NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF OXYMETHOLONE

(CAS NO. 434-07-1)

IN F344/N RATS AND TOXICOLOGY STUDIES OF OXYMETHOLONE IN B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

August 1999

NTP TR 485

NIH Publication No. 99-3975

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory 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 Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

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. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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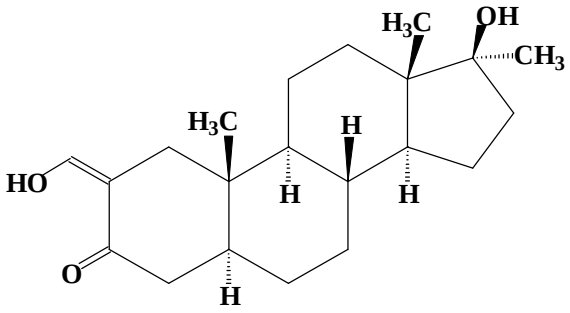
ABSTRACT



OXYMETHOLONE

CAS No. 434-07-1

Chemical Formula: $C_{21}H_{32}O_3$ Molecular Weight: 332.5

Synonyms: Adroidin; anadroyd; anasteron; anasteronal; anasterone; androstan-3-one, androstano[2,3-c]1,2,5-oxadiazol-17-ol, 17-methyl-, (5-α,17-β)-; becorel; 4,5-dihydro-2-hydroxymethylene-17-α-methyltestosterone; dynasten; HMD; 17β-hydroxy-2-(hydroxymethyl)-17-methyl-5-α-androstan-3-one; 17-hydroxy-2-(hydroxymethylene)-17-methyl-(5-α,17-β)-; 17-hydroxy-2-(hydroxymethylene)-17-methyl-5-α-17-β-androst-3-one; 17β-hydroxy-2-(hydroxymethylene)-17-α-methyl-5-α-androstan-3-one; 17β-hydroxy-2-(hydroxymethylene)-17-methyl-5α-androstan-3-one; 17-hydroxy-2-(hydroxymethylene)-17-methyl-5-α-17-β-androstan-3-one; 17β-hydroxy-2-hydroxymethylene-17α-methyl-3-androstanone; 2-hydroxymethylene-17-α-methyl-5-α-androstan-17-β-ol-3-one; 2-hydroxymethylene-17α-methyl dihydrotestosterone; 2-hydroxymethylene-17-α-methyl-17-β-hydroxy-3-androstanone; methabol; 17α-methyl-2-hydroxymethylene-17-hydroxy-5-α-androstan-3-one; oximetholonum; oximetolona; oxitosona-50; oxymethenolone; roboral; zenalosyn

Trade names: Adroyd; Anadrol; Anapolon; Anapolon 50; Nastenon; Pardroyd; Pavisoid; Plenastril; Protanabol; Synasteron

Oxymetholone is a synthetic anabolic steroid used to treat a variety of conditions, including hypogonadism and delayed puberty. It is also used to correct hereditary angioneurotic edema, manage carcinoma of the breast, promote a positive nitrogen balance following injury or surgery, and stimulate erythropoiesis. Considerable amounts of androgens are consumed by athletes in attempts to improve athletic performance. The National Institute of Environmental Health Sciences and the National Cancer Institute nominated oxymetholone for study based on its extensive illicit pharmaceutical use and the limited evidence that it is a potential human carcinogen. Male and female F344/N rats received oxymetholone (greater than 99% pure) in 0.5% methylