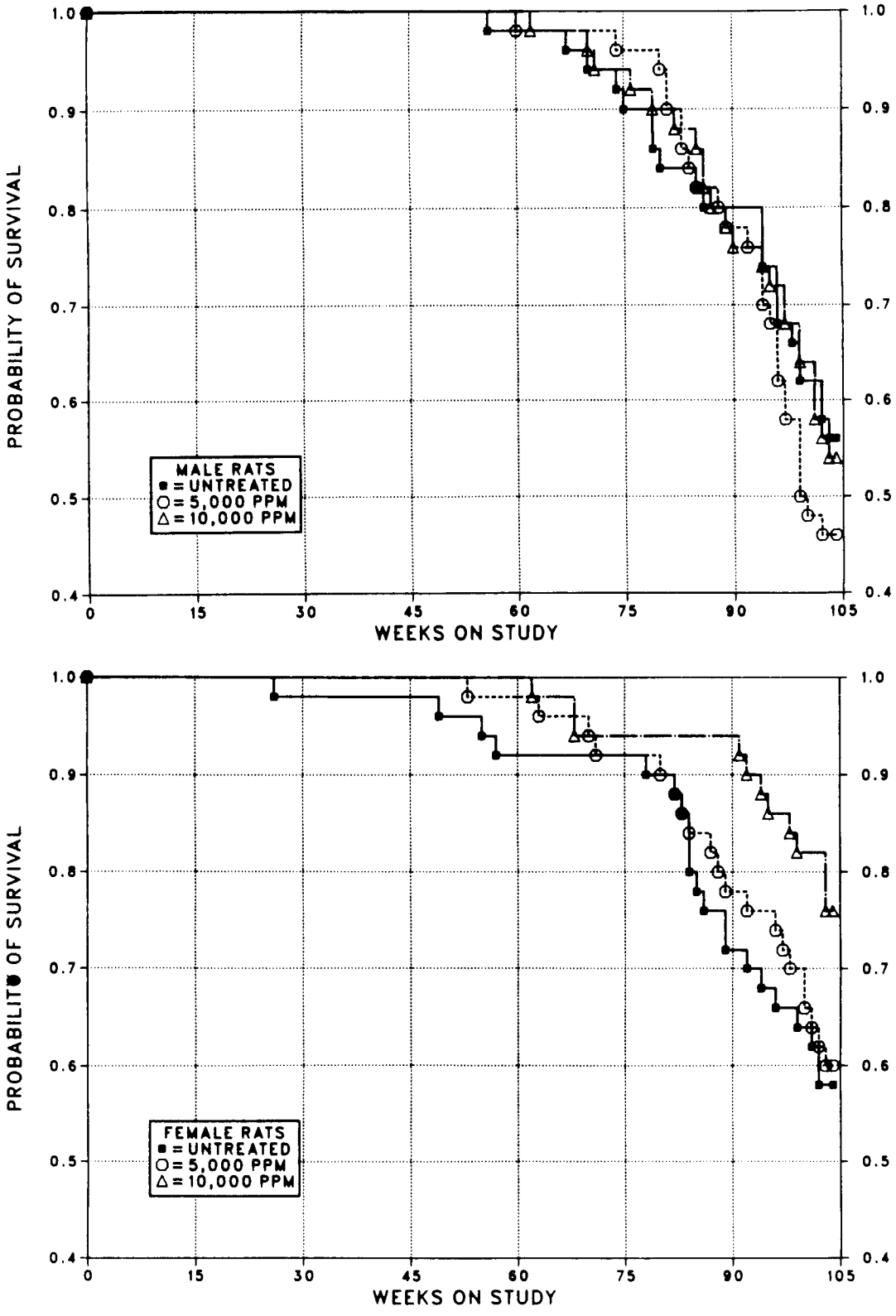

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING ERYTHROMYCIN STEARATE FOR TWO YEARS

Oral Cavity: The incidence of oral cavity squamous cell papillomas was increased in the dosed groups of female rats compared with that in the controls; although the increase was not statistically significant, it is noteworthy, since oral cavity tumors are uncommon in female rats (Table 10).

Adrenal Gland: Pheochromocytomas in female rats occurred with a positive trend; the incidence in the high dose group was significantly greater than that in the controls by the incidental tumor test (Table 11). Results of the incidental tumor test in this study were notably different from results of the life table and Fisher exact tests. Because the results of the incidental tumor test may have been influenced by the choice of time intervals used in the analysis, logistic regression (an alternative procedure for analysis of incidental tumors which does not require selection of time intervals) was carried out as a supplemental test (Dinse and Lagakos, 1983; Dinse and Haseman, 1986). By this approach, neither the trend (P = 0.077) nor the high dose incidence (P = 0.104) was statistically significant.

TABLE 10. ANALYSIS OF ORAL CAVITY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (a)

	Control	5,000 ppm (b)	10,000 ppm (b)
Squamous Cell Papilloma (c)			
Overall Rates	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates	3.4%	6.7%	7.4%
Terminal Rates	1/29 (3%)	2/30 (7%)	2/38 (5%)
Week of First Observation	104	104	95
Life Table Tests	P = 0.316	P = 0.512	P = 0.405
Incidental Tumor Tests	P = 0.308	P = 0.512	P = 0.395

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix B, Table B3 (footnotes).
(b) The estimated dose in milligrams per kilograms per day is given in Chapter III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix G.
(c) Historical incidence of squamous cell tumors at study laboratory: 0/150; historical incidence in NTP studies (mean): 1/1,984 (0.05%)

TABLE 11. ANALYSIS OF ADRENAL GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Control	5,000 ppm	10,000 ppm
Medullary Hyperplasia			
Overall Rates	6/50 (12%)	4/49 (8%)	6/50 (12%)
Pheochromocytoma (a)			
Overall Rates	1/50 (2%)	4/49 (8%)	5/50 (10%)
Adjusted Rates	2.3%	11.4%	12.4%
Terminal Rates	0/29 (0%)	2/29 (7%)	4/38 (11%)
Week of First Observation	83	84	91
Life Table Tests	P = 0.146	P = 0.189	P = 0.169
Incidental Tumor Tests	P = 0.025	P = 0.138	P = 0.041

(a) Historical incidence of pheochromocytomas or malignant pheochromocytomas (combined) at study laboratory (mean ± SD): 13/149 (9% ± 6%); historical incidence in NTP studies: 98/1,966 (5% ± 4%)

Testis: Interstitial cell tumors in male rats occurred with a significant positive trend; the incidence in the high dose group was greater than that in the controls (Table 12).

Liver: Granulomas were observed at increased incidences ($P<0.01$) in high dose rats (male: control, 1/50; low dose, 2/50; high dose, 10/50; female: 18/50; 27/50; 43/50). The granulomas seen in dosed rats were generally larger than those observed in controls, and they consisted of focal aggregates of macrophages surrounded by varied numbers of lymphocytes.

Spleen: Granulomatous inflammation or granulomas (combined) was observed in dosed female rats (male: none observed; female: control, 0/48; low dose, 1/49; high dose, 3/50). These lesions, which are rarely observed in the spleen of control rats, were similar to the granulomas occurring in the liver.

Bone Marrow: Reticulum cell hyperplasia was observed at increased incidences in dosed female rats (male: control, 2/49; low dose, 3/49; high dose, 4/49; female: 10/50; 14/50; 25/50). This lesion consisted of small focal aggregates of large polygonal cells with abundant cytoplasm characteristic of macrophages.

Zymbal Gland: Carcinomas in male rats occurred with a significant ($P<0.03$) negative trend (male: control, 4/50; low dose, 1/50; high dose, 0/50; female: 0/50; 1/50; 0/50); the incidences in the dosed groups were not significantly lower than that in the controls.

Eye: Mineralization of the crystalline lens was observed at an increased incidence ($P<0.05$) in low dose male rats (male: control, 3/50; low dose, 10/50; high dose, 1/50; female: 1/50; 4/50; 1/50). Cataracts were observed at an increased incidence ($P<0.001$) in low dose female rats (male: 8/50; 13/50; 9/50; female: 1/50; 19/50; 4/50). At study week 101, the average light intensity was estimated to be 2,054 total footcandles. Low dose male and female rat cages occupied the top two tiers, high dose male and female rat cages occupied the middle two tiers, and control male and female rat cages occupied the bottom two tiers of the rack. Cages were not rotated during the studies.

TABLE 12. ANALYSIS OF TESTICULAR LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Control	5,000 ppm	10,000 ppm
Hyperplasia			
Overall Rates	17/50 (34%)	17/50 (34%)	16/50 (32%)
Interstitial Cell Tumor (a)			
Overall Rates	32/50 (64%)	36/50 (72%)	43/50 (86%)
Adjusted Rates	86.2%	91.8%	100.0%
Terminal Rates	23/28 (82%)	20/23 (87%)	27/27 (100%)
Week of First Observation	74	80	76
Life Table Tests	P=0.024	P=0.076	P=0.022
Incidental Tumor Tests	P=0.003	P=0.208	P=0.003
Cochran-Armitage Trend Test	P=0.008		
Fisher Exact Test		P=0.260	P=0.010

(a) Historical incidence at study laboratory (mean ± SD): 133/150 (89% ± 6%); historical incidence in NTP studies: 1,681/1,909 (88% ± 7%)

FOURTEEN-DAY STUDIES

Two of the female mice that received 50,000 ppm died before the end of the studies (Table 13). None of the dosed groups of male or female mice gained weight. Feed consumption by mice that received 25,000 and 50,000 ppm was notably less than that by controls. Lethargy and rough coats were observed at all but the lowest dose. Hydration of the cornea was observed in mice that received 6,250, 12,500, or 25,000 ppm. In mice that received 50,000 ppm, one male had a hyperemic jejunum and cecum, one male had a hemorrhagic spleen, and one female had hemorrhagic intestines.

THIRTEEN-WEEK STUDIES

None of the mice died before the end of the studies (Table 14). Final mean body weights of mice that received 10,000 or 20,000 ppm were 15% or 19% lower than those of controls for males and 5% or 14% lower for females. Estimated feed consumption by dosed groups was comparable to that by the controls. No compound-related clinical signs or microscopic pathologic effects were observed.

Dose Selection Rationale: Because of lower weight gain at higher concentrations, dietary concentrations of erythromycin stearate selected for mice for the 2-year studies were 2,500 and 5,000 ppm.

TABLE 13. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF ERYTHROMYCIN STEARATE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	20.5 ± 0.8	21.4 ± 0.9	+0.9 ± 1.0	--	3.8	3.5
3,125	5/5	22.0 ± 0.7	21.5 ± 0.9	−0.5 ± 0.3	100.5	4.0	3.8
6,250	5/5	21.2 ± 0.5	20.2 ± 0.6	−1.0 ± 0.4	94.4	3.6	3.3
12,500	5/5	23.2 ± 1.2	22.1 ± 1.2	−1.1 ± 0.4	103.3	3.2	3.7
25,000	5/5	22.4 ± 0.5	22.1 ± 0.3	−0.3 ± 0.5	103.3	2.3	2.7
50,000	5/5	20.4 ± 1.0	19.2 ± 1.0	−1.2 ± 0.2	89.7	1.6	2.5
FEMALE							
0	5/5	17.3 ± 0.3	17.5 ± 0.6	+0.2 ± 0.4	--	3.8	3.3
3,125	5/5	18.1 ± 0.8	18.1 ± 0.5	0.0 ± 0.3	103.4	3.9	3.4
6,250	5/5	18.2 ± 0.5	18.1 ± 0.2	−0.1 ± 0.3	103.4	3.7	3.2
12,500	5/5	17.8 ± 0.4	17.6 ± 0.2	−0.2 ± 0.2	100.6	2.9	3.1
25,000	5/5	18.3 ± 0.8	17.0 ± 0.5	−1.3 ± 0.4	97.1	2.2	2.4
50,000	(e) 3/5	17.6 ± 0.4	17.8 ± 1.3	−0.4 ± 1.4	101.7	1.9	2.9

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed consumed per animal per day; not corrected for scatter.
(e) Day of death: 9,10

TABLE 14. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF ERYTHROMYCIN STEARATE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 4	Week 12
MALE							
0	10/10	20.9 ± 0.4	31.1 ± 1.2	+10.2 ± 1.3	--	2.5	3.1
1,250	10/10	21.5 ± 0.5	32.1 ± 1.1	+10.6 ± 1.3	103.2	3.1	3.1
2,500	10/10	22.2 ± 0.5	31.0 ± 0.5	+8.8 ± 0.6	99.7	2.9	3.5
5,000	10/10	21.8 ± 0.1	30.2 ± 0.7	+8.4 ± 0.7	97.1	2.8	3.1
10,000	10/10	21.3 ± 0.4	26.5 ± 0.6	+5.2 ± 0.6	85.2	2.9	3.2
20,000	10/10	21.5 ± 0.2	25.1 ± 0.3	+3.6 ± 0.4	80.7	3.0	2.8
FEMALE							
0	10/10	17.2 ± 0.2	24.0 ± 0.5	+6.8 ± 0.5	--	2.1	2.6
1,250	10/10	17.9 ± 0.2	25.5 ± 0.5	+7.6 ± 0.4	106.3	2.4	2.9
2,500	10/10	18.4 ± 0.3	24.5 ± 0.8	+6.1 ± 0.5	102.1	2.6	2.9
5,000	10/10	17.8 ± 0.2	26.0 ± 0.7	+8.2 ± 0.6	108.3	2.4	2.8
10,000	10/10	18.8 ± 0.2	22.7 ± 0.4	+3.9 ± 0.4	94.6	2.4	2.5
20,000	10/10	18.3 ± 0.1	20.7 ± 0.5	+2.4 ± 0.5	86.3	3.2	2.8

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean weight change of the group ± standard error of the mean
(d) Grams of feed consumed per animal per day; not corrected for scatter.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of dosed and control mice were generally comparable throughout the studies (Table 15 and Figure 5). The average daily feed consumption by low dose and high dose male mice was 103% and 100% that by controls (Appendix G, Table G3) and by low dose and high dose female mice, 92% that by controls (Table G4). The average amount of erythromycin stearate consumed per day was approximately 270 or 545 mg/kg by low or high dose male mice and 250 or 500 mg/kg by low or high dose female mice. No compound-related clinical signs were observed.

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

Weeks on Study	Control		2,500 ppm			5,000 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
1	25.5	50	24.6	96	50	24.6	96	50
2	26.2	50	25.3	97	50	25.3	97	50
3	27.7	50	26.9	97	50	26.4	95	50
4	28.1	50	27.6	98	50	27.1	96	49
5	29.0	50	28.3	98	50	27.6	95	49
6	29.9	50	29.2	98	50	28.3	95	49
7	30.3	50	30.0	99	50	28.7	95	49
8	30.9	50	30.5	99	50	29.6	96	49
9	31.3	50	31.2	100	50	30.1	96	49
10	31.7	50	31.9	101	50	30.1	95	49
11	32.2	50	32.2	100	50	30.8	96	49
12	34.3	50	32.6	95	50	31.5	92	49
13	33.0	50	32.9	100	50	32.3	98	49
16	33.4	50	35.1	105	50	33.5	100	49
20	35.4	50	35.8	101	50	34.5	97	49
26	35.1	50	37.0	105	49	35.1	100	49
30	36.3	50	36.4	100	49	35.4	98	49
34	37.2	50	37.5	101	49	36.6	98	49
38	36.9	50	38.0	103	49	36.8	100	49
42	38.4	50	39.0	102	49	38.8	101	49
46	39.5	49	39.6	100	49	39.0	99	49
50	39.7	49	40.0	101	47	39.1	98	49
55	39.7	48	39.5	99	47	39.0	98	49
58	39.4	48	39.3	100	47	39.0	99	49
63	40.2	48	40.2	100	47	39.7	99	49
68	39.5	48	40.0	101	47	39.0	99	49
72	39.1	48	39.3	101	46	38.5	98	48
77	39.1	47	38.4	98	45	38.0	97	46
81	39.2	47	38.6	98	44	37.7	96	45
85	38.0	44	37.8	99	41	37.8	99	42
89	37.8	43	39.3	104	39	38.3	101	41
94	37.5	42	38.3	102	38	37.2	99	41
98	37.4	40	39.5	106	35	37.7	101	40
103	37.5	34	38.5	103	33	37.3	99	40
FEMALE								
1	20.0	50	19.4	97	50	19.7	99	50
2	20.7	50	20.5	99	50	20.5	99	50
3	21.7	50	21.1	97	50	21.0	97	50
4	21.9	50	21.4	98	50	21.8	100	50
5	22.6	50	21.9	97	50	22.3	99	50
6	23.1	50	22.7	98	50	23.2	100	50
7	23.7	50	23.1	97	50	23.4	99	50
8	23.9	50	23.5	98	50	23.5	98	50
9	23.9	50	23.9	100	49	24.1	101	50
10	24.7	50	24.3	98	49	24.2	98	50
11	24.8	50	25.0	101	49	24.2	98	50
12	25.8	50	25.7	100	49	25.4	98	50
13	26.3	50	26.5	101	49	26.2	100	50
16	27.2	50	27.8	102	49	27.1	100	50
20	29.5	50	28.9	98	49	28.7	97	50
26	30.4	50	30.3	100	49	29.2	96	49
30	31.8	50	32.0	101	48	30.9	97	49
34	34.3	50	34.0	99	48	33.2	97	49
38	34.8	50	35.0	101	48	33.4	96	49
42	35.2	50	36.2	103	48	35.2	100	49
46	37.4	50	37.4	100	48	36.7	98	49
50	38.1	50	38.3	101	48	37.9	99	49
55	37.7	50	37.8	100	48	37.6	100	49
58	38.6	50	37.0	96	48	37.4	97	49
63	39.7	50	38.5	97	47	39.1	98	49
68	40.1	50	38.9	97	47	39.6	99	49
72	39.7	50	38.6	97	47	40.2	101	49
77	39.1	49	38.5	98	46	39.1	100	48
81	39.9	48	38.9	97	46	39.8	100	48
85	39.9	48	39.5	99	46	40.3	101	47
89	39.3	48	39.0	99	46	39.9	102	47
94	39.5	45	39.2	99	40	40.2	102	46
98	39.5	42	39.9	101	38	40.9	104	44
103	40.4	38	39.6	98	34	40.5	100	41

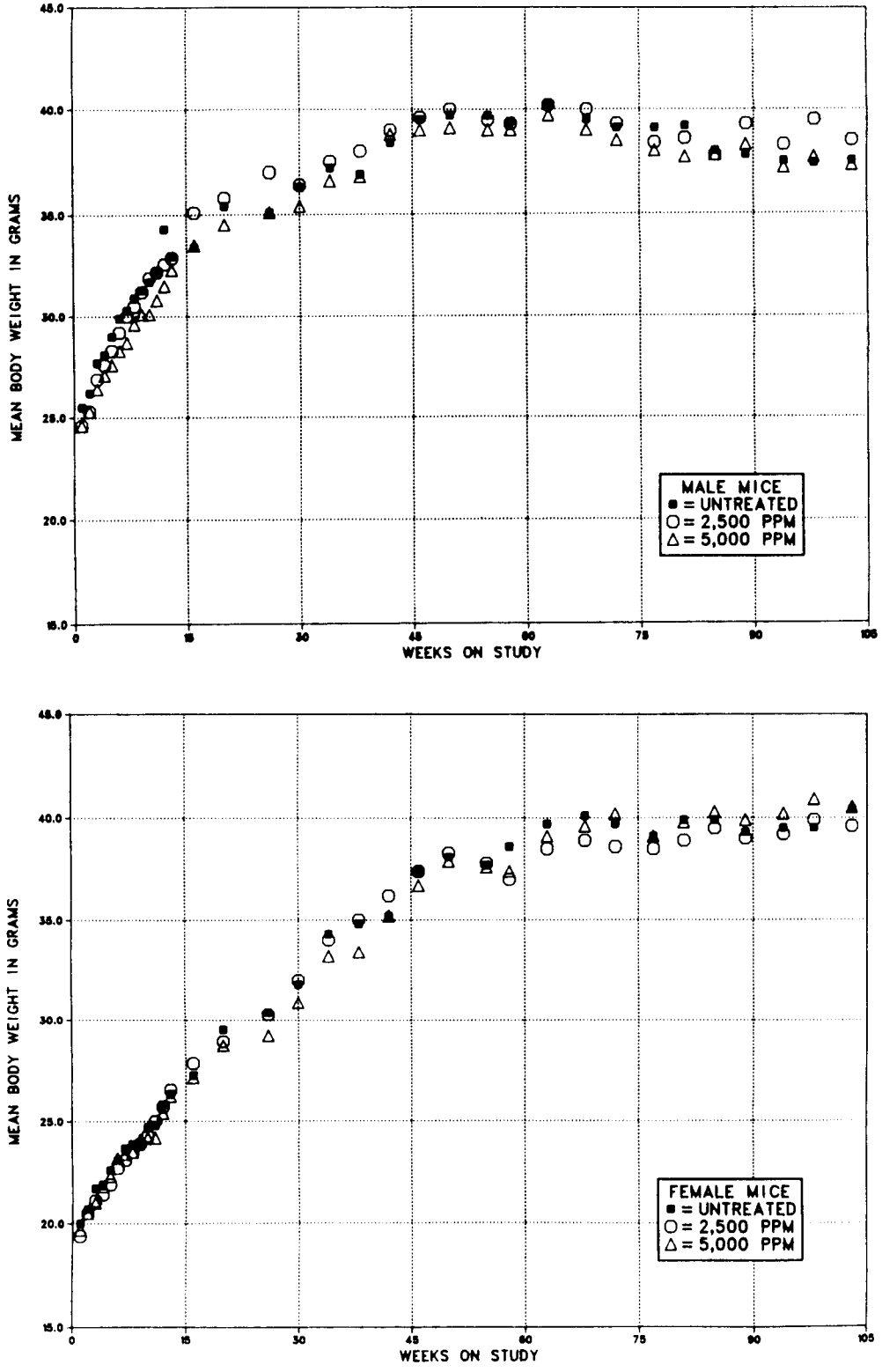

FIGURE 5. GROWTH CURVES FOR MICE FED DIETS CONTAINING ERYTHROMYCIN STEARATE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing erythromycin stearate at the concentrations used in these studies and for controls are shown in Table 16 and in the Kaplan and Meier curves in Figure 6. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes changes in the incidences of mice with nonneoplastic lesions of the glandular stomach and urinary bladder.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 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 Table C3 (footnotes). Findings on nonneoplastic lesions are summarized in Table C4.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 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 Table D3 (footnotes). Findings on nonneoplastic lesions are summarized in Table D4.

Glandular Stomach: Inflammation was observed at increased incidences in dosed male mice (male: control, 1/49; low dose, 4/50; high dose, 6/50; female: 3/49; 4/49; 0/50).

Urinary Bladder: Lymphoid hyperplasia was observed at increased incidences in dosed female mice (male: control, 3/50; low dose, 4/50; high dose, 8/50; female: 1/50; 9/47; 7/48).

TABLE 16. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF ERYTHROMYCIN STEARATE

	Control	2,500 ppm	5,000 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	17	10
Killed at termination	34	32	40
Died during termination period	0	1	0
Survival P values (c)	0.316	0.831	0.328
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	15	10
Accidentally killed	0	1	0
Killed at termination	38	34	40
Survival P values (c)	0.728	0.539	0.789

(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.

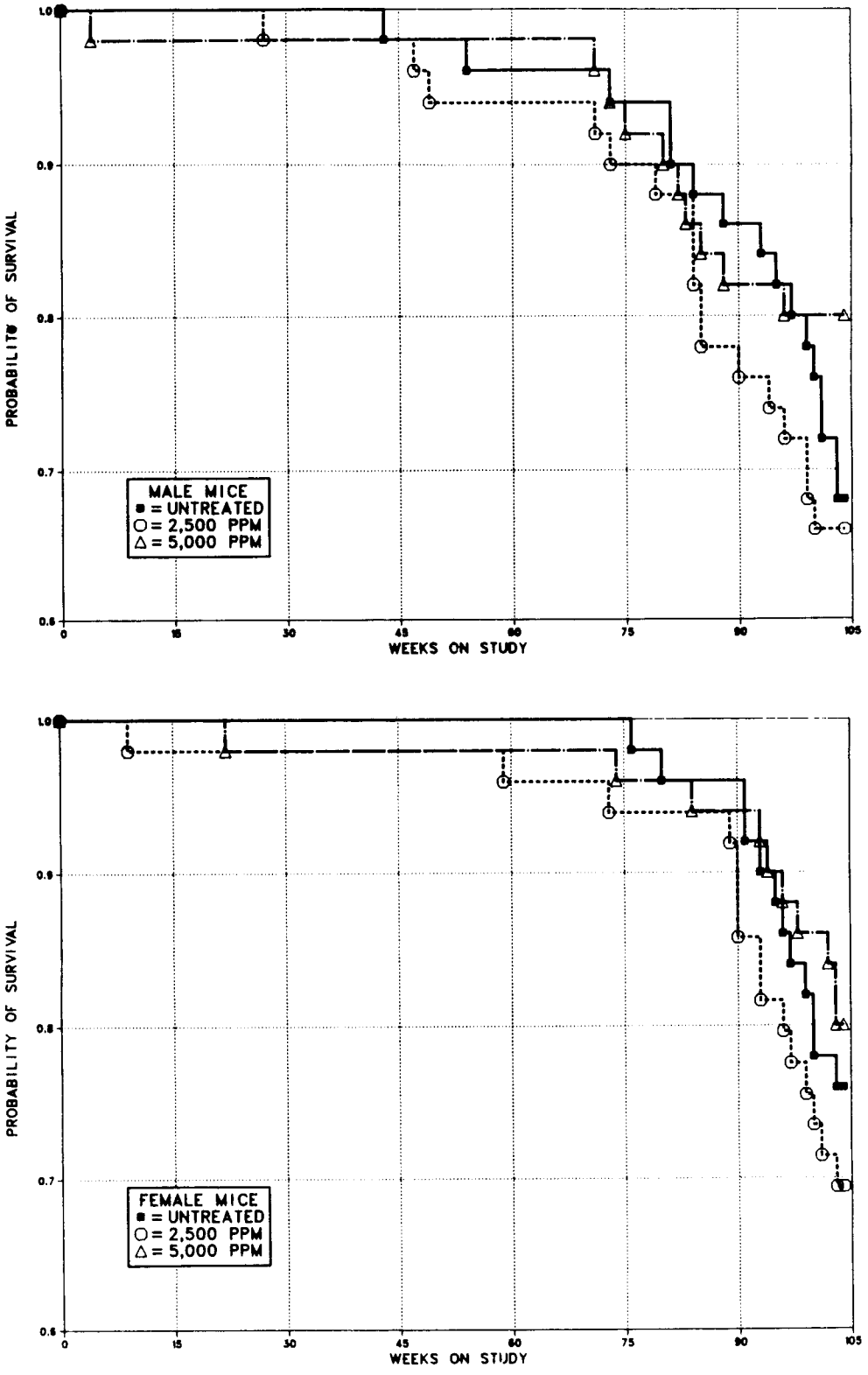

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING ERYTHROMYCIN STEARATE FOR TWO YEARS

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Toxicology and carcinogenesis studies of erythromycin stearate were conducted by administering erythromycin stearate (USP grade, greater than 96% pure) in feed to groups of F344/N rats and B6C3F$_1$ mice for 14 days, 13 weeks, or 2 years. Erythromycin stearate was studied and evaluated because of its widespread use in humans as a broad-spectrum macrolide antibiotic and because of the absence of reported long-term studies for carcinogenicity.

Diets containing up to 50,000 ppm erythromycin stearate (5% of the diet) were given to animals in the 14-day studies; all the rats and male mice survived, but 2/5 female mice receiving 50,000 ppm died. Marked dose-related decreases in weight gain correlated with proportional decreases in feed consumption except in female mice. This seems unusual, since the reported acute oral (gavage) toxicity of erythromycin base is greater for mice than for rats (age, sex, and strain unspecified; NIOSH, 1983). Clinical observations and gross pathologic lesions were indicative of gastrointestinal distress, most likely associated with killing of intestinal bacteria. Histopathologic examinations were not performed in the 14-day studies, and no information is available on target organ toxicity at these dose levels for these studies.

In the 13-week studies, none of the rats or mice receiving dietary concentrations up to 20,000 ppm died before the end of the studies. Final mean body weights of the 20,000-ppm groups of rats and mice were lower than those of the controls, with a proportionately greater reduction in males. The estimated feed consumption rates were similar to control values.

The liver (multinucleated syncytial hepatocytes) was the only organ affected in male rats. No compound-related gross or microscopic pathologic effects were observed in mice. Erythromycin is known to concentrate in the liver and to be excreted in the bile (Sande and Mandell, 1985). In vitro and in vivo studies and case reports in humans suggest that erythromycin is toxic to the liver (Dujovne et al., 1970, 1972; Tolman et al., 1974; Alcalay et al., 1986).

Based on these results, primarily the effects on final body weights, the 2-year studies of erythromycin stearate were conducted by administering erythromycin stearate in the diet at 0, 5,000, or 10,000 ppm to groups of 50 rats of each sex for 103 weeks. Diets containing 0, 2,500, or 5,000 ppm erythromycin stearate were fed to groups of 50 mice of each sex for 103 weeks.

Lower relative mean body weights were observed throughout the studies for high dose rats; females were more affected than were males after week 35, indicating an effect due to administration of erythromycin stearate. The similarity between mean body weights of dosed and control male and female mice suggests that greater dietary concentrations might have been given. The amount of erythromycin stearate consumed, calculated on the basis of estimated feed consumption by group-housed animals, was similar for all four studies: approximately 200-250 mg/kg per day in the low dose groups and 400-500 mg/kg per day in the high dose groups. By contrast, the usual oral therapeutic dosage of 1-2 g per day for a 70-kg human is approximately 15-30 mg/kg per day. No differences in survival were observed between any groups of rats or mice.

Granulomas of the liver in male and female rats and reticulum cell hyperplasia in the bone marrow of female rats are considered to be related to the administration of erythromycin stearate and indicate that the doses used were sufficient to elicit a biologic effect. These lesions may be exacerbated by the potential immunomodulatory effects (increased leukocyte migration) of erythromycin (Anderson et al., 1982, 1983, 1984; Ras and Anderson, 1986; Fraschini et al., 1986). Small granulomas occur in the liver of control rats and generally occur more frequently in females than in males. Although the cause of these spontaneous granulomas is unknown, they may be caused by the absorption of bacteria or bacterial products from the intestine. Estrogens are known to cause some immunosuppression (Luster et al., 1984; Dieter et al., 1987), which may explain the sex difference. In addition, the liver concentrates erythromycin (Sande and Mandell, 1985); crystallization of erythromycin may exacerbate this condition.

No neoplastic lesions were considered to be related to the consumption of erythromycin stearate by male or female rats or mice. Squamous

cell papillomas of the oral mucosa were observed in 1/50 control, 2/50 low dose, and 3/50 high dose female rats. Although these lesions are uncommon in the historical control data base, they are not considered to be related to the administration of erythromycin stearate because the increased incidences in the dosed groups are not statistically different from that in the concurrent control group, one papilloma was seen in each group of control rats, and the biologic importance of these lesions is not clear at this time. Hyperplasia of the oral mucosa was not observed in female rats.

Pheochromocytomas of the adrenal gland in female rats occurred with a positive trend (control, 1/50; low dose, 4/49; high dose, 5/50); the increased incidences were considered to be marginal and were discounted because complementary increases in hyperplasia did not occur (6/50; 4/49; 6/50), the increases were marginal, the lesion is relatively common, and the incidences are similar to the mean historical incidence at this laboratory. Thus, these lesions are not considered to be biologically important.

Male rats showed a dose-related increase in the incidence of interstitial cell tumors of the testis (control, 32/50; low dose, 36/50; high dose, 43/50), but this is a commonly occurring tumor that is observed in almost all older animals. In this particular study, the control incidence was somewhat low relative to that in previous studies (133/150, 89%, at this laboratory; 1,681/1,909, 88%, throughout the Program; Appendix A, Table A4a). This marginal increase is not considered to be biologically important.

Several confounding factors in interpreting these studies are known. Initial killing of intestinal bacteria and reduction in the flora by erythromycin is followed by repopulation by erythromycin-resistant strains and acclimation (natural repopulation of gut flora) (Heimdahl et al., 1984; Nord et al., 1985; Harrison et al., 1985), which may have occurred in the 2-year and 13-week studies but probably not in the 14-day studies. Systemic effects, including gastrointestinal distress, which result from the killing of intestinal flora and the release of bacterial endotoxins may confuse determination of the direct effects of erythromycin mammalian toxicity at the relatively high doses used in these studies.

Another complicating factor is administration of erythromycin stearate salt in the diet. Erythromycin base is known to be inactivated by gastric juice (Boggiano and Gleeson, 1976; Sande and Mandell, 1985), and various derivatives have been prepared to resist decomposition (Sande and Mandell, 1985). Erythromycin stearate is a reasonable choice, although the literature is conflicting on whether administration with or without food affects the amount and rate of erythromycin base absorption (Welling, 1977; Welling et al., 1978; Malmborg, 1979; Rutland et al., 1979; DiSanto and Chodos, 1981; Digranes et al., 1984). To accurately estimate the dose actually delivered, data would be required on the changes in the bacterial flora, absorption rate, disposition, and excretion rates under study conditions. These data are not available.

The experimental and tabulated data for the NTP Technical Report on erythromycin stearate were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix I, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions: Under the conditions of these 2-year studies, there was *no evidence of carcinogenic activity** of erythromycin stearate for male or female F344/N rats administered erythromycin stearate in the diet at 5,000 or 10,000 ppm. There was *no evidence of carcinogenic activity* of erythromycin stearate for male or female $B6C3F_1$ mice administered erythromycin stearate in the diet at 2,500 or 5,000 ppm. Dose-related increases in the incidences of granulomas of the liver were observed in male and female rats. The absence of any biologically important chemical-associated effects in mice suggests that higher doses could have been given to male and female mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

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

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Basal cell tumor		1 (2%)	
Sebaceous adenoma	1 (2%)		
Keratoacanthoma	1 (2%)	1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
Fibroma	1 (2%)	3 (6%)	2 (4%)
Fibrosarcoma	1 (2%)	1 (2%)	
Neurilemoma, malignant			1 (2%)
RESPIRATORY SYSTEM			
#Trachea	(50)	(49)	(48)
Fibrosarcoma, metastatic		1 (2%)	
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)		1 (2%)
Neurilemoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	29 (58%)	27 (54%)	33 (66%)
#Spleen	(46)	(49)	(50)
Leukemia, mononuclear cell		2 (4%)	1 (2%)
CIRCULATORY SYSTEM			
*Sternum	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
*Artery	(50)	(50)	(50)
Fibrosarcoma, metastatic		1 (2%)	
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Fibrosarcoma, metastatic		1 (2%)	
*Tongue	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
#Salivary gland	(49)	(48)	(50)
Neurilemoma, malignant		1 (2%)	
#Submaxillary gland	(49)	(48)	(50)
Neurilemoma, metastatic			1 (2%)
#Liver	(50)	(50)	(50)
Neoplastic nodule	1 (2%)	1 (2%)	3 (6%)
#Colon	(49)	(48)	(49)
Mucinous adenocarcinoma	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	

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

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(47)	(47)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	14 (29%)	14 (30%)	11 (23%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma			1 (2%)
Cortical carcinoma		1 (2%)	1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	19 (38%)	13 (26%)	17 (34%)
Pheochromocytoma, malignant	6 (12%)	1 (2%)	2 (4%)
#Thyroid	(50)	(48)	(50)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma		1 (2%)	1 (2%)
C-cell adenoma	6 (12%)	9 (19%)	5 (10%)
C-cell carcinoma		2 (4%)	1 (2%)
#Pancreatic islets	(48)	(49)	(49)
Islet cell adenoma	2 (4%)	2 (4%)	3 (6%)
Islet cell carcinoma	1 (2%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	
Adenoma, NOS		2 (4%)	
#Testis	(50)	(50)	(50)
Interstitial cell tumor	32 (64%)	36 (72%)	43 (86%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Eyelid	(50)	(50)	(50)
Fibrosarcoma			1 (2%)
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	4 (8%)	1 (2%)	
Keratoacanthoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Lumbar vertebra	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
*Femur	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Lipoma			1 (2%)
Mesothelioma, NOS		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		2 (4%)	
Mesothelioma, malignant			2 (4%)

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

	Untreated Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
Sarcoma, NOS		1 (2%)	
Mesothelioma, NOS	1 (2%)		
Mesothelioma, malignant			1 (2%)
Neurilemoma, malignant			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	3	1
Moribund sacrifice	19	24	22
Terminal sacrifice	28	23	27
TUMOR SUMMARY			
Total animals with primary tumors**	49	49	49
Total primary tumors	126	133	138
Total animals with benign tumors	45	46	47
Total benign tumors	78	85	87
Total animals with malignant tumors	39	38	37
Total malignant tumors	46	44	48
Total animals with secondary tumors##	1	1	1
Total secondary tumors	1	3	2
Total animals with tumors uncertain--benign or malignant	2	4	3
Total uncertain tumors	2	4	3

* 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. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: UNTREATED CONTROL

ANIMAL NUMBER	1117	1136	1009	1116	1111	1003	1466	1550	1444	1441	1005	1207	1333	1223	1337	1440	1331	1006	1115	1335	1338	1334	1001	1002	1004
WEEKS ON STUDY	0566	0667	0700	0744	0775	0779	0799	0800	0885	0886	0994	0994	0994	0996	0996	0996	0998	0999	0999	0999	1002	1022	1033	1041	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma														X											
Keratoacanthoma																						X			
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma								X																	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma										X															
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																						X			
Bile duct	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma																X									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Carcinoma, NOS										X															
Adenoma, NOS	X					X		X				X	X		X						X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma					X						X			X			X						X	X	X
Pheochromocytoma, malignant						X	X															X			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma											X					X									
Parathyroid	–	+	+	+	–	–	+	+	+	+	+	+	+	+	–	+	+	+	–	–	–	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+
Islet cell adenoma																									
Islet cell carcinoma																	X								
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X					X		X			X	X	X		X		X		X	X		X
Prostate	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	+	N	N	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	N
Carcinoma, NOS			X			X												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
Carcinoma, NOS, metastatic			X																						
Mesothelioma, NOS																	X								
Leukemia, mononuclear cell				X	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 A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	107	108	110	112	113	114	118	119	120	121	122	124	125	126	128	129	130	132	139	142	143	145	147	148	149	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Sebaceous adenoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																									X	1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			1
Alveolar/bronchiolar carcinoma								X																		2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
Thymus	+	+	+	−	+	+	−	−	+	+	+	−	−	+	−	+	−	+	+	+	+	+	−	+	−	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mucinous adenocarcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS						X		X				X		X				X	X						X	14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X	X	X	X				X	X				X	X	X	X		X						X	19
Pheochromocytoma, malignant				X													X	X								6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma										X	X												X		X	6
Parathyroid	+	−	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	−	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																			X						X	2
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	32
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS															X											1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
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																										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
Carcinoma, NOS, metastatic																										1
Mesothelioma, NOS																										1
Leukemia, mononuclear cell	X	X	X	X	X		X	X	X		X	X	X	X		X		X			X	X	X		X	29

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: LOW DOSE

ANIMAL NUMBER	00091	00121	00441	00011	00445	00057	00173	00385	00255	00503	00113	00227	00047	00233	00311	00474	00022	00088	00228	00229	00455	00066	00116	00224	00336
WEEKS ON STUDY	06070	07074	08080	08081	08081	08083	08083	08084	08085	08088	08089	09092	09094	09094	09094	09095	09096	09096	09096	09097	09097	09099	09099	09099	09099
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																			X						
Keratoacanthoma																		X							
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									X
Fibrosarcoma															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic															X										
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	+	+	+	+	+	+	–	–	–	+	+	+	+	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic															X										
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic															X										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma							X																		
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+
Adenoma, NOS		X			X							X							X	X			X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma																									
Pheochromocytoma									X				X				X							X	X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																								X	
C-cell adenoma				X					X			X		X				X							
C-cell carcinoma														X											
Parathyroid	–	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma											X														

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	035	046	003	007	010	011	014	015	018	019	020	021	022	026	030	032	033	034	037	039	040	042	043	048	049	TOTAL:
WEEKS ON STUDY	100	102	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	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor																										1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma		X											X													3
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																	X						X			2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	–	–	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, metastatic																										1
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, metastatic																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neurilemoma, malignant																X										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule							X																			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS		X					X		X		X		X	X					X			X				14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical carcinoma																						X				1
Pheochromocytoma		X							X		X					X				X	X		X	X		13
Pheochromocytoma, malignant				X																						1
Thyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma				X																						1
Follicular cell carcinoma																										1
C-cell adenoma							X	X											X						X	9
C-cell carcinoma																		X								2
Parathyroid	+	–	+	+	+	+	+	+	+	+	–	–	–	+	+	+	–	+	+	+	–	+	+	–	–	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma					X														X							2
Islet cell carcinoma																										1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	009	012	041	001	044	005	017	038	025	050	013	027	004	023	031	047	002	008	028	029	045	006	016	024	036
WEEKS ON STUDY	060	074	080	081	081	083	083	084	085	088	089	092	094	094	094	095	096	096	096	097	097	099	099	099	099
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Adenocarcinoma, NOS																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X	X		X	X		X		X		X	X	X		X	X			X	X		X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																						X			
Adenoma, 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
Carcinoma, NOS																							X		
Keratoacanthoma																								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
Sarcoma, NOS																					X				
Hemangiosarcoma																									
Osteosarcoma		X																							
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS										X													X		
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
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
Sarcoma, NOS			X																						
Leukemia, mononuclear cell				X		X	X	X	X	X		X	X			X	X	X	X	X	X	X	X	X	X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	035	046	003	007	010	011	014	015	018	019	020	021	022	026	030	032	033	034	037	039	040	042	043	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	100	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	*50
Adenocarcinoma, 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	X	X	36
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS											X															2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Keratoacanthoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Hemangiosarcoma														X												1
Osteosarcoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										2
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
Mesothelioma, NOS															X											1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Leukemia, mononuclear cell	X	X		X	X	X								X					X	X				X		27

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: HIGH DOSE

ANIMAL NUMBER	056	075	087	089	077	054	095	063	066	070	067	086	062	057	059	069	071	088	053	080	094	051	073	052	055
WEEKS ON STUDY	062	070	071	076	079	082	085	086	086	087	089	090	094	095	097	097	099	099	101	101	101	102	103	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								X	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																			X						
Fibroma																			X						
Neurilemoma, malignant				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Neurilemoma, metastatic				X																					
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	–	+	+	+	+	–	+	+	–	+	+	–	–	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, metastatic				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	+
Adenoma, NOS	X				X	X			X								X								X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Cortical carcinoma																									
Pheochromocytoma											X		X		X			X	X			X		X	X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma											X											X		X	X
C-cell carcinoma								X																	
Parathyroid	–	–	+	–	+	+	+	+	+	–	+	–	–	+	–	+	+	+	+	+	+	–	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma									X																
Islet cell carcinoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, malignant																							X		
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lipoma																									
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											
Neurilemoma, malignant																							X		
Leukemia, mononuclear cell			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	058	060	061	064	065	068	072	074	076	078	079	081	082	083	084	085	090	091	092	093	096	097	098	099	100	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
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma														X												2
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																1
Alveolar/bronchiolar carcinoma								X																		1
Neurilemoma, metastatic																										1
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																	X									1
Lymph nodes	+	+	+	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	−	+	−	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																						X				1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, metastatic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule			X						X									X								3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS		X					X									X							X	X		11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																						X				1
Cortical carcinoma		X																								1
Pheochromocytoma	X				X		X	X			X						X			X		X		X		17
Pheochromocytoma, malignant											X								X							2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma		X																								1
C-cell adenoma														X												5
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Islet cell adenoma			X			X																				3
Islet cell carcinoma							X																			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	*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	X	X	X	X	X	X	43
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma											X															1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, malignant														X												2
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
Lipoma						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
Mesothelioma, malignant																										1
Neurilemoma, malignant																										1
Leukemia, mononuclear cell	X				X	X	X	X			X	X	X	X		X			X	X	X				X	33

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Control	5,000 ppm	10,000 ppm
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	3.6%	11.5%	6.7%
Terminal Rates (c)	1/28 (4%)	1/23 (4%)	1/27 (4%)
Week of First Observation	104	99	101
Life Table Tests (d)	P=0.396	P=0.242	P=0.495
Incidental Tumor Tests (d)	P=0.375	P=0.310	P=0.481
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.309	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	(e) 2/50 (4%)
Adjusted Rates (b)	5.8%	13.8%	6.7%
Terminal Rates (c)	1/28 (4%)	1/23 (4%)	1/27 (4%)
Week of First Observation	80	94	101
Life Table Tests (d)	P=0.577	P=0.288	P=0.692N
Incidental Tumor Tests (d)	P=0.588	P=0.411	P=0.666N
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.339	P=0.691
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	10.3%	3.4%	7.4%
Terminal Rates (c)	2/28 (7%)	0/23 (0%)	2/27 (7%)
Week of First Observation	103	99	104
Life Table Tests (d)	P=0.413N	P=0.376N	P=0.516N
Incidental Tumor Tests (d)	P=0.420N	P=0.300N	P=0.521N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.309N	P=0.500N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	29/50 (58%)	29/50 (58%)	34/50 (68%)
Adjusted Rates (b)	79.9%	67.0%	73.5%
Terminal Rates (c)	21/28 (75%)	9/23 (39%)	15/27 (56%)
Week of First Observation	74	81	71
Life Table Tests (d)	P=0.234	P=0.323	P=0.237
Incidental Tumor Tests (d)	P=0.192	P=0.529N	P=0.212
Cochran-Armitage Trend Test (d)	P=0.178		
Fisher Exact Test (d)		P=0.580N	P=0.204
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	3.6%	4.3%	11.1%
Terminal Rates (c)	1/28 (4%)	1/23 (4%)	3/27 (11%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.196	P=0.718	P=0.290
Incidental Tumor Tests (d)	P=0.196	P=0.718	P=0.290
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.753	P=0.309
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	14/49 (29%)	14/47 (30%)	11/47 (23%)
Adjusted Rates (b)	37.1%	43.6%	30.9%
Terminal Rates (c)	7/28 (25%)	7/23 (30%)	6/27 (22%)
Week of First Observation	56	74	62
Life Table Tests (d)	P=0.319N	P=0.442	P=0.350N
Incidental Tumor Tests (d)	P=0.324N	P=0.540	P=0.330N
Cochran-Armitage Trend Test (d)	P=0.327N		
Fisher Exact Test (d)		P=0.537	P=0.366N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	5,000 ppm	10,000 ppm
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	15/49 (31%)	14/47 (30%)	11/47 (23%)
Adjusted Rates (b)	38.6%	43.6%	30.9%
Terminal Rates (c)	7/28 (25%)	7/23 (30%)	6/27 (22%)
Week of First Observation	56	74	62
Life Table Tests (d)	P=0.251N	P=0.523	P=0.277N
Incidental Tumor Tests (d)	P=0.238N	P=0.519N	P=0.236N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test (d)		P=0.554N	P=0.287N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	19/50 (38%)	13/50 (26%)	17/50 (34%)
Adjusted Rates (b)	58.2%	42.7%	50.3%
Terminal Rates (c)	15/28 (54%)	7/23 (30%)	11/27 (41%)
Week of First Observation	75	85	89
Life Table Tests (d)	P=0.416N	P=0.307N	P=0.459N
Incidental Tumor Tests (d)	P=0.421N	P=0.209N	P=0.474N
Cochran-Armitage Trend Test (d)	P=0.375N		
Fisher Exact Test (d)		P=0.142N	P=0.418N
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	6/50 (12%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	17.4%	4.3%	7.4%
Terminal Rates (c)	3/28 (11%)	1/23 (4%)	2/27 (7%)
Week of First Observation	79	104	104
Life Table Tests (d)	P=0.081N	P=0.085N	P=0.147N
Incidental Tumor Tests (d)	P=0.061N	P=0.041N	P=0.110N
Cochran-Armitage Trend Test (d)	P=0.070N		
Fisher Exact Test (d)		P=0.056N	P=0.135N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	23/50 (46%)	14/50 (28%)	18/50 (36%)
Adjusted Rates (b)	64.3%	46.3%	53.4%
Terminal Rates (c)	16/28 (57%)	8/23 (35%)	12/27 (44%)
Week of First Observation	75	85	89
Life Table Tests (d)	P=0.220N	P=0.155N	P=0.253N
Incidental Tumor Tests (d)	P=0.191N	P=0.062N	P=0.222N
Cochran-Armitage Trend Test (d)	P=0.175N		
Fisher Exact Test (d)		P=0.049N	P=0.208N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/50 (12%)	9/48 (19%)	5/50 (10%)
Adjusted Rates (b)	18.7%	27.4%	16.3%
Terminal Rates (c)	4/28 (14%)	4/23 (17%)	3/27 (11%)
Week of First Observation	94	81	89
Life Table Tests (d)	P=0.466N	P=0.217	P=0.525N
Incidental Tumor Tests (d)	P=0.413N	P=0.324	P=0.503N
Cochran-Armitage Trend Test (d)	P=0.442N		
Fisher Exact Test (d)		P=0.259	P=0.500N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	10/48 (21%)	6/50 (12%)
Adjusted Rates (b)	18.7%	31.2%	18.3%
Terminal Rates (c)	4/28 (14%)	5/23 (22%)	3/27 (11%)
Week of First Observation	94	81	86
Life Table Tests (d)	P=0.533	P=0.146	P=0.597
Incidental Tumor Tests (d)	P=0.516N	P=0.227	P=0.596N
Cochran-Armitage Trend Test (d)	P=0.556		
Fisher Exact Test (d)		P=0.182	P=0.620N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	5,000 ppm	10,000 ppm
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	2/48 (4%)	2/49 (4%)	3/49 (6%)
Adjusted Rates (b)	7.4%	8.7%	9.8%
Terminal Rates (c)	2/27 (7%)	2/23 (9%)	2/26 (8%)
Week of First Observation	104	104	86
Life Table Tests (d)	P=0.396	P=0.638	P=0.491
Incidental Tumor Tests (d)	P=0.417	P=0.638	P=0.529
Cochran-Armitage Trend Test (d)	P=0.415		
Fisher Exact Test (d)		P=0.684N	P=0.510
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	3/48 (6%)	3/49 (6%)	4/49 (8%)
Adjusted Rates (b)	10.1%	11.0%	13.6%
Terminal Rates (c)	2/27 (7%)	2/23 (9%)	3/26 (12%)
Week of First Observation	98	89	86
Life Table Tests (d)	P=0.411	P=0.599	P=0.489
Incidental Tumor Tests (d)	P=0.449	P=0.645N	P=0.521
Cochran-Armitage Trend Test (d)	P=0.431		
Fisher Exact Test (d)		P=0.651N	P=0.512
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	3.6%	10.1%	0.0%
Terminal Rates (c)	1/28 (4%)	1/23 (4%)	0/27 (0%)
Week of First Observation	104	94	
Life Table Tests (d)	P=0.389N	P=0.258	P=0.507N
Incidental Tumor Tests (d)	P=0.396N	P=0.310	P=0.507N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	32/50 (64%)	36/50 (72%)	43/50 (86%)
Adjusted Rates (b)	86.2%	91.8%	100.0%
Terminal Rates (c)	23/28 (82%)	20/23 (87%)	27/27 (100%)
Week of First Observation	74	80	76
Life Table Tests (d)	P=0.024	P=0.076	P=0.022
Incidental Tumor Tests (d)	P=0.003	P=0.208	P=0.003
Cochran-Armitage Trend Test (d)	P=0.008		
Fisher Exact Test (d)		P=0.260	P=0.010
Zymbal Gland: Carcinoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	10.2%	3.4%	0.0%
Terminal Rates (c)	0/28 (0%)	0/23 (0%)	0/27 (0%)
Week of First Observation	70	99	
Life Table Tests (d)	P=0.029N	P=0.211N	P=0.068N
Incidental Tumor Tests (d)	P=0.024N	P=0.144N	P=0.061N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.181N	P=0.059N
All Sites: Mesothelioma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	2.9%	9.9%	9.7%
Terminal Rates (c)	0/28 (0%)	1/23 (4%)	1/27 (4%)
Week of First Observation	98	88	95
Life Table Tests (d)	P=0.244	P=0.269	P=0.302
Incidental Tumor Tests (d)	P=0.231	P=0.390	P=0.276
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.309	P=0.309

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	5,000 ppm	10,000 ppm
All Sites: Benign Tumors			
Overall Rates (a)	45/50 (90%)	46/50 (92%)	47/50 (94%)
Adjusted Rates (b)	97.8%	100.0%	100.0%
Terminal Rates (c)	27/28 (96%)	23/23 (100%)	27/27 (100%)
Week of First Observation	56	74	62
Life Table Tests (d)	P=0.359	P=0.174	P=0.383
Incidental Tumor Tests (d)	P=0.273	P=0.525	P=0.351
Cochran-Armitage Trend Test (d)	P=0.290		
Fisher Exact Test (d)		P=0.500	P=0.357
All Sites: Malignant Tumors			
Overall Rates (a)	39/50 (78%)	38/50 (76%)	37/50 (74%)
Adjusted Rates (b)	88.4%	79.1%	77.1%
Terminal Rates (c)	23/28 (82%)	13/23 (57%)	16/27 (59%)
Week of First Observation	70	74	71
Life Table Tests (d)	P=0.443N	P=0.359	P=0.471N
Incidental Tumor Tests (d)	P=0.308N	P=0.334N	P=0.349N
Cochran-Armitage Trend Test (d)	P=0.363N		
Fisher Exact Test (d)		P=0.500N	P=0.408N
All Sites: All Tumors			
Overall Rates (a)	49/50 (98%)	49/50 (98%)	49/50 (98%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	28/28 (100%)	23/23 (100%)	27/27 (100%)
Week of First Observation	56	74	62
Life Table Tests (d)	P=0.482	P=0.222	P=0.510
Incidental Tumor Tests (d)	P=0.565N	P=0.549N	P=0.723N
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.752	P=0.752

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) A sarcoma, NOS, was observed in a rat with a fibroma.

TABLE A4a. HISTORICAL INCIDENCE OF TESTICULAR INTERSTITIAL CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Physiological Research Laboratories	
Ephedrine sulfate	45/50
Phenylephrine hydrochloride	47/50
Oxytetracycline hydrochloride	41/50
TOTAL	133/150 (88.7%)
SD (b)	6.11%
Range (c)	
High	47/50
Low	41/50
Overall Historical Incidence	
TOTAL	1,681/1,909 (88.1%)
SD (b)	7.32%
Range (c)	
High	49/50
Low	34/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks; no malignant tumors have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF ZYMBAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Physiological Research Laboratories	
Ephedrine sulfate	0/50
Phenylephrine hydrochloride	1/50
Oxytetracycline hydrochloride	0/50
TOTAL	1/150 (0.7%)
SD (b)	1.15%
Range (c)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 15/1,937 (0.8%)
SD (b)	1.27%
Range (c)	
High	(e) 3/50
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes five carcinomas, NOS, nine squamous cell carcinomas, and one ceruminous carcinoma; no benign tumors have been observed.
(e) Second highest: 1/50

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	2 (4%)	1 (2%)	1 (2%)
Ulceration, diffuse		1 (2%)	
Inflammation, suppurative	1 (2%)		
Ulcer, acute	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Hyperkeratosis	5 (10%)		
Acanthosis	1 (2%)		
RESPIRATORY SYSTEM			
#Tracheal submucosa	(50)	(49)	(48)
Cyst, NOS	2 (4%)	2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)	2 (4%)	
#Lung	(50)	(50)	(50)
Congestion, NOS	2 (4%)	1 (2%)	1 (2%)
Edema, interstitial		2 (4%)	
Hemorrhage		1 (2%)	
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Inflammation, interstitial	1 (2%)		1 (2%)
Inflammation, chronic focal	1 (2%)		
Granuloma, NOS	1 (2%)		
Inflammation, granulomatous focal		1 (2%)	
Hyperplasia, adenomatous	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, mesothelial			1 (2%)
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis	1 (2%)		2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(49)	(49)
Hyperemia	1 (2%)		
Atrophy, focal			1 (2%)
Atrophy, diffuse			2 (4%)
Myelofibrosis		1 (2%)	2 (4%)
Hyperplasia, hematopoietic	31 (63%)	28 (57%)	27 (55%)
Hyperplasia, reticulum cell	2 (4%)	3 (6%)	4 (8%)
Mastocytosis	2 (4%)		1 (2%)
#Spleen	(46)	(49)	(50)
Congestion, NOS	2 (4%)	4 (8%)	
Scar	1 (2%)		4 (8%)
Hemosiderosis	5 (11%)	1 (2%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis		1 (2%)	
#Splenic red pulp	(46)	(49)	(50)
Fibrosis, focal	2 (4%)	1 (2%)	1 (2%)
Fibrosis, diffuse			1 (2%)
#Lymph node	(48)	(48)	(46)
Dilatation/sinus	4 (8%)		
Cyst, NOS	4 (8%)	1 (2%)	1 (2%)
Congestion, NOS	2 (4%)		1 (2%)
Edema, NOS	1 (2%)		1 (2%)
Hemorrhage	1 (2%)	3 (6%)	1 (2%)
Inflammation, acute	1 (2%)		
Fibrosis		1 (2%)	
Histiocytosis		2 (4%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
#Lymph node (Continued)	(48)	(48)	(46)
Plasmacytosis	2 (4%)		
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Mastocytosis	1 (2%)		
#Mandibular lymph node	(48)	(48)	(46)
Cyst, NOS	2 (4%)		1 (2%)
Hemorrhage, chronic			1 (2%)
Inflammation, chronic necrotizing			1 (2%)
Plasmacytosis	3 (6%)	1 (2%)	
#Mesenteric lymph node	(48)	(48)	(46)
Multiple cysts	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
#Peyer's patch	(50)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)
#Duodenum	(50)	(50)	(49)
Plasmacytosis	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(36)	(39)	(37)
Cystic ducts			1 (3%)
Hemorrhage	1 (3%)	2 (5%)	1 (3%)
Inflammation, acute		1 (3%)	
Fibrosis, focal			1 (3%)
Hypertrophy, NOS			2 (5%)
Hyperplasia, epithelial			2 (5%)
CIRCULATORY SYSTEM			
#Brain	(48)	(50)	(50)
Thrombosis, NOS		1 (2%)	
*Tail	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Lung	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)	1 (2%)	
#Heart/atrium	(50)	(48)	(50)
Mineralization	1 (2%)		
Thrombosis, NOS	2 (4%)	3 (6%)	1 (2%)
#Left ventricle	(50)	(48)	(50)
Dilatation, NOS	1 (2%)		
#Myocardium	(50)	(48)	(50)
Inflammation, acute suppurative			1 (2%)
Degeneration, NOS	49 (98%)	45 (94%)	40 (80%)
#Mitral valve	(50)	(48)	(50)
Thrombosis, NOS			1 (2%)
Degeneration, mucoid	5 (10%)	3 (6%)	5 (10%)
#Aortic valve	(50)	(48)	(50)
Degeneration, mucoid	1 (2%)		
*Artery	(50)	(50)	(50)
Metaplasia, cartilaginous	4 (8%)		4 (8%)
*Coronary artery	(50)	(50)	(50)
Arteriosclerosis, NOS			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
Edema, NOS		1 (2%)	
Arteriolosclerosis	1 (2%)		
Hypertrophy, NOS		2 (4%)	2 (4%)
#Liver	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)	1 (2%)	
Arteriolosclerosis	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Kidney/capsule	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
#Adrenal	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
*Tongue	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)		
#Salivary gland	(49)	(48)	(50)
Cystic ducts		2 (4%)	
Inflammation, chronic			1 (2%)
Necrosis, focal			1 (2%)
Nuclear enlargement	1 (2%)		2 (4%)
Atrophy, focal	7 (14%)	3 (6%)	1 (2%)
Hyperplasia, focal	2 (4%)		
#Submaxillary gland	(49)	(48)	(50)
Atrophy, pressure			1 (2%)
#Liver	(50)	(50)	(50)
Accessory structure	1 (2%)		
Congestion, chronic	2 (4%)	1 (2%)	
Lymphocytic inflammatory infiltrate	2 (4%)		
Inflammation, acute focal			1 (2%)
Inflammation, acute necrotizing	2 (4%)		
Inflammation, chronic focal	3 (6%)		1 (2%)
Granuloma, NOS	1 (2%)	2 (4%)	10 (20%)
Degeneration, cystic	9 (18%)	10 (20%)	8 (16%)
Necrosis, NOS	1 (2%)		
Atrophy, focal	1 (2%)		
Angiectasis			1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
Degeneration, NOS		1 (2%)	
#Liver/periportal	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
#Liver/hepatocytes	(50)	(50)	(50)
Cytoplasmic vacuolization	5 (10%)	7 (14%)	3 (6%)
Focal cellular change	27 (54%)	19 (38%)	27 (54%)
Hyperplasia, focal		1 (2%)	2 (4%)
Regenerative nodule	8 (16%)	5 (10%)	14 (28%)
#Bile duct	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Hyperplasia, NOS	48 (96%)	47 (94%)	50 (100%)
#Pancreas	(48)	(49)	(49)
Cyst, NOS		2 (4%)	
Cystic ducts		1 (2%)	
Inflammation, acute	1 (2%)		
Atrophy, focal	19 (40%)	22 (45%)	22 (45%)
Atrophy, diffuse	1 (2%)	1 (2%)	5 (10%)
Hypertrophy, focal			1 (2%)
Hyperplasia, focal	1 (2%)	2 (4%)	2 (4%)
#Glandular stomach	(50)	(50)	(50)
Cyst, NOS	23 (46%)	33 (66%)	22 (44%)
Edema, NOS		1 (2%)	
Ulcer, NOS		1 (2%)	
Erosion			1 (2%)
Fibrosis, focal			1 (2%)
Hyperplasia, focal		3 (6%)	1 (2%)
Hyperplasia, diffuse			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Edema, NOS	2 (4%)	2 (4%)	1 (2%)
Ulcer, NOS	1 (2%)	1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute diffuse		2 (4%)	
Ulcer, perforated	1 (2%)		
Infection, bacterial			1 (2%)
Hyperplasia, epithelial	2 (4%)	1 (2%)	1 (2%)
Hyperkeratosis			1 (2%)
#Duodenum	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Jejunum	(50)	(50)	(49)
Ulcer, chronic	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Pyelonephritis, acute		1 (2%)	
Inflammation, acute suppurative			1 (2%)
Pyelonephritis, chronic		1 (2%)	
Scar		1 (2%)	
Nephropathy	49 (98%)	49 (98%)	49 (98%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS		2 (4%)	2 (4%)
#Kidney/pelvis	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(50)	(49)	(49)
Calculus, gross observation only		1 (2%)	
Edema, NOS	1 (2%)		1 (2%)
Inflammation, acute diffuse		1 (2%)	
Inflammation, acute hemorrhagic		1 (2%)	
Degeneration, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(49)	(47)	(47)
Hemorrhage			1 (2%)
#Pituitary intermedia	(49)	(47)	(47)
Cyst, NOS	1 (2%)		2 (4%)
#Anterior pituitary	(49)	(47)	(47)
Cyst, NOS	7 (14%)	3 (6%)	5 (11%)
Necrosis, hemorrhagic		1 (2%)	
Pigmentation, NOS	1 (2%)		
Hyperplasia, focal	20 (41%)	15 (32%)	19 (40%)
Hyperplasia, cystic	1 (2%)	2 (4%)	2 (4%)
Angiectasis		1 (2%)	
#Pituitary posterior	(49)	(47)	(47)
Cyst, NOS		1 (2%)	
Inflammation, chronic			1 (2%)
Gliosis		1 (2%)	1 (2%)
#Adrenal/capsule	(50)	(50)	(50)
Hyperplasia, focal			2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(50)	(50)
Multiple cysts			1 (2%)
Hemorrhage	1 (2%)		1 (2%)
Necrosis, focal	1 (2%)	2 (4%)	
Cytoplasmic vacuolization	9 (18%)	3 (6%)	6 (12%)
Atrophy, pressure	1 (2%)		
Hypertrophy, focal	8 (16%)	6 (12%)	5 (10%)
Hyperplasia, focal	20 (40%)	24 (48%)	25 (50%)
Angiectasis	2 (4%)		
#Adrenal medulla	(50)	(50)	(50)
Hemorrhagic cyst		1 (2%)	
Hyperplasia, focal	7 (14%)	16 (32%)	6 (12%)
Angiectasis	1 (2%)		
#Thyroid	(50)	(48)	(50)
Ultimobranchial cyst	1 (2%)		
Follicular cyst, NOS	1 (2%)	1 (2%)	
Atrophy, diffuse	1 (2%)		
Hyperplasia, C-cell	9 (18%)	5 (10%)	13 (26%)
Hyperplasia, follicular cell		1 (2%)	
#Parathyroid	(37)	(36)	(37)
Hyperplasia, focal	1 (3%)	1 (3%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele			1 (2%)
Hemorrhagic cyst		1 (2%)	
Inflammation, focal	1 (2%)	1 (2%)	
Fibrosis			1 (2%)
Hyperplasia, NOS	5 (10%)	7 (14%)	1 (2%)
Hyperplasia, cystic	12 (24%)	7 (14%)	6 (12%)
*Prepuce	(50)	(50)	(50)
Ulcer, NOS	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	2 (4%)		
Atrophy, focal	1 (2%)		
Atrophy, diffuse	9 (18%)	4 (8%)	6 (12%)
#Prostate	(49)	(50)	(50)
Mineralization	1 (2%)		
Cyst, NOS			1 (2%)
Inflammation, suppurative			1 (2%)
Inflammation, acute focal	2 (4%)	2 (4%)	
Inflammation, chronic focal	28 (57%)	23 (46%)	25 (50%)
Inflammation, chronic diffuse	9 (18%)	7 (14%)	6 (12%)
Atrophy, diffuse	1 (2%)		
Hyperplasia, focal	1 (2%)		
Hyperplasia, cystic			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Atrophy, diffuse	10 (20%)	3 (6%)	8 (16%)
Hyperplasia, diffuse	2 (4%)		
#Testis	(50)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
Edema, NOS			1 (2%)
Inflammation, acute		1 (2%)	
Degeneration, NOS	12 (24%)	12 (24%)	8 (16%)
Necrosis, coagulative			1 (2%)
Infarct, acute		1 (2%)	
Hyperplasia, interstitial cell	17 (34%)	17 (34%)	16 (32%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Lateral ventricle	(48)	(50)	(50)
Dilatation, NOS		2 (4%)	
#Third ventricle	(48)	(50)	(50)
Dilatation, NOS		1 (2%)	
#Fourth ventricle	(48)	(50)	(50)
Dilatation, NOS			1 (2%)
#Brain	(48)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Inflammation, focal	1 (2%)		
Necrosis, hemorrhagic		1 (2%)	
#Brain stem	(48)	(50)	(50)
Hemorrhage			1 (2%)
Atrophy, pressure	1 (2%)		
*Spinal cord	(50)	(50)	(50)
Hemorrhage			1 (2%)
Degeneration, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Inflammation, chronic		2 (4%)	
*Eye/anterior chamber	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
*Eyeball, tunica fibrosa	(50)	(50)	(50)
Mineralization	2 (4%)		
*Eye/cornea	(50)	(50)	(50)
Scar		1 (2%)	
*Eye/choroid	(50)	(50)	(50)
Inflammation, chronic	1 (2%)	2 (4%)	
*Eye/iris	(50)	(50)	(50)
Inflammation, NOS	2 (4%)	1 (2%)	
Synechia, posterior	1 (2%)	2 (4%)	2 (4%)
*Eye/retina	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Degeneration, NOS	1 (2%)	1 (2%)	1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Mineralization	3 (6%)	10 (20%)	1 (2%)
Cataract	8 (16%)	13 (26%)	9 (18%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Pleural mesothelium	(50)	(50)	(50)
Granulation tissue	1 (2%)		
Hypertrophy, NOS			1 (2%)
*Mesentery	(50)	(50)	(50)
Diverticulum	1 (2%)		
Necrosis, fat	6 (12%)	3 (6%)	3 (6%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Bacterial septicemia			1 (2%)
Diaphragm			
Hernia, NOS			1
Adipose tissue			
Hyperemia	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 B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
Fibroma	1 (2%)	1 (2%)	
Fibrosarcoma			2 (4%)
Lipoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(49)	(49)	(49)
Alveolar/bronchiolar adenoma		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	14 (28%)	19 (38%)	9 (18%)
#Spleen	(48)	(49)	(50)
Leukemia, mononuclear cell			1 (2%)
#Mandibular lymph node	(45)	(45)	(49)
Fibrosarcoma, metastatic			1 (2%)
#Liver	(50)	(50)	(50)
Kupffer cell sarcoma		1 (2%)	
#Thymus	(42)	(35)	(41)
Thymoma, malignant			1 (2%)
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Neurilemoma, malignant	1 (2%)		
*Pulmonary vein	(50)	(50)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Squamous cell papilloma		2 (4%)	1 (2%)
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		1 (2%)
*Gum of mandible	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
#Salivary gland	(48)	(49)	(49)
Neurilemoma, malignant		1 (2%)	
#Liver	(50)	(50)	(50)
Neoplastic nodule		1 (2%)	2 (4%)
#Small intestine	(49)	(50)	(50)
Leiomyosarcoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Tubular cell adenoma	1 (2%)	1 (2%)	
Tubular cell adenocarcinoma			1 (2%)
#Urinary bladder	(47)	(48)	(48)
Transitional cell papilloma			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(50)
Carcinoma, NOS	4 (8%)	2 (4%)	2 (4%)
Adenoma, NOS	18 (37%)	18 (36%)	16 (32%)
#Adrenal cortex	(50)	(49)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	1 (2%)	3 (6%)	
#Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma	1 (2%)	4 (8%)	5 (10%)
#Thyroid	(50)	(50)	(50)
C-cell adenoma	9 (18%)	8 (16%)	3 (6%)
C-cell carcinoma		2 (4%)	2 (4%)
#Parathyroid	(35)	(31)	(34)
Adenoma, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
Adenocarcinoma, NOS	2 (4%)		
Fibroadenoma	13 (26%)	13 (26%)	15 (30%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	
Adenoma, NOS	5 (10%)	3 (6%)	3 (6%)
#Uterus	(50)	(49)	(50)
Sarcoma, NOS		1 (2%)	
Endometrial stromal polyp	10 (20%)	5 (10%)	14 (28%)
Endometrial stromal sarcoma	3 (6%)		
#Ovary	(49)	(49)	(50)
Granulosa cell tumor	2 (4%)		
NERVOUS SYSTEM			
#Brain	(50)	(49)	(50)
Carcinoma, NOS, invasive	1 (2%)		
Astrocytoma	3 (6%)		
Oligodendroglioma		2 (4%)	
Meningioma			1 (2%)
#Brain stem	(50)	(49)	(50)
Carcinoma, NOS, invasive	3 (6%)	1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS, metastatic		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	5	2
Moribund sacrifice	19	15	10
Terminal sacrifice	29	30	38
TUMOR SUMMARY			
Total animals with primary tumors**	49	48	42
Total primary tumors	93	96	81
Total animals with benign tumors	38	37	38
Total benign tumors	62	61	60
Total animals with malignant tumors	27	30	17
Total malignant tumors	29	34	19
Total animals with secondary tumors##	5	2	1
Total secondary tumors	5	2	1
Total animals with tumors uncertain-- benign or malignant	2	1	2
Total uncertain tumors	2	1	2

* 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. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: UNTREATED CONTROL

ANIMAL NUMBER	12 25	14 46	11 15	11 10	12 29	13 32	13 37	10 05	10 06	12 28	14 43	14 49	12 33	13 34	14 00	10 02	12 26	14 44	12 24	10 09	11 13	10 11	10 03	10 04	10 07
WEEKS ON STUDY	02 66	04 99	05 55	05 77	07 88	08 22	08 83	08 84	08 44	08 44	08 85	08 66	08 89	08 99	09 92	09 94	09 96	09 99	10 01	10 02	10 02	10 04	10 44	10 44	10 04
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lipoma																					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant	X																								
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, metastatic														X											
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																						X			
Urinary bladder	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS								X				X					X								
Adenoma, NOS				X	X														X	X	X			X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma							X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma													X					X	X						
Parathyroid	+	+	+	−	−	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																			X						
Adenocarcinoma, NOS																									
Fibroadenoma			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			
Endometrial stromal sarcoma										X			X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																X						X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive								X				X					X								
Astrocytoma					X	X																			
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																		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

+ 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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	108	111	112	114	116	117	118	119	120	121	122	127	130	131	133	135	136	138	139	141	142	145	147	148	150	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																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma													X													1
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	45
Thymus	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant																										1
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, metastatic																										1
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma														X												1
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																										1
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS											X															4
Adenoma, NOS	X		X	X	X		X	X	X									X	X		X		X	X		18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS			X																							1
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma							X				X					X			X		X	X				9
Parathyroid	−	+	+	+	+	−	+	+	−	+	−	−	+	+	−	+	+	+	+	+	+	−	−	−	+	35
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																		X			X					2
Fibroadenoma		X				X									X			X	X	X		X				13
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																										1
Adenoma, NOS												X			X				X						X	5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp					X				X						X				X	X	X		X			10
Endometrial stromal sarcoma																						X				3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	49
Granulosa cell tumor																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive											X															4
Astrocytoma																X										3
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										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		14

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: LOW DOSE

ANIMAL NUMBER	0042	0009	0115	0338	0441	0447	0330	0007	0225	0114	0446	0337	0224	0001	0329	0116	0448	0223	0441	0334	0002	0003	0004	0005	0006
WEEKS ON STUDY	0533	0633	0730	0771	0880	0882	0833	0884	0887	0888	0889	0992	0996	0997	0998	1000	1000	1001	1002	1003	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS							X																		
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	−	−	+	−	−	+	+	+	+	−	+	+	+	+	−	+	+	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																					X				
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Kupffer cell sarcoma									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Large intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	●	+	+	●	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS										X															
Adenoma, NOS		X										X	X	X				X							X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS													X												
Pheochromocytoma								X				X													
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma														X								X			
C-cell carcinoma																									
Parathyroid	−	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	−
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma					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																									
Adenoma, NOS																								X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Sarcoma, NOS			X																						
Endometrial stromal polyp																			X	X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive										X															
Oligodendroglioma	X																	X							
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS								X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic			X																						
Leukemia, mononuclear cell				X	X	X			X		X	X	X		X		X		X	X					

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0008	0010	0011	0012	0013	0017	0018	0019	0020	0021	0022	0026	0027	0028	0029	0031	0033	0035	0036	0039	0040	0043	0045	0049	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	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma													X													1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Alveolar/bronchiolar adenoma													X													1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	45
Thymus	+	+	+	−	−	+	+	+	+	−	+	+	−	−	+	−	+	+	+	+	+	+	−	+	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma														X												2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neurilemoma, malignant																					X					1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule														X												1
Kupffer cell sarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma					X																					1
Large intestine	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																				X						2
Adenoma, NOS		X	X	X				X		X		X		X			X	X	X				X		X	18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																			X							1
Adenoma, NOS			X						X																	3
Pheochromocytoma		X							X																	4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma						X			X	X		X						X						X		8
C-cell carcinoma			X													X										2
Parathyroid	−	+	−	−	−	−	−	+	+	+	−	+	−	−	+	+	−	+	+	+	+	+	−	+	−	31
Adenoma, NOS																X										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma		X								X		X						X	X		X	X				13
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					2
Adenoma, NOS				X									X													3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Endometrial stromal polyp											X			X	X											5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, invasive																										1
Oligodendroglioma																										2
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, metastatic																										1
Leukemia, mononuclear cell		X		X										X		X		X	X			X			X	19

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: HIGH DOSE

ANIMAL NUMBER	0074	0066	0092	0077	0069	0061	0075	0082	0098	0057	0060	0093	0051	0052	0053	0054	0055	0056	0058	0059	0062	0063	0064	0065	0067
WEEKS ON STUDY	0062	0068	0068	0091	0092	0094	0095	0098	0099	1003	1003	1003	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma										X					X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell					X																				
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	–	+	+	+	+	–	+	+	+
Thymoma, malignant																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma							X																		
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS									X																
Adenoma, NOS		X		X				X		X		X	X		X								X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X									X											X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									X
C-cell carcinoma																								X	
Parathyroid	–	–	+	–	+	+	+	+	+	+	–	–	–	+	+	–	+	–	–	+	+	–	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma	X		X	X	X	X		X			X						X		X		X				
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp					X												X		X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma																									
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														

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE
(Continued)

ANIMAL NUMBER	0068	0070	0071	0072	0073	0076	0078	0079	0080	0081	0083	0084	0085	0086	0087	0088	0089	0090	0091	0094	0095	0096	0097	0099	0100	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																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
Thymus	+	+	+	+	+	+	−	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	41
Thymoma, malignant						X																				1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma															X							X				3
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule														X						X						2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Transitional cell papilloma				X																						1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																X										2
Adenoma, NOS	X				X							X			X						X			X		16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X	X																							5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma	X																					X				3
C-cell carcinoma		X																								2
Parathyroid	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	−	+	+	−	+	−	+	+	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	*50
Fibroadenoma				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
Adenoma, NOS	X																							X		3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	50
Endometrial stromal polyp	X		X			X				X			X		X	X	X	X		X					X	14
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	50
Meningioma																					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	X		X						X						X	X					9

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Control	5,000 ppm	10,000 ppm
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	14/50 (28%)	19/50 (38%)	10/50 (20%)
Adjusted Rates (b)	38.4%	45.1%	24.7%
Terminal Rates (c)	8/29 (28%)	8/30 (27%)	8/38 (21%)
Week of First Observation	49	71	92
Life Table Tests (d)	P=0.081N	P=0.271	P=0.091N
Incidental Tumor Tests (d)	P=0.363N	P=0.165	P=0.335N
Cochran-Armitage Trend Test (d)	P=0.219N		
Fisher Exact Test (d)		P=0.198	P=0.242N
Oral Cavity: Squamous Cell Papilloma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	3.4%	6.7%	7.4%
Terminal Rates (c)	1/29 (3%)	2/30 (7%)	2/38 (5%)
Week of First Observation	104	104	95
Life Table Tests (d)	P=0.316	P=0.512	P=0.405
Incidental Tumor Tests (d)	P=0.308	P=0.512	P=0.395
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.500	P=0.309
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	18/49 (37%)	18/50 (36%)	16/50 (32%)
Adjusted Rates (b)	52.1%	50.3%	36.7%
Terminal Rates (c)	13/29 (45%)	13/30 (43%)	11/38 (29%)
Week of First Observation	57	63	68
Life Table Tests (d)	P=0.118N	P=0.523N	P=0.145N
Incidental Tumor Tests (d)	P=0.163N	P=0.447N	P=0.191N
Cochran-Armitage Trend Test (d)	P=0.348N		
Fisher Exact Test (d)		P=0.553N	P=0.388N
Anterior Pituitary Gland: Carcinoma			
Overall Rates (a)	4/49 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	10.8%	5.7%	4.9%
Terminal Rates (c)	1/29 (3%)	1/30 (3%)	1/38 (3%)
Week of First Observation	84	88	99
Life Table Tests (d)	P=0.182N	P=0.317N	P=0.249N
Incidental Tumor Tests (d)	P=0.373N	P=0.360N	P=0.484N
Cochran-Armitage Trend Test (d)	P=0.244N		
Fisher Exact Test (d)		P=0.329N	P=0.329N
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	22/49 (45%)	20/50 (40%)	18/50 (36%)
Adjusted Rates (b)	58.5%	54.4%	40.5%
Terminal Rates (c)	14/29 (48%)	14/30 (47%)	12/38 (32%)
Week of First Observation	57	63	68
Life Table Tests (d)	P=0.056N	P=0.364N	P=0.072N
Incidental Tumor Tests (d)	P=0.116N	P=0.307N	P=0.140N
Cochran-Armitage Trend Test (d)	P=0.212N		
Fisher Exact Test (d)		P=0.386N	P=0.243N
Adrenal Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/49 (6%)	0/50 (0%)
Adjusted Rates (b)	3.4%	9.3%	0.0%
Terminal Rates (c)	1/29 (3%)	2/29 (7%)	0/38 (0%)
Week of First Observation	104	96	
Life Table Tests (d)	P=0.300N	P=0.316	P=0.446N
Incidental Tumor Tests (d)	P=0.305N	P=0.332	P=0.446N
Cochran-Armitage Trend Test (d)	P=0.379N		
Fisher Exact Test (d)		P=0.301	P=0.500N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	5,000 ppm	10,000 ppm
Adrenal Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	4/49 (8%)	0/50 (0%)
Adjusted Rates (b)	3.4%	12.7%	0.0%
Terminal Rates (c)	1/29 (3%)	3/29 (10%)	0/38 (0%)
Week of First Observation	104	96	
Life Table Tests (d)	P=0.301N	P=0.187	P=0.446N
Incidental Tumor Tests (d)	P=0.305N	P=0.198	P=0.446N
Cochran-Armitage Trend Test (d)	P=0.391N		
Fisher Exact Test (d)		P=0.175	P=0.500N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	4/49 (8%)	5/50 (10%)
Adjusted Rates (b)	2.3%	11.4%	12.4%
Terminal Rates (c)	0/29 (0%)	2/29 (7%)	4/38 (11%)
Week of First Observation	83	84	91
Life Table Tests (d)	P=0.146	P=0.189	P=0.169
Incidental Tumor Tests (d)	P=0.025	P=0.138	P=0.041
Cochran-Armitage Trend Test (d)	P=0.081		
Fisher Exact Test (d)		P=0.175	P=0.102
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	9/50 (18%)	8/50 (16%)	3/50 (6%)
Adjusted Rates (b)	27.5%	25.4%	7.9%
Terminal Rates (c)	6/29 (21%)	7/30 (23%)	3/38 (8%)
Week of First Observation	89	97	104
Life Table Tests (d)	P=0.017N	P=0.463N	P=0.023N
Incidental Tumor Tests (d)	P=0.023N	P=0.442N	P=0.037N
Cochran-Armitage Trend Test (d)	P=0.053N		
Fisher Exact Test (d)		P=0.500N	P=0.061N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	10/50 (20%)	5/50 (10%)
Adjusted Rates (b)	27.5%	31.9%	13.2%
Terminal Rates (c)	6/29 (21%)	9/30 (30%)	5/38 (13%)
Week of First Observation	89	97	104
Life Table Tests (d)	P=0.062N	P=0.539	P=0.083N
Incidental Tumor Tests (d)	P=0.079N	P=0.559	P=0.122N
Cochran-Armitage Trend Test (d)	P=0.170N		
Fisher Exact Test (d)		P=0.500	P=0.194N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	13/50 (26%)	13/50 (26%)	15/50 (30%)
Adjusted Rates (b)	37.2%	36.1%	32.4%
Terminal Rates (c)	8/29 (28%)	8/30 (27%)	8/38 (21%)
Week of First Observation	55	80	62
Life Table Tests (d)	P=0.422N	P=0.537N	P=0.465N
Incidental Tumor Tests (d)	P=0.463	P=0.482N	P=0.464
Cochran-Armitage Trend Test (d)	P=0.368		
Fisher Exact Test (d)		P=0.590N	P=0.412
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	9.8%	0.0%	0.0%
Terminal Rates (c)	2/29 (7%)	0/30 (0%)	0/38 (0%)
Week of First Observation	101		
Life Table Tests (d)	P=0.026N	P=0.117N	P=0.081N
Incidental Tumor Tests (d)	P=0.026N	P=0.102N	P=0.085N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	5,000 ppm	10,000 ppm
Clitoral Gland: Adenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	17.2%	10.0%	7.9%
Terminal Rates (c)	5/29 (17%)	3/30 (10%)	3/38 (8%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.165N	P=0.334N	P=0.217N
Incidental Tumor Tests (d)	P=0.165N	P=0.334N	P=0.217N
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test (d)		P=0.357N	P=0.357N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	19.3%	16.7%	7.9%
Terminal Rates (c)	5/29 (17%)	5/30 (17%)	3/38 (8%)
Week of First Observation	85	104	104
Life Table Tests (d)	P=0.098N	P=0.475N	P=0.133N
Incidental Tumor Tests (d)	P=0.124N	P=0.492N	P=0.191N
Cochran-Armitage Trend Test (d)	P=0.195N		
Fisher Exact Test (d)		P=0.500N	P=0.243N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	10/50 (20%)	5/49 (10%)	14/50 (28%)
Adjusted Rates (b)	30.8%	15.6%	35.6%
Terminal Rates (c)	8/29 (28%)	3/30 (10%)	13/38 (34%)
Week of First Observation	78	102	92
Life Table Tests (d)	P=0.406	P=0.121N	P=0.499
Incidental Tumor Tests (d)	P=0.306	P=0.112N	P=0.354
Cochran-Armitage Trend Test (d)	P=0.188		
Fisher Exact Test (d)		P=0.140N	P=0.241
Uterus: Endometrial Stromal Sarcoma			
Overall Rates (a)	3/50 (6%)	0/49 (0%)	0/50 (0%)
Adjusted Rates (b)	8.2%	0.0%	0.0%
Terminal Rates (c)	1/29 (3%)	0/30 (0%)	0/38 (0%)
Week of First Observation	84		
Life Table Tests (d)	P=0.029N	P=0.119N	P=0.092N
Incidental Tumor Tests (d)	P=0.073N	P=0.144N	P=0.285N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.125N	P=0.121N
Uterus: Sarcoma or Endometrial Stromal Sarcoma			
Overall Rates (a)	3/50 (6%)	1/49 (2%)	0/50 (0%)
Adjusted Rates (b)	8.2%	2.1%	0.0%
Terminal Rates (c)	1/29 (3%)	0/30 (0%)	0/38 (0%)
Week of First Observation	84	70	
Life Table Tests (d)	P=0.050N	P=0.297N	P=0.092N
Incidental Tumor Tests (d)	P=0.109N	P=0.316N	P=0.285N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test (d)		P=0.316N	P=0.121N
Brain: Astrocytoma			
Overall Rates (a)	3/50 (6%)	0/49 (0%)	0/50 (0%)
Adjusted Rates (b)	7.6%	0.0%	0.0%
Terminal Rates (c)	1/29 (3%)	0/30 (0%)	0/38 (0%)
Week of First Observation	78		
Life Table Tests (d)	P=0.033N	P=0.122N	P=0.105N
Incidental Tumor Tests (d)	P=0.050N	P=0.124N	P=0.178N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.125N	P=0.121N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	5,000 ppm	10,000 ppm
Brain: Astrocytoma or Oligodendroglioma			
Overall Rates (a)	3/50 (6%)	2/49 (4%)	0/50 (0%)
Adjusted Rates (b)	7.6%	5.0%	0.0%
Terminal Rates (c)	1/29 (3%)	0/30 (0%)	0/38 (0%)
Week of First Observation	78	53	
Life Table Tests (d)	P=0.070N	P=0.491N	P=0.105N
Incidental Tumor Tests (d)	P=0.093N	P=0.450N	P=0.178N
Cochran-Armitage Trend Test (d)	P=0.083N		
Fisher Exact Test (d)		P=0.510N	P=0.121N
All Sites: Benign Tumors			
Overall Rates (a)	38/50 (76%)	37/50 (74%)	38/50 (76%)
Adjusted Rates (b)	94.9%	90.1%	77.5%
Terminal Rates (c)	27/29 (93%)	26/30 (87%)	27/38 (71%)
Week of First Observation	55	63	62
Life Table Tests (d)	P=0.050N	P=0.390N	P=0.067N
Incidental Tumor Tests (d)	P=0.118N	P=0.246N	P=0.157N
Cochran-Armitage Trend Test (d)	P=0.546N		
Fisher Exact Test (d)		P=0.500N	P=0.592
All Sites: Malignant Tumors			
Overall Rates (a)	27/50 (54%)	30/50 (60%)	17/50 (34%)
Adjusted Rates (b)	60.1%	63.2%	40.2%
Terminal Rates (c)	12/29 (41%)	13/30 (43%)	13/38 (34%)
Week of First Observation	26	53	92
Life Table Tests (d)	P=0.008N	P=0.448	P=0.008N
Incidental Tumor Tests (d)	P=0.173N	P=0.215	P=0.183N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.343	P=0.035N
All Sites: All Tumors			
Overall Rates (a)	49/50 (98%)	48/50 (96%)	42/50 (84%)
Adjusted Rates (b)	98.0%	96.0%	84.0%
Terminal Rates (c)	28/29 (97%)	28/30 (93%)	30/38 (79%)
Week of First Observation	26	53	62
Life Table Tests (d)	P=0.003N	P=0.388N	P=0.004N
Incidental Tumor Tests (d)	P=0.017N	P=0.512N	P=0.043N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.500N	P=0.016N

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

TABLE B4a. HISTORICAL INCIDENCE OF ORAL CAVITY SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls
Historical Incidence at Physiological Research Laboratories	0/150
Overall Historical Incidence	(b) 1/1,984 (0.05%)

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Squamous cell carcinoma of the tongue observed in the rotenone study

TABLE B4b. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls	
	Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence at Physiological Research Laboratories		
Ephedrine sulfate	1/49	1/49
Phenylephrine hydrochloride	6/50	6/50
Oxytetracycline hydrochloride	6/50	6/50
TOTAL	13/149 (8.7%)	13/149 (8.7%)
SD (b)	5.75%	5.75%
Range (c)		
High	6/50	6/50
Low	1/49	1/49
Overall Historical Incidence		
TOTAL	92/1,966 (4.7%)	98/1,966 (5.0%)
SD (b)	3.69%	3.57%
Range (c)		
High	8/50	8/50
Low	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, NOS			1 (2%)
Inflammation, focal	1 (2%)		
Hyperkeratosis	1 (2%)		
Polypoid hyperplasia			1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
#Tracheal submucosa	(50)	(50)	(50)
Cyst, NOS	1 (2%)	2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate			1 (2%)
#Lung	(49)	(49)	(49)
Atelectasis	2 (4%)		
Congestion, NOS		2 (4%)	
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)	4 (8%)	1 (2%)
Lymphocytic inflammatory infiltrate	4 (8%)		4 (8%)
Inflammation, interstitial			1 (2%)
Inflammation, acute focal		1 (2%)	
Inflammation, chronic focal			2 (4%)
Hyperplasia, adenomatous	1 (2%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Atrophy, focal	1 (2%)		
Myelofibrosis		2 (4%)	2 (4%)
Hyperplasia, hematopoietic	25 (50%)	21 (42%)	13 (26%)
Hyperplasia, reticulum cell	10 (20%)	14 (28%)	25 (50%)
#Spleen	(48)	(49)	(50)
Inflammation, granulomatous			1 (2%)
Granuloma, NOS		1 (2%)	2 (4%)
Scar			2 (4%)
Infarct, NOS	1 (2%)		
Hemosiderosis	7 (15%)	5 (10%)	9 (18%)
Hematopoiesis	3 (6%)		
#Splenic capsule	(48)	(49)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, chronic		1 (2%)	
#Lymph node	(45)	(45)	(49)
Dilatation/sinus	1 (2%)	2 (4%)	
Hemorrhage	2 (4%)	3 (7%)	3 (6%)
Inflammation, granulomatous			1 (2%)
Hemosiderosis	2 (4%)		
Histiocytosis		1 (2%)	
#Mandibular lymph node	(45)	(45)	(49)
Dilatation/sinus		4 (9%)	
Cyst, NOS			3 (6%)
Pigmentation, NOS			1 (2%)
Histiocytosis	1 (2%)	2 (4%)	
Hyperplasia, lymphoid	2 (4%)		2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(45)	(45)	(49)
Dilatation/sinus			1 (2%)
Inflammation, chronic		1 (2%)	
Histiocytosis		1 (2%)	
#Thymus	(42)	(35)	(41)
Dilatation/sinus	1 (2%)		
Cyst, NOS	1 (2%)		1 (2%)
Hypertrophy, NOS	1 (2%)		
Hyperplasia, epithelial	1 (2%)	3 (9%)	1 (2%)
Hyperplasia, lymphoid	2 (5%)		
CIRCULATORY SYSTEM			
#Spleen	(48)	(49)	(50)
Arteriosclerosis, NOS		1 (2%)	
#Lung	(49)	(49)	(49)
Thrombus, fibrin		1 (2%)	
#Heart	(50)	(50)	(50)
Atrophy, diffuse			1 (2%)
#Heart/atrium	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
#Myocardium	(50)	(50)	(50)
Fibrosis, focal		2 (4%)	
Degeneration, NOS	47 (94%)	44 (88%)	47 (94%)
#Mitral valve	(50)	(50)	(50)
Degeneration, mucoid	1 (2%)	1 (2%)	2 (4%)
*Artery	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
Degeneration, mucoid			1 (2%)
Metaplasia, cartilaginous	1 (2%)	1 (2%)	2 (4%)
*Aorta	(50)	(50)	(50)
Metaplasia, cartilaginous	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Edema, NOS		1 (2%)	
#Hepatic sinusoid	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(49)	(49)
Cystic ducts	1 (2%)		
Inflammation, focal	1 (2%)	1 (2%)	2 (4%)
Inflammation, suppurative			1 (2%)
Basophilic cyto change	1 (2%)		
Atrophy, focal	4 (8%)	3 (6%)	5 (10%)
Atrophy, diffuse		1 (2%)	
Hyperplasia, focal			2 (4%)
#Liver	(50)	(50)	(50)
Accessory structure	5 (10%)	5 (10%)	10 (20%)
Congestion, NOS	1 (2%)	1 (2%)	
Inflammation, acute focal		2 (4%)	
Granuloma, NOS	18 (36%)	27 (54%)	43 (86%)
Degeneration, cystic	1 (2%)		
Angiectasis	1 (2%)		1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
#Liver/periportal	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	1 (2%)
Atrophy, NOS	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver/hepatocytes	(50)	(50)	(50)
Necrosis, central		1 (2%)	
Cytoplasmic vacuolization	3 (6%)	5 (10%)	2 (4%)
Focal cellular change	42 (84%)	38 (76%)	36 (72%)
Regenerative nodule	2 (4%)	4 (8%)	2 (4%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	34 (68%)	36 (72%)	38 (76%)
#Pancreas	(49)	(49)	(50)
Cystic ducts		2 (4%)	
Lymphocytic inflammatory infiltrate			2 (4%)
Inflammation, interstitial		1 (2%)	1 (2%)
Inflammation, chronic focal	1 (2%)		
Fibrosis, focal		1 (2%)	
Cytoplasmic vacuolization			1 (2%)
Atrophy, focal	22 (45%)	18 (37%)	16 (32%)
Atrophy, diffuse		2 (4%)	1 (2%)
#Glandular stomach	(49)	(50)	(50)
Cyst, NOS	21 (43%)	23 (46%)	24 (48%)
Edema, NOS	1 (2%)		
Erosion	1 (2%)		
#Stomach wall	(49)	(50)	(50)
Inflammation, chronic			1 (2%)
#Forestomach	(49)	(50)	(50)
Edema, NOS	3 (6%)	2 (4%)	
Ulcer, NOS	1 (2%)		
Hyperplasia, epithelial		2 (4%)	1 (2%)
Hyperkeratosis		1 (2%)	2 (4%)
#Duodenum	(49)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
#Colon	(49)	(47)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Hydronephrosis		1 (2%)	
Congestion, NOS		1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, interstitial		1 (2%)	
Scar			1 (2%)
Nephropathy	37 (76%)	36 (72%)	27 (54%)
#Kidney/tubule	(49)	(50)	(50)
Degeneration, NOS	6 (12%)	8 (16%)	8 (16%)
Hyperplasia, epithelial		1 (2%)	
#Kidney/pelvis	(49)	(50)	(50)
Mineralization	1 (2%)		
#Urinary bladder	(47)	(48)	(48)
Edema, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, hemorrhagic	1 (2%)		
Hyperplasia, epithelial		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
#Anterior pituitary	(49)	(50)	(50)
Cyst, NOS	28 (57%)	34 (68%)	35 (70%)
Hemorrhagic cyst		1 (2%)	
Necrosis, focal	1 (2%)		
Hyperplasia, focal	6 (12%)	11 (22%)	10 (20%)
Angiectasis	2 (4%)	1 (2%)	2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal/capsule	(50)	(49)	(50)
Hyperplasia, focal			1 (2%)
#Adrenal cortex	(50)	(49)	(50)
Ectopia		1 (2%)	
Congestion, NOS		1 (2%)	
Hemorrhage			1 (2%)
Necrosis, focal	1 (2%)	1 (2%)	
Cytoplasmic vacuolization	5 (10%)	3 (6%)	6 (12%)
Hypertrophy, focal	19 (38%)	14 (29%)	20 (40%)
Hyperplasia, focal	30 (60%)	24 (49%)	28 (56%)
Angiectasis	3 (6%)	4 (8%)	1 (2%)
#Adrenal medulla	(50)	(49)	(50)
Ectopia			1 (2%)
Necrosis, focal		1 (2%)	
Hyperplasia, focal	6 (12%)	4 (8%)	5 (10%)
Hyperplasia, diffuse			1 (2%)
#Thyroid	(50)	(50)	(50)
Ultimobranchial cyst	2 (4%)		
Hyperplasia, C-cell	21 (42%)	24 (48%)	23 (46%)
Hyperplasia, follicular cell	1 (2%)		
#Thyroid follicle	(50)	(50)	(50)
Ultimobranchial cyst		1 (2%)	
#Pancreatic islets	(49)	(49)	(50)
Atrophy, NOS		1 (2%)	
Hypertrophy, NOS	1 (2%)	3 (6%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	5 (10%)	5 (10%)	2 (4%)
Inflammation, chronic focal			4 (8%)
Inflammation, chronic diffuse			1 (2%)
Hyperplasia, cystic	27 (54%)	32 (64%)	21 (42%)
*Mammary duct	(50)	(50)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	
Inflammation, chronic suppurative	1 (2%)		
Fibrosis	2 (4%)		
*Endometrial cavity	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
*Clitoral gland	(50)	(50)	(50)
Cystic ducts	1 (2%)	1 (2%)	
Inflammation, suppurative			1 (2%)
Inflammation, chronic suppurative	1 (2%)		
Atrophy, diffuse			1 (2%)
#Uterus	(50)	(49)	(50)
Dilatation, NOS	3 (6%)	4 (8%)	5 (10%)
Hemosiderosis	1 (2%)		
Decidual alteration, NOS	2 (4%)		
#Uterus/endometrium	(50)	(49)	(50)
Cyst, NOS	1 (2%)	1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute diffuse	1 (2%)		
Inflammation, chronic	1 (2%)		
Inflammation, chronic suppurative	1 (2%)		
Hyperplasia, cystic	1 (2%)	3 (6%)	6 (12%)
#Endometrial gland	(50)	(49)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	4 (8%)
#Fallopian tube	(50)	(49)	(50)
Cyst, NOS		1 (2%)	1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Ovary	(49)	(49)	(50)
Cyst, NOS	2 (4%)	5 (10%)	3 (6%)
Follicular cyst, NOS	2 (4%)	6 (12%)	6 (12%)
Parovarian cyst	2 (4%)	1 (2%)	2 (4%)
Lymphocytic inflammatory infiltrate			1 (2%)
Necrosis, focal			1 (2%)
Atrophy, diffuse	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(49)	(50)
Hemorrhage		2 (4%)	
Metaplasia, osseous	1 (2%)		
#Lateral ventricle	(50)	(49)	(50)
Dilatation, NOS		1 (2%)	2 (4%)
Hemorrhage			1 (2%)
#Third ventricle	(50)	(49)	(50)
Dilatation, NOS			2 (4%)
Hemorrhage		1 (2%)	
#Fourth ventricle	(50)	(49)	(50)
Dilatation, NOS		1 (2%)	
#Brain	(50)	(49)	(50)
Spongiosis	1 (2%)	4 (8%)	3 (6%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Inflammation, granulomatous	1 (2%)		
Gliosis	1 (2%)		1 (2%)
Degeneration, myelin			1 (2%)
Atrophy, pressure	1 (2%)		2 (4%)
#Brain stem	(50)	(49)	(50)
Atrophy, pressure	6 (12%)	6 (12%)	3 (6%)
#Medulla oblongata	(50)	(49)	(50)
Inflammation, focal	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Inflammation, chronic diffuse		4 (8%)	1 (2%)
*Eye/iris	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Synechia, anterior		1 (2%)	
Synechia, posterior		5 (10%)	1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Mineralization	1 (2%)	4 (8%)	1 (2%)
Cataract	1 (2%)	19 (38%)	4 (8%)
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
Atrophy, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Dyschondroplasia	1 (2%)		
*Skeletal muscle	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Necrosis, fat	6 (12%)	3 (6%)	8 (16%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
Hyperplasia, cystic		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	3 (6%)	3 (6%)	6 (12%)
Fibrosarcoma	12 (24%)	†7 (14%)	5 (10%)
Lipoma		1 (2%)	
Neurofibrosarcoma	1 (2%)		
Neurilemoma		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	4 (8%)	2 (4%)	4 (8%)
Alveolar/bronchiolar carcinoma	2 (4%)	3 (6%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undifferentiated type	1 (2%)		
Malignant lymphoma, histiocytic type	1 (2%)		
Malignant lymphoma, mixed type	4 (8%)	1 (2%)	3 (6%)
#Spleen	(50)	(49)	(50)
Malignant lymphoma, undifferentiated type		1 (2%)	
Malignant lymphoma, mixed type	2 (4%)	1 (2%)	1 (2%)
#Lung	(50)	(50)	(50)
Malignant lymphoma, histiocytic type	1 (2%)		
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Spleen	(50)	(49)	(50)
Hemangiosarcoma			1 (2%)
#Myocardium	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(50)	(50)
Hemangioma	1 (2%)	1 (2%)	
Hemangiosarcoma	2 (4%)	1 (2%)	2 (4%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Fibrosarcoma, metastatic		1 (2%)	
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	8 (16%)	6 (12%)	7 (14%)
Hepatocellular carcinoma	8 (16%)	3 (6%)	5 (10%)
Lipoma			1 (2%)
#Duodenum	(48)	(45)	(48)
Carcinoma, NOS			1 (2%)
URINARY SYSTEM			
None			

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
#Adrenal	(49)	(48)	(48)
Cortical adenoma		1 (2%)	
#Adrenal/capsule	(49)	(48)	(48)
Adenoma, NOS			1 (2%)
#Adrenal medulla	(49)	(48)	(48)
Pheochromocytoma	3 (6%)	1 (2%)	2 (4%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(49)	(49)	(50)
Follicular cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	1 (2%)
Adenoma, NOS	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Pleura	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
Diaphragm			
Alveolar/bronchiolar carcinoma, metastatic		1	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	8	2
Moribund sacrifice	11	10	8
Terminal sacrifice	34	32	40
TUMOR SUMMARY			
Total animals with primary tumors**	37	26	29
Total primary tumors	60	38	41
Total animals with benign tumors	16	15	19
Total benign tumors	21	19	22
Total animals with malignant tumors	30	15	17
Total malignant tumors	39	19	19
Total animals with secondary tumors##		2	1
Total secondary tumors		3	1

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: UNTREATED CONTROL

ANIMAL NUMBER	15 00	10 06	10 21	11 11	11 19	12 11	10 01	10 03	11 12	14 46	12 99	14 44	10 04	12 66	13 32	14 22	10 05	10 07	10 08	10 09	11 00	11 13	11 14	11 15	11 16
WEEKS ON STUDY	04 33	05 44	07 33	08 11	08 11	08 44	08 88	09 30	09 55	09 97	09 99	10 00	10 11	10 11	10 33	10 33	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma									X									X							
Fibrosarcoma				X	X			X			X	X		X											
Hemangiosarcoma						X																			
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar carcinoma									X																
Malignant lymphoma, histiocytic type									X																
Trachea	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	+	+	+	+	−	+	+	−	−	−	−	+	+	+	+	+	−	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X				X		X						X						
Hepatocellular carcinoma			X	X					X				X		X							X		X	
Hemangioma							X																		
Hemangiosarcoma			X																						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X								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	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																					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, undifferentiated type									X																
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 C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	117	118	120	122	123	124	125	127	128	130	131	133	134	135	136	137	138	139	140	141	143	145	147	148	149	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 carcinoma																					X					1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS		X																								1
Fibroma																							X			3
Fibrosarcoma	X		X				X		X								X						X			12
Hemangiosarcoma																										1
Neurofibrosarcoma									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X						X		X				4
Alveolar/bronchiolar carcinoma		X																								2
Malignant lymphoma, histiocytic type																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type															X					X						2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Thymus	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X				X												X	X						8
Hepatocellular carcinoma																	X									8
Hemangioma																										1
Hemangiosarcoma				X																						2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma							X																			3
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	−	−	+	+	−	+	+	−	−	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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																		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
Mal. lymphoma, undifferentiated type																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type											X		X													4

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: LOW DOSE

ANIMAL NUMBER	02 20	04 43	00 09	00 06	00 03	01 10	01 13	01 14	01 15	03 32	03 35	04 41	02 24	01 21	00 07	02 22	01 18	00 01	00 02	00 04	00 05	00 08	01 11	01 16	01 17
WEEKS ON STUDY	02 77	04 77	04 99	07 11	07 73	07 79	08 44	08 44	08 44	08 85	08 85	09 00	09 94	09 96	09 99	09 99	10 00	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								X	
Fibrosarcoma				X						@X	X		X	X	X	X									
Lipoma																									
Neurilemoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																			X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, undifferentiated type				X																					
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	+	+	+	−	+	−	−	+	−	−	+	−	−	−	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																				X			X		
Hepatocellular carcinoma												X				X									
Hemangioma																									
Hemangiosarcoma																	X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Cortical adenoma																									
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	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Carcinoma, NOS																									
Adenoma, NOS					X																				
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic																									
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, mixed type																						X			
Diaphragm, NOS																									
Alveolar/bronchiolar carcinoma, metastatic																									

@: Multiple occurrence of morphology

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0119	0211	0233	0255	0266	0277	0288	0299	0301	0311	0333	0344	0366	0377	0388	0399	0400	0422	0444	0445	0466	0477	0488	0499	0500	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																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma											X	X														3
Fibrosarcoma																										7
Lipoma																	X									1
Neurilemoma				X																						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X						X															2
Alveolar/bronchiolar carcinoma						X																			X	3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mal. lymphoma, undifferentiated type																										1
Malignant lymphoma, mixed type						X																				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	−	+	+	−	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X																	X						X	6
Hepatocellular carcinoma	X																									3
Hemangioma																					X					1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma																									X	1
Pheochromocytoma		X																								1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																	X									1
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	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																			X							1
Adenoma, NOS																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, meta																									X	1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type																										1
Diaphragm, NOS																										
Alveolar/bronchiolar carcinoma, meta																									X	1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: HIGH DOSE

ANIMAL NUMBER	0069	0078	0071	0060	0099	0091	0052	0068	0092	0075	0051	0053	0054	0055	0056	0057	0058	0059	0061	0062	0063	0064	0065	0066	0067
WEEKS ON STUDY	004	071	073	075	080	082	083	085	088	096	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma							X					X													
Fibrosarcoma			X			X			X											X					
Neurilemoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic								X																	
Alveolar/bronchiolar adenoma			X																			X			X
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Malignant lymphoma, mixed type																									
Lymph nodes	−	+	+	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X														X	X				X	
Hepatocellular carcinoma					X		X	X															X		
Lipoma												X													
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Parathyroid	−	−	+	+	−	+	−	−	+	−	+	+	+	+	+	−	+	−	−	−	+	+	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0701	0712	0713	0714	0716	0717	0719	0801	0802	0803	0804	0805	0806	0807	0808	0809	0901	0903	0904	0905	0906	0907	0908	1000	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma	X																				X	X	X		6
Fibrosarcoma			X																						5
Neurilemoma																									1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																									1
Alveolar/bronchiolar adenoma	X																								4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																	1
Malignant lymphoma, mixed type		X																							1
Lymph nodes	+	+	+	+	+	−	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	42
Thymus	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	−	−	39
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma														X							X			X	7
Hepatocellular carcinoma			X																						5
Lipoma																									1
Hemangiosarcoma									X											X					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																	X								1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS								X																	1
Pheochromocytoma						X													X						2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	+	+	−	+	+	−	+	+	+	−	−	−	+	+	+	+	+	−	−	+	+	31
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
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	*50
Carcinoma, NOS																								X	1
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type	X																X	X							3

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Control	2,500 ppm	5,000 ppm
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	8.1%	9.1%	14.5%
Terminal Rates (c)	2/34 (6%)	3/33 (9%)	5/40 (13%)
Week of First Observation	95	104	83
Life Table Tests (d)	P=0.240	P=0.641	P=0.308
Incidental Tumor Tests (d)	P=0.185	P=0.606	P=0.223
Cochran-Armitage Trend Test (d)	P=0.178		
Fisher Exact Test (d)		P=0.661	P=0.243
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	12/50 (24%)	7/50 (14%)	5/50 (10%)
Adjusted Rates (b)	28.8%	16.7%	11.2%
Terminal Rates (c)	6/34 (18%)	0/33 (0%)	2/40 (5%)
Week of First Observation	81	71	73
Life Table Tests (d)	P=0.043N	P=0.221N	P=0.050N
Incidental Tumor Tests (d)	P=0.146N	P=0.221N	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.154N	P=0.054N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	(e) 13/50 (26%)	7/50 (14%)	5/50 (10%)
Adjusted Rates (b)	31.3%	16.7%	11.2%
Terminal Rates (c)	7/34 (21%)	0/33 (0%)	2/40 (5%)
Week of First Observation	81	71	73
Life Table Tests (d)	P=0.026N	P=0.164N	P=0.031N
Incidental Tumor Tests (d)	P=0.089N	P=0.156N	P=0.070N
Cochran-Armitage Trend Test (d)	P=0.022N		
Fisher Exact Test (d)		P=0.105N	P=0.033N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	14/50 (28%)	10/50 (20%)	11/50 (22%)
Adjusted Rates (b)	32.9%	24.3%	24.6%
Terminal Rates (c)	7/34 (21%)	3/33 (9%)	7/40 (18%)
Week of First Observation	81	71	73
Life Table Tests (d)	P=0.236N	P=0.323N	P=0.259N
Incidental Tumor Tests (d)	P=0.539	P=0.364N	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.277N		
Fisher Exact Test (d)		P=0.241N	P=0.322N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	(e) 15/50 (30%)	10/50 (20%)	11/50 (22%)
Adjusted Rates (b)	35.4%	24.3%	24.6%
Terminal Rates (c)	8/34 (24%)	3/33 (9%)	7/40 (18%)
Week of First Observation	81	71	73
Life Table Tests (d)	P=0.175N	P=0.255N	P=0.194N
Incidental Tumor Tests (d)	P=0.456N	P=0.279N	P=0.405N
Cochran-Armitage Trend Test (d)	P=0.206N		
Fisher Exact Test (d)		P=0.178N	P=0.247N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	11.0%	6.1%	9.4%
Terminal Rates (c)	3/34 (9%)	2/33 (6%)	3/40 (7%)
Week of First Observation	97	104	73
Life Table Tests (d)	P=0.509N	P=0.359N	P=0.576N
Incidental Tumor Tests (d)	P=0.570N	P=0.394N	P=0.632
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.339N	P=0.643

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	2,500 ppm	5,000 ppm
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.3%	9.1%	0.0%
Terminal Rates (c)	1/34 (3%)	3/33 (9%)	0/40 (0%)
Week of First Observation	95	104	
Life Table Tests (d)	P=0.175N	P=0.478	P=0.224N
Incidental Tumor Tests (d)	P=0.248N	P=0.437	P=0.405N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	16.0%	15.2%	9.4%
Terminal Rates (c)	4/34 (12%)	5/33 (15%)	3/40 (7%)
Week of First Observation	95	104	73
Life Table Tests (d)	P=0.242N	P=0.533N	P=0.307N
Incidental Tumor Tests (d)	P=0.337N	P=0.590N	P=0.476N
Cochran-Armitage Trend Test (d)	P=0.309N		
Fisher Exact Test (d)		P=0.500N	P=0.370N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	6/50 (12%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	16.8%	6.1%	10.0%
Terminal Rates (c)	5/34 (15%)	2/33 (6%)	4/40 (10%)
Week of First Observation	97	104	104
Life Table Tests (d)	P=0.221N	P=0.148N	P=0.283N
Incidental Tumor Tests (d)	P=0.278N	P=0.167N	P=0.374N
Cochran-Armitage Trend Test (d)	P=0.290N		
Fisher Exact Test (d)		P=0.135N	P=0.371N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	8/50 (16%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	21.0%	8.1%	10.0%
Terminal Rates (c)	5/34 (15%)	2/33 (6%)	4/40 (10%)
Week of First Observation	95	71	104
Life Table Tests (d)	P=0.091N	P=0.124N	P=0.128N
Incidental Tumor Tests (d)	P=0.181N	P=0.165N	P=0.327N
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Test (d)		P=0.100N	P=0.179N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	7.1%	2.9%	7.5%
Terminal Rates (c)	1/34 (3%)	0/33 (0%)	3/40 (7%)
Week of First Observation	73	100	104
Life Table Tests (d)	P=0.552N	P=0.329N	P=0.614N
Incidental Tumor Tests (d)	P=0.576	P=0.310N	P=0.560N
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.309N	P=0.661
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	9.2%	5.9%	7.5%
Terminal Rates (c)	1/34 (3%)	1/33 (3%)	3/40 (7%)
Week of First Observation	73	100	104
Life Table Tests (d)	P=0.379N	P=0.370N	P=0.458N
Incidental Tumor Tests (d)	P=0.413N	P=0.301N	P=0.385N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.339N	P=0.500N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	2,500 ppm	5,000 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	7/50 (14%)
Adjusted Rates (b)	20.9%	18.2%	16.8%
Terminal Rates (c)	5/34 (15%)	6/33 (18%)	6/40 (15%)
Week of First Observation	88	104	80
Life Table Tests (d)	P=0.342N	P=0.426N	P=0.405N
Incidental Tumor Tests (d)	P=0.441N	P=0.438N	P=0.556N
Cochran-Armitage Trend Test (d)	P=0.443N		
Fisher Exact Test (d)		P=0.387N	P=0.500N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	8/50 (16%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	19.3%	8.1%	11.3%
Terminal Rates (c)	3/34 (9%)	1/33 (3%)	2/40 (5%)
Week of First Observation	73	90	80
Life Table Tests (d)	P=0.194N	P=0.136N	P=0.249N
Incidental Tumor Tests (d)	P=0.340N	P=0.137N	P=0.414N
Cochran-Armitage Trend Test (d)	P=0.209N		
Fisher Exact Test (d)		P=0.100N	P=0.277N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	8/50 (16%)	11/50 (22%)
Adjusted Rates (b)	35.5%	22.5%	25.3%
Terminal Rates (c)	8/34 (24%)	6/33 (18%)	8/40 (20%)
Week of First Observation	73	90	80
Life Table Tests (d)	P=0.148N	P=0.117N	P=0.184N
Incidental Tumor Tests (d)	P=0.262N	P=0.109N	P=0.327N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.077N	P=0.247N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/49 (6%)	1/48 (2%)	2/48 (4%)
Adjusted Rates (b)	8.4%	3.1%	5.0%
Terminal Rates (c)	2/34 (6%)	1/32 (3%)	2/40 (5%)
Week of First Observation	101	104	104
Life Table Tests (d)	P=0.345N	P=0.336N	P=0.437N
Incidental Tumor Tests (d)	P=0.442N	P=0.365N	P=0.588N
Cochran-Armitage Trend Test (d)	P=0.408N		
Fisher Exact Test (d)		P=0.316N	P=0.510N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	4/49 (8%)	1/48 (2%)	2/48 (4%)
Adjusted Rates (b)	11.2%	3.1%	5.0%
Terminal Rates (c)	3/34 (9%)	1/32 (3%)	2/40 (5%)
Week of First Observation	101	104	104
Life Table Tests (d)	P=0.195N	P=0.205N	P=0.274N
Incidental Tumor Tests (d)	P=0.261N	P=0.225N	P=0.390N
Cochran-Armitage Trend Test (d)	P=0.246N		
Fisher Exact Test (d)		P=0.187N	P=0.349N
All Sites: Benign Tumors			
Overall Rates (a)	16/50 (32%)	15/50 (30%)	19/50 (38%)
Adjusted Rates (b)	40.2%	43.7%	42.9%
Terminal Rates (c)	11/34 (32%)	14/33 (42%)	15/40 (38%)
Week of First Observation	88	73	73
Life Table Test (d)	P=0.477	P=0.560N	P=0.505
Incidental Tumor Test (d)	P=0.298	P=0.566	P=0.233
Cochran-Armitage Trend Test (d)	P=0.298		
Fisher Exact Test (d)		P=0.500N	P=0.338

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	2,500 ppm	5,000 ppm
All Sites: Malignant Tumors			
Overall Rates (a)	30/50 (60%)	15/50 (30%)	17/50 (34%)
Adjusted Rates (b)	63.8%	35.5%	36.7%
Terminal Rates (c)	17/34 (50%)	6/33 (18%)	11/40 (28%)
Week of First Observation	73	71	73
Life Table Test (d)	P=0.008N	P=0.019N	P=0.009N
Incidental Tumor Test (d)	P=0.036N	P=0.005N	P=0.032N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.003N	P=0.008N
All Sites: All Tumors			
Overall Rates (a)	37/50 (74%)	26/50 (52%)	29/50 (58%)
Adjusted Rates (b)	77.1%	60.3%	61.7%
Terminal Rates (c)	23/34 (68%)	16/33 (48%)	22/40 (55%)
Week of First Observation	73	71	73
Life Table Test (d)	P=0.041N	P=0.096N	P=0.044N
Incidental Tumor Test (d)	P=0.180N	P=0.051N	P=0.178N
Cochran-Armitage Trend Test (d)	P=0.062N		
Fisher Exact Test (d)		P=0.019N	P=0.070N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) A neurofibrosarcoma was observed in an animal with a fibrosarcoma.

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, NOS	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute	2 (4%)		
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Ulcer, chronic		1 (2%)	
Granuloma, foreign body			1 (2%)
Inflammation with fibrosis	1 (2%)		1 (2%)
Fibrosis	1 (2%)		3 (6%)
Exanthematous inflammation	1 (2%)		
Calcification, NOS			1 (2%)
Alopecia		2 (4%)	1 (2%)
Hyperkeratosis	2 (4%)		
*Subcutaneous tissue	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#Trachea	(49)	(50)	(48)
Inflammation, chronic focal		1 (2%)	
#Tracheal gland	(49)	(50)	(48)
Inflammation, acute	1 (2%)		
#Lung/bronchus	(50)	(50)	(50)
Multiple cysts	1 (2%)		
#Lung	(50)	(50)	(50)
Atelectasis			1 (2%)
Congestion, NOS	2 (4%)	5 (10%)	2 (4%)
Hemorrhage	2 (4%)		
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal	3 (6%)		1 (2%)
Fibrosis		1 (2%)	
Perivascular cuffing	3 (6%)	3 (6%)	8 (16%)
Alveolar macrophages	3 (6%)	4 (8%)	1 (2%)
Hyperplasia, adenomatous	2 (4%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	8 (16%)	3 (6%)	7 (14%)
#Bone marrow	(50)	(50)	(50)
Atrophy, NOS			1 (2%)
Hyperplasia, NOS	6 (12%)	2 (4%)	3 (6%)
Angiectasis	1 (2%)		1 (2%)
Hyperplasia, granulocytic	13 (26%)	8 (16%)	11 (22%)
#Spleen	(50)	(49)	(50)
Fibrosis, focal		1 (2%)	
Amyloidosis			1 (2%)
Atrophy, NOS	2 (4%)		2 (4%)
Angiectasis		1 (2%)	1 (2%)
Hyperplasia, reticulum cell	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	11 (22%)	20 (41%)	21 (42%)
Hematopoiesis	20 (40%)	6 (12%)	10 (20%)
#Splenic red pulp	(50)	(49)	(50)
Mastocytosis	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(48)	(48)	(42)
Hemorrhage	2 (4%)		1 (2%)
Hemosiderosis	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Renal lymph node	(48)	(48)	(42)
Hemorrhage		1 (2%)	
Plasmacytosis	1 (2%)		
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid		1 (2%)	
#Lung	(50)	(50)	(50)
Leukocytosis, NOS	3 (6%)	3 (6%)	3 (6%)
Hyperplasia, lymphoid	2 (4%)	3 (6%)	4 (8%)
*Pericardium	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Salivary gland	(50)	(50)	(50)
Hyperplasia, lymphoid	8 (16%)	13 (26%)	13 (26%)
#Liver	(50)	(50)	(50)
Hematopoiesis	3 (6%)		1 (2%)
#Forestomach	(49)	(50)	(50)
Mastocytosis	1 (2%)		
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	15 (30%)	13 (26%)	17 (34%)
#Urinary bladder	(50)	(50)	(50)
Hyperplasia, lymphoid	3 (6%)	4 (8%)	8 (16%)
#Prostate	(50)	(49)	(50)
Hyperplasia, lymphoid	6 (12%)	4 (8%)	5 (10%)
#Thymus	(39)	(36)	(39)
Cyst, NOS	7 (18%)	5 (14%)	4 (10%)
Multiple cysts	3 (8%)	1 (3%)	2 (5%)
Necrosis, NOS	1 (3%)		
Atrophy, NOS	3 (8%)	3 (8%)	
Hyperplasia, epithelial		1 (3%)	2 (5%)
CIRCULATORY SYSTEM			
*Knee	(50)	(50)	(50)
Perivasculitis		1 (2%)	
#Mandibular lymph node	(48)	(48)	(42)
Lymphangiectasis		1 (2%)	
#Myocardium	(50)	(50)	(50)
Fibrosis, focal			1 (2%)
Degeneration, NOS		1 (2%)	1 (2%)
#Pancreas	(49)	(49)	(49)
Perivasculitis			1 (2%)
#Prostate	(50)	(49)	(50)
Perivasculitis	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Atrophy, NOS		4 (8%)	1 (2%)
#Liver	(50)	(50)	(50)
Multiple cysts			1 (2%)
Inflammation, chronic focal		1 (2%)	
Necrosis, focal	6 (12%)	5 (10%)	4 (8%)
Infarct, NOS	1 (2%)		
Metamorphosis, fatty		1 (2%)	
Pigmentation, NOS		1 (2%)	
Focal cellular change	1 (2%)		1 (2%)
#Liver/hepatocytes	(50)	(50)	(50)
Nuclear alteration	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
*Gallbladder	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
*Gallbladder/mucosa	(50)	(50)	(50)
Cyst, NOS		1 (2%)	1 (2%)
Multiple cysts	2 (4%)		1 (2%)
Degeneration, hyaline			2 (4%)
*Gallbladder/mucous gland	(50)	(50)	(50)
Fibrosis	1 (2%)		
#Bile duct	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Hyperplasia, NOS	1 (2%)		
#Pancreas	(49)	(49)	(49)
Inflammation, chronic			1 (2%)
Fibrosis	1 (2%)	1 (2%)	
Lipoidosis			1 (2%)
Atrophy, NOS	1 (2%)		1 (2%)
#Pancreatic acinus	(49)	(49)	(49)
Cytoplasmic vacuolization		3 (6%)	1 (2%)
Hypertrophy, focal		2 (4%)	1 (2%)
#Esophageal submucosa	(48)	(50)	(48)
Perivascular cuffing		1 (2%)	
#Stomach	(49)	(50)	(50)
Granuloma, NOS			1 (2%)
#Glandular stomach	(49)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
Cyst, NOS	3 (6%)	4 (8%)	5 (10%)
Multiple cysts	1 (2%)		
Inflammation, acute/chronic		3 (6%)	1 (2%)
Inflammation, chronic focal	1 (2%)	1 (2%)	5 (10%)
Necrosis, focal		1 (2%)	
Calcification, NOS	2 (4%)		
Hyperplasia, epithelial			1 (2%)
Dysplasia, NOS	1 (2%)		
#Gastric serosa	(49)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
#Forestomach	(49)	(50)	(50)
Cyst, NOS		1 (2%)	1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, chronic focal		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
Hyperkeratosis			1 (2%)
Dysplasia, NOS			2 (4%)
#Duodenal mucosa	(48)	(45)	(48)
Cyst, NOS	1 (2%)		
#Ileal submucosa	(48)	(45)	(48)
Amyloidosis		1 (2%)	
*Rectum	(50)	(50)	(50)
Prolapse	1 (2%)	1 (2%)	1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Mineralization	8 (16%)	7 (14%)	3 (6%)
Hydronephrosis		1 (2%)	
Cyst, NOS	3 (6%)	2 (4%)	
Multiple cysts			1 (2%)
Congestion, NOS			1 (2%)
Glomerulonephritis, acute	1 (2%)	1 (2%)	1 (2%)
Pyelonephritis, acute	1 (2%)		
Inflammation, acute	1 (2%)		
Pyelonephritis, chronic	1 (2%)		
Inflammation, chronic focal		1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney (Continued)	(50)	(50)	(50)
Fibrosis, focal		1 (2%)	
Perivascular cuffing		1 (2%)	
Nephropathy	11 (22%)	12 (24%)	11 (22%)
Atrophy, NOS	3 (6%)	3 (6%)	1 (2%)
Metaplasia, osseous	1 (2%)		
#Kidney/medulla	(50)	(50)	(50)
Necrosis, focal		1 (2%)	
#Renal papilla	(50)	(50)	(50)
Calcification, NOS	1 (2%)		
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis		1 (2%)	
#Convoluted tubules	(50)	(50)	(50)
Degeneration, hyaline	1 (2%)		
Metamorphosis, fatty	1 (2%)		
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
*Ureter	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
#Urinary bladder	(50)	(50)	(50)
Calculus, gross observation only	1 (2%)		
Inflammation, acute	2 (4%)	1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	2 (4%)	1 (2%)	1 (2%)
#Urinary bladder/mucosa	(50)	(50)	(50)
Ulcer, NOS	1 (2%)		
Degeneration, NOS	1 (2%)		
Degeneration, hyaline	1 (2%)		
Hyperplasia, epithelial	1 (2%)	1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(50)
Cyst, NOS	2 (4%)	1 (2%)	4 (8%)
Multiple cysts	1 (2%)	1 (2%)	1 (2%)
Focal cellular change	2 (4%)		2 (4%)
#Adrenal/capsule	(49)	(48)	(48)
Hyperplasia, stromal	28 (57%)	28 (58%)	35 (73%)
#Adrenal cortex	(49)	(48)	(48)
Ectopia	2 (4%)		5 (10%)
Degeneration, lipoid	3 (6%)		2 (4%)
Pigmentation, NOS			1 (2%)
Focal cellular change	1 (2%)		
Hypertrophy, focal	11 (22%)	10 (21%)	18 (38%)
Hyperplasia, focal	3 (6%)	4 (8%)	2 (4%)
#Adrenal medulla	(49)	(48)	(48)
Hyperplasia, focal	4 (8%)	7 (15%)	
#Thyroid	(49)	(49)	(50)
Follicular cyst, NOS	1 (2%)		
Inflammation, chronic focal			1 (2%)
Degeneration, NOS	1 (2%)	1 (2%)	
#Thyroid follicle	(49)	(49)	(50)
Corpora amylacea		1 (2%)	
Atrophy, NOS	1 (2%)		
Hyperplasia, cystic			1 (2%)
#Parathyroid	(32)	(35)	(31)
Ectopia	1 (3%)		
Cyst, NOS		2 (6%)	1 (3%)
Multiple cysts	1 (3%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Prepuce	(50)	(50)	(50)
Impaction, NOS			1 (2%)
Congestion, NOS		1 (2%)	
Ulcer, NOS		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)
Metaplasia, squamous	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	1 (2%)
Multiple cysts	2 (4%)		
Inflammation, NOS	13 (26%)	14 (28%)	9 (18%)
Metaplasia, squamous	16 (32%)	13 (26%)	12 (24%)
#Prostate	(50)	(49)	(50)
Multiple cysts			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, NOS	8 (16%)	13 (27%)	8 (16%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)	4 (8%)	3 (6%)
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)	
#Testis	(50)	(48)	(50)
Inflammation, chronic focal	1 (2%)		
Calcification, NOS	6 (12%)	1 (2%)	2 (4%)
Atrophy, NOS	3 (6%)	2 (4%)	2 (4%)
Hyperplasia, interstitial cell		1 (2%)	1 (2%)
Angiectasis	1 (2%)		
#Testis/tubule	(50)	(48)	(50)
Cytomegaly			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Perivascular cuffing	1 (2%)		
#Brain/thalamus	(50)	(50)	(50)
Calcification, NOS	25 (50%)	25 (50%)	21 (42%)
#Medulla oblongata	(50)	(50)	(50)
Calcification, NOS			1 (2%)
*Sciatic nerve	(50)	(50)	(50)
Inflammation, pyogranulomatous	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Atrophy, NOS		1 (2%)	
Osteosclerosis	3 (6%)	4 (8%)	
*Joint	(50)	(50)	(50)
Dyschondroplasia		1 (2%)	
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
Knee			
Dyschondroplasia	19	15	13
Adipose tissue			
Necrosis, fat	1	3	2
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Tail	(50)	(49)	(50)
Fibrous histiocytoma		1 (2%)	
*Skin	(50)	(49)	(50)
Adenoma, NOS		1 (2%)	
*Subcutaneous tissue	(50)	(49)	(50)
Fibrosarcoma	1 (2%)		
Myxoma		1 (2%)	
Neurilemoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(49)
Alveolar/bronchiolar adenoma	3 (6%)	3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)
Teratoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Malignant lymphoma, NOS	1 (2%)	1 (2%)	
Malignant lymphoma, undifferentiated type		1 (2%)	
Malignant lymphoma, histiocytic type		1 (2%)	1 (2%)
Malignant lymphoma, mixed type	25 (50%)	19 (39%)	26 (52%)
Lymphocytic leukemia		1 (2%)	
#Spleen	(50)	(49)	(50)
Malignant lymphoma, mixed type	3 (6%)		1 (2%)
#Renal lymph node	(45)	(44)	(48)
Teratoma, metastatic			1 (2%)
#Liver	(50)	(49)	(50)
Malignant lymphoma, histiocytic type		1 (2%)	1 (2%)
#Thymus	(41)	(46)	(41)
Thymoma, benign	1 (2%)		
Malignant lymphoma, lymphocytic type		1 (2%)	
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)	
*Subcutaneous tissue	(50)	(49)	(50)
Hemangioma			1 (2%)
#Spleen	(50)	(49)	(50)
Hemangioma		1 (2%)	
Hemangiosarcoma		1 (2%)	
#Myocardium	(50)	(49)	(49)
Hemangiosarcoma	1 (2%)		
#Uterus	(50)	(49)	(50)
Hemangioma		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Hepatocellular adenoma	3 (6%)	5 (10%)	1 (2%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Teratoma, metastatic		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	
Adenoma, NOS	18 (37%)	14 (29%)	14 (28%)
#Adrenal/capsule	(50)	(48)	(50)
Adenoma, NOS	1 (2%)		
#Adrenal medulla	(50)	(48)	(50)
Pheochromocytoma			1 (2%)
#Thyroid	(50)	(48)	(48)
Follicular cell adenoma			1 (2%)
#Pancreatic islets	(49)	(47)	(49)
Islet cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(50)
Adenocarcinoma, NOS	1 (2%)		
Adenosquamous carcinoma			1 (2%)
#Uterus	(50)	(49)	(50)
Leiomyoma	1 (2%)		
Endometrial stromal polyp	1 (2%)		
#Ovary	(48)	(46)	(48)
Luteoma	1 (2%)	1 (2%)	2 (4%)
Granulosa cell tumor	1 (2%)	2 (4%)	2 (4%)
Teratoma, NOS	1 (2%)	1 (2%)	
Teratoma, malignant		1 (2%)	1 (2%)
#Mesovarium	(48)	(46)	(48)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(50)
Carcinoma, NOS		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
ALL OTHER SYSTEMS			
Tail			
Osteosarcoma		1	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	5	2
Moribund sacrifice	7	10	8
Terminal sacrifice	38	34	40
Accidentally killed, NOS		1	
TUMOR SUMMARY			
Total animals with primary tumors**	44	41	39
Total primary tumors	67	63	58
Total animals with benign tumors	24	24	22
Total benign tumors	30	28	22
Total animals with malignant tumors	31	27	31
Total malignant tumors	35	32	34
Total animals with secondary tumors##		1	2
Total secondary tumors		2	3
Total animals with tumors uncertain-- benign or malignant	2	3	2
Total uncertain tumors	2	3	2

* Number of animals receiving complete necropsy examinations; 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 D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: UNTREATED CONTROL

ANIMAL NUMBER	13202	10206	10909	15050	14808	13909	12707	14040	13606	10808	11141	14949	10101	10202	10303	10404	10505	10707	11010	11111	11212	11313	11515	11616	11717
WEEKS ON STUDY	07706	08080	09091	09911	09903	09905	09906	09907	09909	10000	10030	10303	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																								X	
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	–	+	+	+	+	–	–	–	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X									
Hepatocellular carcinoma		X																							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS				X																					
Adenoma, NOS						X					X				X		X		X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	–	+	+	+	+	–	+	–	–	+	–	+	–	+	+	–	+	–	–	+	–	–	–	+
Pancreatic islets	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X						
REPRODUCTIVE SYSTEM																									
Mammary gland	–	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Adenocarcinoma, NOS														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																X									
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma						X																			
Granulosa cell tumor																									
Teratoma, NOS																									
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, NOS		X																							
Malignant lymphoma, mixed type				X	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 D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	118	119	120	121	122	123	124	125	126	128	129	130	131	133	134	135	137	138	141	142	143	144	145	146	147	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																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma			X																							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X				X		X			3
Alveolar/bronchiolar carcinoma											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type												X											X			3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	–	41
Thymoma, benign																	X									1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X												X													3
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS		X		X	X	X		X		X	X	X	X	X			X							X	X	18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																				X						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	–	+	+	–	+	+	–	+	–	+	–	+	–	–	+	+	–	+	+	+	+	+	–	+	+	29
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Endometrial stromal polyp																		X								1
Ovary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Luteoma																										1
Granulosa cell tumor																					X					1
Teratoma, NOS			X																							1
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, NOS																										1
Malignant lymphoma, mixed type	X	X	X			X			X	X	X				X	X	X		X	X		X			X	25

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: LOW DOSE

ANIMAL NUMBER	0110	0129	0007	0115	0446	0603	0009	0032	0228	0400	0001	0447	0004	0618	0336	0311	0002	0005	0006	0008	0111	0112	0113	0114	0116
WEEKS ON STUDY	0009	0289	0599	0733	0889	0990	0900	0903	0933	0936	0997	0999	1000	1001	1013	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Subcutaneous tissue	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myxoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X															X				
Teratoma, metastatic	X																								
Trachea	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma								X																	
Hemangiosarcoma																									
Lymph nodes	–	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Thymus	+	+	+	B	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+
Malignant lymphoma, lymphocytic type														X											
CIRCULATORY SYSTEM																									
Heart	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X						X							
Hepatocellular carcinoma																									
Malignant lymphoma, histiocytic type														X											
Bile duct	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	B	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	B	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Esophagus	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	B	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	B	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma, metastatic	X																								
Urinary bladder	+	–	+	B	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS										X	X								X		X	X			
Adrenal	+	+	+	B	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	–	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	+	–	B	+	+	+	–	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																				X					
Ovary	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Luteoma																									
Granulosa cell tumor														X											
Teratoma, NOS																									
Teratoma, malignant	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	B	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	B	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma						X																			
Malignant lymphoma, NOS																X									
Malignant lymphoma, undifferentiated type												X													
Malignant lymphoma, histiocytic type																				X					
Malignant lymphoma, mixed type					X		X		X				X		X			X					X		
Lymphocytic leukemia																									
Tail				B																					
Fibrous histiocytoma																								X	
Osteosarcoma																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0171	0191	0201	0211	0222	0233	0244	0255	0266	0277	0300	0331	0343	0354	0367	0383	0399	0411	0422	0433	0444	0455	0488	0499	0505	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenoma, NOS																								X		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Myxoma																							X			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																									X	3
Teratoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Hemangiosarcoma					X																					1
Lymph nodes	+	–	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Malignant lymphoma, lymphocytic type																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma				X														X		X						5
Hepatocellular carcinoma																						X				1
Malignant lymphoma, histiocytic type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Teratoma, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS															X											1
Adenoma, NOS	X	X		X		X		X							X	X		X							X	14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	–	+	–	+	+	–	–	+	+	+	–	+	+	+	+	–	–	–	+	–	–	+	+	+	–	31
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Ovary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	46
Luteoma			X																							1
Granulosa cell tumor			X																							2
Teratoma, NOS											X															1
Teratoma, malignant																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Hemangiosarcoma																										1
Malignant lymphoma, NOS																										1
Mal. lymphoma, undifferentiated type																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type	X	X		X	X		X	X			X		X	X	X				X					X		19
Lymphocytic leukemia									X																	1
Tail																										
Fibrous histiocytoma																										1
Osteosarcoma								X																		1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE: HIGH DOSE

ANIMAL NUMBER	0065	0062	0063	0095	0086	0066	0089	0068	0053	0067	0051	0052	0054	0055	0056	0057	0058	0059	0060	0061	0064	0069	0070	0071	0072
WEEKS ON STUDY	0222	0774	0844	0933	0944	0996	0998	1002	1033	1031	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																					X				
Neurilemoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma, metastatic	X																								
Thymus	+	+	+	+	+	−	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma										X															
Malig lymphoma, histiocytic type			X																						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	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
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma											X														
Parathyroid	−	+	−	+	+	+	+	+	−	−	−	−	+	+	+	+	+	+	−	−	+	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenosquamous carcinoma																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic								X																	
Luteoma																									
Granulosa cell tumor																									
Teratoma, malignant	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma NOS												X													
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, 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, histiocytic type							X																		
Malignant lymphoma, mixed type					X	X			X	X		X	X	X		X	X			X	X	X	X		

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	073	074	075	076	077	078	079	080	081	082	083	084	085	087	088	090	091	092	093	094	096	097	098	099	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																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangioma																										1
Neurilemoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																					X					1
Lymph nodes	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Teratoma, metastatic																										1
Thymus	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																			X							1
Hepatocellular carcinoma																										1
Malignant lymphoma, histiocytic type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS					X						X		X		X								X		X	14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X																								1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	48
Follicular cell adenoma																										1
Parathyroid	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	−	−	+	+	+	+	+	−	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenosquamous carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, meta																										1
Luteoma																X					X					2
Granulosa cell tumor															X					X						2
Teratoma, malignant																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, meta																										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, histiocytic type																										1
Malignant lymphoma, mixed type						X			X		X	X	X	X	X	X		X		X		X	X	X		26

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Control	2,500 ppm	5,000 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	1/49 (2%)
Adjusted Rates (b)	7.9%	8.0%	2.6%
Terminal Rates (c)	3/38 (8%)	2/34 (6%)	1/39 (3%)
Week of First Observation	104	90	104
Life Table Tests (d)	P=0.237N	P=0.614	P=0.296N
Incidental Tumor Tests (d)	P=0.267N	P=0.642	P=0.296N
Cochran-Armitage Trend Test (d)	P=0.246N		
Fisher Exact Test (d)		P=0.651	P=0.316N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/49 (6%)	2/49 (4%)
Adjusted Rates (b)	10.5%	8.0%	4.8%
Terminal Rates (c)	4/38 (11%)	2/34 (6%)	1/39 (3%)
Week of First Observation	104	90	102
Life Table Tests (d)	P=0.258N	P=0.557N	P=0.321N
Incidental Tumor Tests (d)	P=0.297N	P=0.530N	P=0.338N
Cochran-Armitage Trend Test (d)	P=0.273N		
Fisher Exact Test (d)		P=0.511N	P=0.349N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	28/50 (56%)	19/49 (39%)	27/50 (54%)
Adjusted Rates (b)	63.3%	48.0%	61.3%
Terminal Rates (c)	22/38 (58%)	14/34 (41%)	23/40 (58%)
Week of First Observation	91	89	94
Life Table Tests (d)	P=0.378N	P=0.154N	P=0.404N
Incidental Tumor Tests (d)	P=0.477N	P=0.097N	P=0.496N
Cochran-Armitage Trend Test (d)	P=0.460N		
Fisher Exact Test (d)		P=0.065N	P=0.500N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	29/50 (58%)	23/49 (47%)	29/50 (58%)
Adjusted Rates (b)	64.1%	54.5%	63.0%
Terminal Rates (c)	22/38 (58%)	15/34 (44%)	23/40 (58%)
Week of First Observation	80	89	84
Life Table Tests (d)	P=0.447N	P=0.347N	P=0.477N
Incidental Tumor Tests (d)	P=0.469	P=0.236N	P=0.499
Cochran-Armitage Trend Test (d)	P=0.540		
Fisher Exact Test (d)		P=0.184N	P=0.580N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	29/50 (58%)	24/49 (49%)	29/50 (58%)
Adjusted Rates (b)	64.1%	56.9%	63.0%
Terminal Rates (c)	22/38 (58%)	16/34 (47%)	23/40 (58%)
Week of First Observation	80	89	84
Life Table Tests (d)	P=0.446N	P=0.417N	P=0.477N
Incidental Tumor Tests (d)	P=0.471	P=0.307N	P=0.499
Cochran-Armitage Trend Test (d)	P=0.540		
Fisher Exact Test (d)		P=0.243N	P=0.580N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	4/49 (8%)	1/50 (2%)
Adjusted Rates (b)	2.1%	10.1%	2.5%
Terminal Rates (c)	0/38 (0%)	2/34 (6%)	1/40 (3%)
Week of First Observation	91	90	104
Life Table Tests (d)	P=0.591N	P=0.156	P=0.757N
Incidental Tumor Tests (d)	P=0.455	P=0.198	P=0.654
Cochran-Armitage Trend Test (d)	P=0.600		
Fisher Exact Test (d)		P=0.175	P=0.753

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	2,500 ppm	5,000 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/50 (6%)	5/49 (10%)	1/50 (2%)
Adjusted Rates (b)	7.9%	14.0%	2.5%
Terminal Rates (c)	3/38 (8%)	4/34 (12%)	1/40 (3%)
Week of First Observation	104	97	104
Life Table Tests (d)	P=0.249N	P=0.298	P=0.287N
Incidental Tumor Tests (d)	P=0.255N	P=0.305	P=0.287N
Cochran-Armitage Trend Test (d)	P=0.264N		
Fisher Exact Test (d)		P=0.346	P=0.309N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	6/49 (12%)	2/50 (4%)
Adjusted Rates (b)	9.8%	16.9%	4.8%
Terminal Rates (c)	3/38 (8%)	5/34 (15%)	1/40 (3%)
Week of First Observation	80	97	103
Life Table Tests (d)	P=0.274N	P=0.307	P=0.320N
Incidental Tumor Tests (d)	P=0.314N	P=0.334	P=0.410N
Cochran-Armitage Trend Test (d)	P=0.291N		
Fisher Exact Test (d)		P=0.357	P=0.339N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	18/49 (37%)	14/49 (29%)	14/50 (28%)
Adjusted Rates (b)	44.8%	38.4%	31.5%
Terminal Rates (c)	16/38 (42%)	12/34 (35%)	10/40 (25%)
Week of First Observation	95	93	93
Life Table Tests (d)	P=0.186N	P=0.393N	P=0.216N
Incidental Tumor Tests (d)	P=0.181N	P=0.352N	P=0.213N
Cochran-Armitage Trend Test (d)	P=0.204N		
Fisher Exact Test (d)		P=0.259N	P=0.238N
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	19/49 (39%)	14/49 (29%)	14/50 (28%)
Adjusted Rates (b)	45.9%	38.4%	31.5%
Terminal Rates (c)	16/38 (42%)	12/34 (35%)	10/40 (25%)
Week of First Observation	91	93	93
Life Table Tests (d)	P=0.139N	P=0.322N	P=0.166N
Incidental Tumor Tests (d)	P=0.144N	P=0.269N	P=0.187N
Cochran-Armitage Trend Test (d)	P=0.149N		
Fisher Exact Test (d)		P=0.196N	P=0.178N
Ovary: Luteoma or Granulosa Cell Tumor			
Overall Rates (a)	2/48 (4%)	2/46 (4%)	4/48 (8%)
Adjusted Rates (b)	4.9%	5.8%	10.0%
Terminal Rates (c)	1/36 (3%)	1/31 (3%)	4/40 (10%)
Week of First Observation	95	100	104
Life Table Tests (d)	P=0.295	P=0.645	P=0.379
Incidental Tumor Tests (d)	P=0.247	P=0.668	P=0.342
Cochran-Armitage Trend Test (d)	P=0.253		
Fisher Exact Test (d)		P=0.675	P=0.339
All Sites: Benign Tumors			
Overall Rates (a)	24/50 (48%)	24/49 (49%)	22/50 (44%)
Adjusted Rates (b)	59.8%	60.9%	49.8%
Terminal Rates (c)	22/38 (58%)	19/34 (56%)	18/40 (45%)
Week of First Observation	95	90	93
Life Table Test (d)	P=0.305N	P=0.374	P=0.335N
Incidental Tumor Test (d)	P=0.367N	P=0.418	P=0.369N
Cochran-Armitage Trend Test (d)	P=0.382N		
Fisher Exact Test (d)		P=0.541	P=0.421N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Control	2,500 ppm	5,000 ppm
All Sites: Malignant Tumors			
Overall Rates (a)	31/50 (62%)	27/49 (55%)	31/50 (62%)
Adjusted Rates (b)	67.0%	61.0%	64.5%
Terminal Rates (c)	23/38 (61%)	17/34 (50%)	23/40 (58%)
Week of First Observation	80	9	22
Life Table Test (d)	P=0.445N	P=0.500N	P=0.474N
Incidental Tumor Test (d)	P=0.484	P=0.290N	P=0.538
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.311N	P=0.582N
All Sites: All Tumors			
Overall Rates (a)	44/50 (88%)	41/49 (84%)	39/50 (78%)
Adjusted Rates (b)	91.6%	87.2%	79.6%
Terminal Rates (c)	34/38 (89%)	28/34 (82%)	30/40 (75%)
Week of First Observation	80	9	22
Life Table Test (d)	P=0.134N	P=0.467	P=0.143N
Incidental Tumor Test (d)	P=0.137N	P=0.429N	P=0.148N
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.371N	P=0.144N

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

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(50)
Ulcer, acute	1 (2%)	1 (2%)	
Hyperkeratosis		1 (2%)	
RESPIRATORY SYSTEM			
#Tracheal gland	(50)	(49)	(49)
Cyst, NOS			1 (2%)
Multiple cysts			1 (2%)
#Lung	(50)	(49)	(49)
Atelectasis		1 (2%)	1 (2%)
Congestion, NOS	2 (4%)		1 (2%)
Hemorrhage	1 (2%)	4 (8%)	2 (4%)
Lymphocytic inflammatory infiltrate	1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)	2 (4%)	
Perivascular cuffing			1 (2%)
Alveolar macrophages	1 (2%)		
Osteophyte	1 (2%)		
Hyperplasia, adenomatous	1 (2%)	3 (6%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Hyperplasia, lymphoid	7 (14%)	6 (12%)	6 (12%)
*Subcutaneous tissue	(50)	(49)	(50)
Mastocytosis	1 (2%)		
#Bone marrow	(50)	(49)	(50)
Cyst, NOS			1 (2%)
Fibrosis, focal	2 (4%)		1 (2%)
Lipoidosis	1 (2%)		
Atrophy, NOS	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, NOS	3 (6%)	3 (6%)	
Angiectasis	1 (2%)	1 (2%)	
Hyperplasia, granulocytic	13 (26%)	6 (12%)	5 (10%)
#Spleen	(50)	(49)	(50)
Inflammation, acute/chronic			1 (2%)
Amyloidosis	1 (2%)		
Hemosiderosis	1 (2%)	1 (2%)	1 (2%)
Leukemoid reaction	1 (2%)		
Hyperplasia, reticulum cell		3 (6%)	2 (4%)
Hyperplasia, lymphoid	11 (22%)	17 (35%)	11 (22%)
Hematopoiesis	9 (18%)	7 (14%)	6 (12%)
#Mandibular lymph node	(45)	(44)	(48)
Hemorrhage		1 (2%)	1 (2%)
Angiectasis	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)		2 (4%)
Mastocytosis		1 (2%)	
#Renal lymph node	(45)	(44)	(48)
Plasmacytosis	1 (2%)		
#Lung	(50)	(49)	(49)
Leukocytosis, NOS		1 (2%)	
Hyperplasia, lymphoid	2 (4%)	3 (6%)	
#Salivary gland	(50)	(49)	(50)
Hyperplasia, lymphoid	3 (6%)	7 (14%)	4 (8%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Liver	(50)	(49)	(50)
Hematopoiesis	2 (4%)		
#Pancreas	(49)	(47)	(49)
Hyperplasia, lymphoid		1 (2%)	
#Kidney	(50)	(49)	(50)
Hyperplasia, lymphoid	9 (18%)	7 (14%)	8 (16%)
#Urinary bladder	(50)	(47)	(48)
Hyperplasia, lymphoid	1 (2%)	9 (19%)	7 (15%)
#Mesovarium	(48)	(46)	(48)
Hyperplasia, lymphoid	1 (2%)		
#Anterior pituitary	(49)	(49)	(50)
Hyperplasia, eosinophilic		1 (2%)	
#Adrenal cortex	(50)	(48)	(50)
Hematopoiesis	2 (4%)		
#Thymus	(41)	(46)	(41)
Cyst, NOS	3 (7%)	5 (11%)	2 (5%)
Multiple cysts	6 (15%)	5 (11%)	8 (20%)
Atrophy, NOS	2 (5%)	1 (2%)	2 (5%)
Hyperplasia, epithelial		2 (4%)	1 (2%)
Hyperplasia, lymphoid	4 (10%)	6 (13%)	1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(49)	(50)
Perivasculitis	1 (2%)		
#Lung/bronchus	(50)	(49)	(49)
Thrombosis, NOS	1 (2%)		
#Myocardium	(50)	(49)	(49)
Fibrosis, focal		1 (2%)	
Perivascular cuffing		1 (2%)	
#Ovary	(48)	(46)	(48)
Thrombosis, NOS	2 (4%)		1 (2%)
#Thyroid	(50)	(48)	(48)
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(50)
Ectopia			1 (2%)
Mineralization		1 (2%)	
Dilatation/ducts		1 (2%)	
Multiple cysts			1 (2%)
Necrosis, focal	1 (2%)		
Atrophy, focal			1 (2%)
#Liver	(50)	(49)	(50)
Ectopia	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Inflammation, acute focal			1 (2%)
Degeneration, NOS	1 (2%)	1 (2%)	
Necrosis, focal	9 (18%)	5 (10%)	8 (16%)
Necrosis, coagulative		1 (2%)	
Metamorphosis, fatty		1 (2%)	1 (2%)
Pigmentation, NOS	1 (2%)		
Basophilic cyto change			1 (2%)
Focal cellular change	1 (2%)		1 (2%)
Clear cell change		1 (2%)	1 (2%)
Hepatocytomegaly	1 (2%)	1 (2%)	
*Gallbladder	(50)	(49)	(50)
Cyst, NOS	1 (2%)	2 (4%)	1 (2%)
Hemosiderosis			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Bile duct	(50)	(49)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Degeneration, hyaline		1 (2%)	
#Pancreas	(49)	(47)	(49)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, chronic			1 (2%)
Atrophy, NOS	3 (6%)	2 (4%)	1 (2%)
#Pancreatic acinus	(49)	(47)	(49)
Cytoplasmic vacuolization		1 (2%)	
Hypertrophy, focal	1 (2%)	1 (2%)	
#Stomach	(49)	(49)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic focal		1 (2%)	
#Glandular stomach	(49)	(49)	(50)
Mineralization		1 (2%)	
Cyst, NOS	3 (6%)	4 (8%)	5 (10%)
Multiple cysts	3 (6%)	3 (6%)	1 (2%)
Inflammation, acute/chronic	1 (2%)	3 (6%)	
Inflammation, chronic	2 (4%)	1 (2%)	
Degeneration, hyaline			1 (2%)
Calcification, NOS	1 (2%)	3 (6%)	2 (4%)
Dysplasia, NOS	1 (2%)		1 (2%)
#Forestomach	(49)	(49)	(50)
Cyst, NOS	1 (2%)		
Multiple cysts	2 (4%)		
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal		1 (2%)	
Erosion	1 (2%)		
Crystals, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Cyst, NOS	1 (2%)	1 (2%)	1 (2%)
Multiple cysts	1 (2%)		
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Glomerulonephritis, acute	1 (2%)	1 (2%)	
Pyelonephritis, acute	1 (2%)		
Glomerulonephritis, subacute	1 (2%)		
Glomerulonephritis, chronic		2 (4%)	
Nephropathy	4 (8%)	3 (6%)	3 (6%)
Nephrosis, NOS			1 (2%)
Nephrosis, hemoglobinuric		1 (2%)	
Calcification, NOS			1 (2%)
Metaplasia, osseous	2 (4%)	2 (4%)	
#Renal papilla	(50)	(49)	(50)
Necrosis, NOS	1 (2%)		
#Perirenal tissue	(50)	(49)	(50)
Inflammation, acute/chronic			1 (2%)
Necrosis, fat			1 (2%)
#Kidney/glomerulus	(50)	(49)	(50)
Amyloidosis	1 (2%)		1 (2%)
#Convoluted tubules	(50)	(49)	(50)
Degeneration, hyaline			4 (8%)
#Kidney/pelvis	(50)	(49)	(50)
Amyloidosis	1 (2%)		
#Urinary bladder	(50)	(47)	(48)
Perivascular cuffing	1 (2%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary	(49)	(49)	(50)
Angiectasis	3 (6%)	1 (2%)	2 (4%)
#Pituitary intermedia	(49)	(49)	(50)
Hyperplasia, focal	1 (2%)		
#Anterior pituitary	(49)	(49)	(50)
Cyst, NOS	2 (4%)	1 (2%)	
Focal cellular change	2 (4%)	2 (4%)	2 (4%)
Hypertrophy, focal		1 (2%)	1 (2%)
Hyperplasia, focal	15 (31%)	14 (29%)	12 (24%)
#Pituitary acidophil cell	(49)	(49)	(50)
Hyperplasia, NOS			1 (2%)
#Pituitary posterior	(49)	(49)	(50)
Gliosis	1 (2%)		
#Adrenal/capsule	(50)	(48)	(50)
Cyst, NOS	1 (2%)		
Hyperplasia, stromal	49 (98%)	44 (92%)	50 (100%)
#Adrenal cortex	(50)	(48)	(50)
Ectopia	6 (12%)	5 (10%)	2 (4%)
Cyst, NOS	1 (2%)		
Degeneration, lipoid	2 (4%)	2 (4%)	1 (2%)
Amyloidosis			1 (2%)
Hypertrophy, focal	3 (6%)	3 (6%)	1 (2%)
Hyperplasia, focal		1 (2%)	1 (2%)
#Adrenal medulla	(50)	(48)	(50)
Focal cellular change			1 (2%)
Hyperplasia, focal		1 (2%)	
#Thyroid	(50)	(48)	(48)
Follicular cyst, NOS			1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		1 (2%)
Hyperplasia, follicular cell			1 (2%)
#Thyroid follicle	(50)	(48)	(48)
Multiple cysts	1 (2%)		
Inflammation, acute	1 (2%)		
Degeneration, NOS			1 (2%)
Hyperplasia, papillary	9 (18%)	6 (13%)	8 (17%)
Hyperplasia, cystic		2 (4%)	1 (2%)
#Parathyroid	(29)	(31)	(34)
Ectopia		1 (3%)	
Cyst, NOS		1 (3%)	1 (3%)
Multiple cysts	1 (3%)		1 (3%)
#Pancreatic islets	(49)	(47)	(49)
Hyperplasia, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(50)
Dilatation/ducts	5 (10%)	7 (14%)	8 (16%)
Cyst, NOS	1 (2%)		
Fibrosis		1 (2%)	
Hyperplasia, NOS		1 (2%)	
*Mammary duct	(50)	(49)	(50)
Dilatation, NOS		1 (2%)	
#Uterus	(50)	(49)	(50)
Dilatation, NOS	2 (4%)	9 (18%)	1 (2%)
Cyst, NOS		1 (2%)	
Pyometra			1 (2%)
#Uterus/endometrium	(50)	(49)	(50)
Multiple cysts	3 (6%)	3 (6%)	2 (4%)
Hemorrhage			1 (2%)
Inflammation, suppurative		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
#Uterus/endometrium (Continued)	(50)	(49)	(50)
Inflammation, acute	1 (2%)		
Hyperplasia, cystic	44 (88%)	38 (78%)	45 (90%)
Hyperplasia, stromal	1 (2%)		
Angiectasis	3 (6%)	2 (4%)	5 (10%)
#Fallopian tube	(50)	(49)	(50)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)		
#Ovary/parovarian	(48)	(46)	(48)
Inflammation, acute/chronic			1 (2%)
#Ovary	(48)	(46)	(48)
Cyst, NOS	6 (13%)	10 (22%)	10 (21%)
Multiple cysts	2 (4%)	3 (7%)	4 (8%)
Hematoma, NOS	5 (10%)	7 (15%)	5 (10%)
Abscess, NOS	3 (6%)		
Calcification, NOS			2 (4%)
Angiectasis	3 (6%)	2 (4%)	2 (4%)
#Mesovarium	(48)	(46)	(48)
Multiple cysts			1 (2%)
Necrosis, fat			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(49)	(50)
Congestion, NOS	1 (2%)		
Hemorrhage		2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Perivascular cuffing	1 (2%)		
#Brain/thalamus	(50)	(49)	(50)
Calcification, NOS	16 (32%)	12 (24%)	18 (36%)
#Cerebellum	(50)	(49)	(50)
Perivascular cuffing		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(49)	(50)
Inflammation, acute		1 (2%)	
*Ear	(50)	(49)	(50)
Hemorrhage	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(49)	(50)
Fibrous osteodystrophy	1 (2%)		
Osteosclerosis	17 (34%)	17 (35%)	17 (34%)
*Skeletal muscle	(50)	(49)	(50)
Necrosis, NOS		1 (2%)	
BODY CAVITIES			
*Pleura	(50)	(49)	(50)
Inflammation, suppurative	1 (2%)		
*Mesentery	(50)	(49)	(50)
Inflammation, acute			1 (2%)
Inflammation, acute/chronic			1 (2%)
Necrosis, fat			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE (Continued)

	Untreated Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Amyloidosis	1 (2%)	1 (2%)	
Tail			
Osteosclerosis			1
Knee			
Dyschondroplasia	4	3	7
Adipose tissue			
Necrosis, fat	3	1	3
SPECIAL MORPHOLOGY SUMMARY			
No necropsy performed		1	

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

APPENDIX E

GENETIC TOXICOLOGY OF

ERYTHROMYCIN STEARATE

TABLE E1. MUTAGENICITY OF ERYTHROMYCIN STEARATE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	108 ± 3.2	104 ± 4.6	134 ± 8.3	117 ± 5.3	116 ± 7.8	133 ± 10.4
	0.3	--	117 ± 2.8	--	140 ± 1.9	--	140 ± 6.1
	1	168 ± 10.3	101 ± 6.8	114 ± 12.4	120 ± 14.9	120 ± 9.3	136 ± 8.5
	3	129 ± 4.8	103 ± 7.2	90 ± 6.5	128 ± 7.1	142 ± 18.3	125 ± 12.6
	10	95 ± 13.6	72 ± 7.4	63 ± 7.2	114 ± 5.8	116 ± 9.7	114 ± 6.8
	33	Toxic	13 ± 1.8	(c) 0 ± 0.0	(c) 24 ± 24.0	(c) 0 ± 0.0	57 ± 5.5
	100	Toxic	--	(c) 0 ± 0.0	--	Toxic	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	467 ± 18.0	419 ± 12.6	2,355 ± 34.5	778 ± 10.2	846 ± 26.4	495 ± 23.2
TA1535	0	31 ± 0.7	32 ± 1.8	42 ± 3.6	35 ± 4.3	41 ± 5.5	24 ± 1.3
	0.3	--	20 ± 3.9	--	22 ± 3.9	--	32 ± 2.0
	1	39 ± 3.2	27 ± 3.8	31 ± 3.3	20 ± 3.3	43 ± 5.3	29 ± 2.3
	3	31 ± 5.7	25 ± 2.6	26 ± 1.9	18 ± 1.5	35 ± 4.2	27 ± 0.6
	10	23 ± 3.5	24 ± 2.6	32 ± 3.2	15 ± 1.9	42 ± 5.2	19 ± 1.2
	33	21 ± 3.0	16 ± 2.1	(c) 6 ± 6.0	14 ± 2.6	27 ± 0.9	23 ± 4.9
	100	(c) 0 ± 0.0	--	(c) 0 ± 0.0	--	11 ± 1.9	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	443 ± 29.1	379 ± 22.3	645 ± 25.2	356 ± 53.3	331 ± 13.7	120 ± 13.2
TA1537	0	11 ± 1.8	6 ± 0.6	19 ± 4.7	7 ± 0.7	14 ± 1.2	15 ± 1.2
	0.3	--	6 ± 0.3	--	11 ± 3.3	--	13 ± 0.7
	1	9 ± 2.5	5 ± 1.3	14 ± 0.3	7 ± 0.9	11 ± 1.5	13 ± 3.2
	3	16 ± 1.5	4 ± 0.9	10 ± 2.2	5 ± 1.2	10 ± 1.2	9 ± 0.3
	10	14 ± 3.5	7 ± 1.7	15 ± 1.7	9 ± 2.6	11 ± 4.0	11 ± 2.7
	33	7 ± 1.2	3 ± 1.0	(c) 2 ± 2.0	7 ± 2.3	8 ± 2.4	6 ± 1.5
	100	Toxic	--	(c) 0 ± 0.0	--	(c) 1 ± 1.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	388 ± 33.5	277 ± 25.1	591 ± 16.8	454 ± 17.6	266 ± 9.8	204 ± 14.8
TA98	0	28 ± 2.2	18 ± 3.8	48 ± 5.8	26 ± 2.9	37 ± 2.3	33 ± 4.0
	0.3	--	22 ± 1.7	--	31 ± 4.4	--	31 ± 5.2
	1	29 ± 2.0	17 ± 0.3	27 ± 3.8	27 ± 3.6	48 ± 7.9	40 ± 6.7
	3	25 ± 0.6	19 ± 5.2	29 ± 0.3	28 ± 0.9	43 ± 1.2	35 ± 5.0
	10	25 ± 2.3	10 ± 1.2	22 ± 3.0	24 ± 4.2	34 ± 6.6	24 ± 1.5
	33	20 ± 2.6	8 ± 2.2	9 ± 4.4	22 ± 1.5	35 ± 7.1	29 ± 2.2
	100	Toxic	--	(c) 0 ± 0.0	--	22 ± 4.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	758 ± 14.2	730 ± 18.6	1,856 ± 19.6	477 ± 29.8	436 ± 5.1	401 ± 33.1

(a) Study performed at SRI International. The detailed protocol is presented by Haworth et al. (1983). Cells and study compound or solvent (95% ethanol) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE E2. MUTAGENICITY OF ERYTHROMYCIN STEARATE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
-S9					
Trial 1					
Ethanol (d)		82.5 ± 3.9	100.0 ± 2.7	175.3 ± 17.3	70.5 ± 3.3
Erythromycin stearate	6.25	91.0 ± 9.3	77.3 ± 2.3	190.3 ± 8.3	70.7 ± 5.5
	12.5	89.0 ± 7.1	81.7 ± 10.5	222.7 ± 8.2	84.3 ± 4.9
	25	96.7 ± 1.9	81.0 ± 2.5	213.3 ± 12.3	73.7 ± 4.9
	50	81.0 ± 1.5	53.0 ± 1.2	210.0 ± 3.5	86.7 ± 2.0
	100	75.0 ± 6.4	6.0 ± 0.6	265.3 ± 19.7	(f) 118.0 ± 3.8
	(e) 150	75.3 ± 5.8	3.3 ± 0.3	352.0 ± 55.6	(f) 154.7 ± 17.6
	200	Lethal	--	--	--
Ethyl methanesulfonate	250	69.3 ± 0.9	47.0 ± 3.6	1,096.7 ± 85.0	(f) 527.7 ± 38.8
Trial 2					
Ethanol (d)		71.3 ± 9.2	100.0 ± 10.4	98.5 ± 7.2	47.8 ± 4.8
Erythromycin stearate	25	57.3 ± 7.7	71.3 ± 7.9	60.3 ± 10.1	34.7 ± 2.7
	50	64.0 ± 8.3	23.7 ± 1.5	83.3 ± 18.4	42.0 ± 5.8
	75	59.3 ± 3.0	19.7 ± .1.3	86.0 ± 11.0	48.0 ± 4.4
	100	62.7 ± 3.3	16.7 ± 0.3	122.3 ± 4.1	65.3 ± 2.3
	125	53.7 ± 4.8	15.0 ± 1.0	118.7 ± 9.4	(f) 74.0 ± 2.5
	(e) 150	60.3 ± 8.5	17.3 ± 1.3	105.7 ± 13.5	58.3 ± 1.5
Ethyl methanesulfonate	250	50.0 ± 6.7	59.0 ± 7.5	772.7 ± 19.2	(f) 532.3 ± 63.8
Trial 3					
Ethanol (d)		100.0 ± 5.8	100.3 ± 2.7	75.3 ± 8.3	25.0 ± 2.2
Erythromycin stearate	40	71.0 ± 12.0	27.0 ± 4.0	55.0 ± 6.0	26.0 ± 2.0
	60	76.0 ± 6.6	11.3 ± 2.6	68.3 ± 16.2	29.7 ± 5.8
	80	63.0 ± 1.5	5.3 ± 0.3	78.0 ± 17.9	(f) 41.0 ± 9.1
	100	54.3 ± 2.2	3.7 ± 0.3	79.7 ± 5.2	(f) 49.3 ± 2.9
	(g) 120	50.0 ± 13.0	4.0 ± 1.0	57.5 ± 7.5	40.0 ± 5.0
	(e,g) 140	55.5 ± 3.5	4.0 ± 0.0	75.0 ± 1.0	(f) 45.5 ± 3.5
Methyl methanesulfonate	5	76.0 ± 9.2	60.7 ± 10.8	453.0 ± 93.9	(f) 196.3 ± 26.8
+S9 (h)					
Trial 1					
Ethanol (d)		86.8 ± 4.2	99.8 ± 12.4	265.3 ± 23.4	102.0 ± 6.6
Erythromycin stearate	31.3	49.3 ± 4.5	58.0 ± 7.0	243.0 ± 10.3	(f) 166.3 ± 7.6
	62.5	71.0 ± 7.0	72.7 ± 2.9	228.0 ± 4.4	109.7 ± 12.9
	125	69.0 ± 5.0	71.7 ± 5.0	245.0 ± 14.6	119.3 ± 10.5
	(e) 250	80.3 ± 11.8	59.3 ± 6.2	339.0 ± 44.8	142.0 ± 12.1
	500	65.0 ± 6.5	39.0 ± 4.5	380.7 ± 15.2	(f) 197.7 ± 15.0
	(i) 750	42	8	416	329
	1,000	Lethal	--	--	--
Methylcholanthrene	2.5	71.7 ± 2.6	49.0 ± 10.7	712.7 ± 4.3	(f) 334.3 ± 13.0

TABLE E2. MUTAGENICITY OF ERYTHROMYCIN STEARATE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
+S9 (Continued)					
Trial 2					
Ethanol (d)		72.0 ± 4.8	100.0 ± 5.7	140.5 ± 4.2	66.3 ± 5.6
Erythromycin stearate	100	69.0 ± 6.4	86.0 ± 9.5	86.3 ± 3.5	42.7 ± 5.8
	(e) 200	76.0 ± 6.7	91.7 ± 16.2	127.0 ± 16.6	57.7 ± 11.1
	400	62.3 ± 12.4	47.3 ± 7.3	117.7 ± 24.7	75.0 ± 32.1
	500	47.3 ± 12.3	10.7 ± 4.2	193.0 ± 15.9	(f) 148.0 ± 23.3
	600	44.3 ± 9.0	11.0 ± 5.0	211.3 ± 18.6	(f) 174.7 ± 42.8
	700	62.3 ± 6.7	37.3 ± 19.4	182.7 ± 19.1	(f) 102.3 ± 22.1
	800	Lethal	--	--	--
Methylcholanthrene	2.5	70.7 ± 5.2	71.0 ± 5.5	580.7 ± 46.3	(f) 275.0 ± 25.9

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate unless otherwise specified; the average for the three tests is presented in the table. 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 and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error of replicate trials for approximately (3×10^6) cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Data presented are the results of four tests.
(e) Precipitate present at this and all higher doses.
(f) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(g) Data presented are the results of two tests; doses were lethal in one test.
(h) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent.
(i) Value given is for one test only; doses in two tests were lethal.

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY ERYTHROMYCIN STEARATE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,046	476	0.46	9.5	26.0	
		50	1,052	463	0.44	9.3	26.0	
Erythromycin stearate	5	50	1,050	462	0.44	9.2	26.0	98.9
	16	31	650	278	0.43	9.0	26.0	96.8
	50	50	1,046	483	0.46	9.7	26.0	104.3
	160	50	1,047	472	0.45	9.4	26.0	101.1
Mitomycin C	0.001	50	1,049	853	0.81	17.1	26.0	183.9
	0.010	10	209	619	2.96	61.9	26.0	665.6
Trial 2--Summary: Negative								
Dimethyl sulfoxide		50	1,041	425	0.41	8.5	26.5	
Erythromycin stearate	25	50	1,029	377	0.37	7.5	26.5	88.2
	50	50	1,027	425	0.41	8.5	26.5	100.0
	100	50	1,016	396	0.39	7.9	26.5	92.9
	160	0	--	--	--	--	(d) 31.5	--
Mitomycin C	0.001	50	1,044	557	0.53	11.1	26.5	130.6
	0.010	10	210	490	2.33	49.0	26.5	576.5
+S9 (e)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,052	417	0.40	8.3	27.0	
		50	1,050	418	0.40	8.4	27.0	
Erythromycin stearate	50	50	1,050	374	0.36	7.5	27.0	89.3
	160	50	1,050	426	0.41	8.5	27.0	101.2
	500	50	1,051	449	0.43	9.0	27.0	107.1
Cyclophosphamide	0.3	50	1,052	765	0.73	15.3	27.0	182.1
	2	10	210	493	2.35	49.3	27.0	586.9
Trial 2--Summary: Negative								
Dimethyl sulfoxide		50	1,042	467	0.45	9.3	26.0	
Erythromycin stearate	300	50	1,049	450	0.43	9.0	26.0	96.8
	400	50	1,050	440	0.42	8.8	26.0	94.6
	500	50	1,050	475	0.45	9.5	26.0	102.2
Cyclophosphamide	0.3	50	1,048	643	0.61	12.9	26.0	138.7
	2	10	210	356	1.70	35.6	26.0	382.8

(a) Study performed at Environmental Health Research and Testing Laboratory. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) 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 BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY ERYTHROMYCIN STEARATE (a)

Trial 1					Trial 2				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b)--Harvest time 12.5 h					**−S9 (b)**--Harvest time 12.0 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	1	0.01	1		100	2	0.02	2
	100	0	0.00	0					
Erythromycin stearate					Erythromycin stearate				
16	100	0	0.00	0	160	100	4	0.04	3
50	100	2	0.02	2	300	100	3	0.03	3
160	100	3	0.03	3	400	100	3	0.03	3
500	100	0	0.00	0	500	100	1	0.01	1
Summary: Negative					Summary: Negative				
Mitomycin C					Mitomycin C				
0.250	100	36	0.36	28	0.150	100	7	0.07	6
1	50	27	0.54	40	0.250	100	26	0.26	20
+S9 (c)--Harvest time 12.0 h									
Dimethyl sulfoxide									
	100	0	0.00	0					
	100	1	0.01	1					
Erythromycin stearate									
50	100	0	0.00	0					
160	100	0	0.00	0					
500	100	1	0.01	1					
Summary: Negative									
Cyclophosphamide									
15	100	10	0.10	9					
50	50	27	0.54	38					

(a) Study performed at Environmental Health Research and Testing Laboratory. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX F

SENTINEL ANIMAL PROGRAM

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

II. Results

No positive results were obtained.

APPENDIX G

FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF ERYTHROMYCIN STEARATE

TABLE G1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

Week	Control		5,000 ppm				10,000 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)
1	16	168	16	167	1.0	479	15	164	0.9	915
6	14	293	15	292	1.1	257	14	278	1.0	504
10	15	335	15	336	1.0	223	14	316	0.9	443
13	16	369	16	369	1.0	217	15	350	0.9	429
17	16	396	15	393	0.9	191	16	375	1.0	427
21	15	407	16	406	1.1	197	15	390	1.0	385
27	16	432	16	426	1.0	188	16	410	1.0	390
31	16	442	15	439	0.9	171	15	424	0.9	354
35	15	445	15	445	1.0	169	15	430	1.0	349
40	15	458	15	458	1.0	164	15	443	1.0	339
44	14	457	14	451	1.0	155	13	438	0.9	297
48	15	468	15	462	1.0	162	15	453	1.0	331
52	15	469	15	469	1.0	160	15	455	1.0	330
57	14	467	14	471	1.0	149	14	455	1.0	308
61	14	470	15	472	1.1	159	15	457	1.1	328
65	14	464	14	466	1.0	150	14	454	1.0	308
70	14	467	14	452	1.0	155	13	449	0.9	290
75	15	466	14	464	0.9	151	14	448	0.9	313
79	14	461	13	452	0.9	144	14	440	1.0	318
83	15	465	15	453	1.0	166	14	445	0.9	315
87	15	462	13	449	0.9	145	13	436	0.9	298
91	12	444	12	445	1.0	135	12	425	1.0	282
96	13	438	14	460	1.1	152	13	421	1.0	309
100	13	437	13	427	1.0	152	13	416	1.0	313
Mean	14.6	424	14.5	422	1.0	183	14.3	407	1.0	370
SD (d)	1.1		1.1		0.06	69	1.0		0.06	129
CV(e)	7.5		7.6		6.0	37.7	7.0		6.0	34.9

(a) Grams of feed removed from feeder 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) Milligrams of erythromycin stearate consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE G2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

Week	Control		5,000 ppm				10,000 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)
1	10	126	10	127	1.0	394	10	124	1.0	806
6	10	179	10	181	1.0	276	10	172	1.0	581
10	10	196	10	198	1.0	253	9	187	0.9	481
13	10	205	10	208	1.0	240	10	196	1.0	510
17	10	219	10	222	1.0	225	11	209	1.1	526
21	10	220	10	227	1.0	220	10	212	1.0	472
27	10	233	11	238	1.1	231	10	222	1.0	450
31	10	238	9	245	0.9	184	10	229	1.0	437
35	10	255	11	247	1.1	223	10	230	1.0	435
40	10	249	11	256	1.1	215	10	234	1.0	427
44	10	256	10	261	1.0	192	10	241	1.0	415
48	11	263	12	273	1.1	220	11	250	1.0	440
52	11	273	11	283	1.0	194	11	257	1.0	428
57	11	289	11	292	1.0	188	10	266	0.9	376
61	11	293	12	304	1.1	197	11	275	1.0	400
65	11	302	11	313	1.0	176	11	283	1.0	389
70	11	313	12	322	1.1	186	11	292	1.0	377
75	11	317	12	326	1.1	184	11	295	1.0	373
79	11	321	11	327	1.0	168	11	294	1.0	374
83	11	323	11	328	1.0	168	11	297	1.0	370
87	11	326	13	330	1.2	197	10	296	0.9	338
91	11	316	10	328	0.9	152	9	290	0.8	310
96	11	330	11	336	1.0	164	11	299	1.0	368
100	10	329	11	328	1.1	168	11	300	1.1	367
Mean	10.5	265	10.8	271	1.0	209	10.4	248	1.0	435
SD (d)	0.5		0.9		0.1	50	0.6		0.1	101
CV (e)	4.8		8.3		10.0	23.9	5.8		10.0	23.2

(a) Grams of feed removed from feeder 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) Milligrams of erythromycin stearate consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE G3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

Week	Control		2,500 ppm				5,000 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)
2	3	26.2	3	25.3	1.0	296	3	25.3	1.0	593
8	4	30.9	4	30.5	1.0	328	4	29.6	1.0	676
9	4	31.3	4	31.2	1.0	321	3	30.1	0.8	498
13	4	33.0	4	32.9	1.0	304	4	32.3	1.0	619
16	4	33.4	4	35.1	1.0	285	4	33.5	1.0	597
20	4	35.4	4	35.8	1.0	279	4	34.5	1.0	580
26	4	35.1	4	37.0	1.0	270	4	35.1	1.0	570
30	4	36.3	4	36.4	1.0	275	4	35.4	1.0	565
34	4	37.2	4	37.5	1.0	267	4	36.6	1.0	546
38	4	36.9	4	38.0	1.0	263	4	36.8	1.0	543
42	4	38.4	4	39.0	1.0	256	4	38.8	1.0	515
46	4	39.5	4	39.6	1.0	253	4	39.0	1.0	513
50	4	39.7	4	40.0	1.0	250	4	39.1	1.0	512
55	4	39.7	4	39.5	1.0	253	4	39.0	1.0	513
58	4	39.4	4	39.3	1.0	254	4	39.0	1.0	513
63	4	40.2	4	40.2	1.0	249	4	39.7	1.0	504
68	4	39.5	4	40.0	1.0	250	4	39.0	1.0	513
72	4	39.1	4	39.3	1.0	254	4	38.5	1.0	519
77	4	39.1	4	38.4	1.0	260	4	38.0	1.0	526
81	4	39.2	4	38.6	1.0	259	4	37.7	1.0	531
85	4	38.0	4	37.8	1.0	265	4	37.8	1.0	529
89	3	37.8	4	39.3	1.3	254	4	38.3	1.3	522
94	4	37.5	4	38.3	1.0	261	4	37.2	1.0	538
98	4	37.4	4	39.5	1.0	253	4	37.7	1.0	531
Mean	3.9	36.7	4.0	37.0	1.0	269	3.9	36.2	1.0	544
SD (d)	0.3		0.2		0.1	22	0.3		0.1	43
CV (e)	7.7		5.0		10.0	8.2	7.7		10.0	7.9

(a) Grams of feed removed from feeder 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) Milligrams of erythromycin stearate consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE G4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF ERYTHROMYCIN STEARATE

	Control		2,500 ppm				5,000 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)
2	3	20.7	3	20.5	1.0	366	3	20.5	1.0	732
8	3	23.9	3	23.5	1.0	319	3	23.5	1.0	638
9	3	23.9	3	23.9	1.0	314	3	24.1	1.0	622
13	3	26.3	3	26.5	1.0	283	3	26.2	1.0	573
16	3	27.2	3	27.8	1.0	270	3	27.1	1.0	554
20	4	29.5	3	28.9	0.8	260	3	28.7	0.8	523
26	3	30.4	3	30.3	1.0	248	3	29.2	1.0	514
30	3	31.8	3	32.0	1.0	234	4	30.9	1.3	647
34	4	34.3	3	34.0	0.8	221	3	33.2	0.8	452
38	3	34.8	3	35.0	1.0	214	3	33.4	1.0	449
42	3	35.2	3	36.2	1.0	207	3	35.2	1.0	426
46	4	37.4	3	37.4	0.8	201	4	36.7	1.0	545
50	4	38.1	4	38.3	1.0	261	4	37.9	1.0	528
55	4	37.7	3	37.8	0.8	198	4	37.6	1.0	532
58	4	38.6	4	37.0	1.0	270	4	37.4	1.0	535
63	4	39.7	3	38.5	0.8	195	3	39.1	0.8	384
68	4	40.1	4	38.9	1.0	257	4	39.6	1.0	505
72	4	39.7	4	38.6	1.0	259	4	40.2	1.0	498
77	4	39.1	4	38.5	1.0	260	3	39.1	0.8	384
81	4	39.9	3	38.9	0.8	193	4	39.8	1.0	503
85	4	39.9	3	39.5	0.8	190	3	40.3	0.8	372
89	3	39.3	3	39.0	1.0	192	3	39.9	1.0	376
94	4	39.5	4	39.2	1.0	255	3	40.2	0.8	373
98	4	39.5	4	39.9	1.0	251	3	40.9	0.8	367
Mean	3.6	34.4	3.3	34.2	0.9	247	3.3	34.2	0.9	501
SD (d)	0.5		0.5		0.1	45	0.5		0.1	99
CV (e)	13.9		15.2		11.1	18.2	15.2		11.1	19.8

(a) Grams of feed removed from feeder 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) Milligrams of erythromycin stearate consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX H

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 H1. 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
Dried brewer's 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 H2. 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
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
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 H3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number 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
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 for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine

TABLE H4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.41 ± 0.15	0.13-0.93	24
Cadmium (ppm) (a)	<0.10		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) (f,g)	8.0 ± 7.91	<3-23	23
E. coli (MPN/g) (f,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 H4. 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) The 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 produced on 4/27/81 contained less than 0.5 ppm; the value was <0.04.
(f) MPN = most probable number
(g) Mean, standard deviation, and range exclude one high value of 150 obtained for the batch produced on 8/26/82.
(h) Mean, standard deviation, and range include the high value listed in footnote (g).
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude one very high value of 101.6 ppb obtained for the batch produced on 1/26/81 and one very high value of 100.3 ppb obtained for the batch produced on 4/27/81.
(k) Mean, standard deviation, and range include the high values listed in footnote (j).
(l) Mean, standard deviation, and range exclude one very high value of 97.9 ppb obtained for the batch produced on 1/26/81 and one very high value of 99 ppb obtained for the batch produced on 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 date it was obtained are given under the range.
(p) There were two observations above the detection limit; the values and dates they were obtained are given under the range.
(q) Ten batches contained more than 0.05 ppm.

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The experimental data, documents, and pathology materials for the 2-year toxicology and carcinogenesis studies of erythromycin stearate in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (fully implemented by the NTP on October 1, 1981). The studies were conducted for the NTP by Physiological Research Laboratories, Minneapolis, Minnesota, under a subcontract with Tracor Jitco, Inc., until February 28, 1983, and then under contract with the National Institute of Environmental Health Sciences (NIEHS). Animal dosing with erythromycin stearate in feed began on December 9, 1980, for rats and on December 23, 1980, for mice. The retrospective audit was conducted at the NTP Archives, Research Triangle Park, North Carolina, in January 1987 by Argus Research Laboratories, Paul A. Wennerberg, D.V.M., M.S., Principal Investigator. Other individuals involved in the conduct of the audit are listed in the full audit report, which is on file at the NIEHS. The audit included a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) Body weight, clinical observation, and feed consumption data for a random 10% sample of study animals.
(3) All inlife records involving protocol, correspondence, environmental conditions, mortality, animal identification, and correlation of final inlife observation of masses, date of death, and disposition with necropsy records.
(4) All postmortem records for individual animals concerning identification, disposition codes, condition codes, correlation between gross observations and microscopic diagnoses, and tissue accountability.
(5) All chemistry records.
(6) All wet tissue bags for inventory and wet tissues from a random 10% sample of the study animals plus other relevant cases to verify animal identification and to examine for untrimmed lesions.
(7) Blocks and slides of tissues from all control and high dose animals to examine for proper match and inventory.
(8) Tabulated pathology diagnoses for a random 10% of study animals to verify computer data entry.
(9) Data and results pertaining to the 2-year studies of erythromycin stearate in the Preliminary Draft (3/87) of the NTP Technical Report.

The audit showed that the studies were conducted following the prescribed statement of work. Inlife procedures and events were documented adequately by the archival records with the exception that information on procedural details for randomization and the disposition of surplus animals was incomplete. Audit findings from review of the inlife records were few in number and minor in nature and involved only the clinical records. For example, 4 rats and 1 mouse had masses during their last month of survival which lacked corresponding necropsy observation, and 10 rats had observations involving eyes (pale, red crust, or opaque) which were not recorded either in the inlife or necropsy records. Also, the date and mode of death entered into separate records maintained for animal census and clinical observations were either not internally consistent or sometimes not listed in both records for five rats and five mice; however, one of the two records was always in agreement with the disposition code listed on the necropsy record form. Analytical chemistry records were present with only minor exceptions and documented study conduct and data adequately.

Animals were identified individually by toe clip (numbers 1-99) or a combination of toe clip and ear punch (numbers 100-150) per sex and species. Neither toes nor ears were saved for animals that died early in the study, and only toes were saved for animals killed at the end of the studies. Accordingly, inspection of wet tissues could only partly confirm animal identification; none of the 89 rats and 64 mice examined was incorrectly identified or could possibly have been involved in an animal mixup.

The audit identified 19 untrimmed potential lesions (4 in target organs) in the wet tissues of 19/89 rats examined, and 3 untrimmed potential lesions in 3/64 mice examined. As a result, NTP staff initiated a complete review of wet tissues for untrimmed lesions. The complete review of wet tissues of rats from these studies identified 164 potential untrimmed lesions in 108 rats (male and female); these diagnoses have been incorporated in the tables of the Technical Report. Analysis of the lesions in mice indicated that further review was not required. There were a variety of gross observations without a corresponding microscopic correlate (22 in rats with 7 involving target organs, and 9 in mice), which were distributed across study groups. Full details about these and other audit findings are presented in the audit report.

In conclusion, the study records at the NTP Archives support the data and results presented in this NTP Technical Report.

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-*p*-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
229	Guar Gum
230	Agar
231	Stannous Chloride
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four strains of rats)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	o-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
336	Penicillin VK
337	Nitrofurazone
339	2-Amino-4-nitrophenol

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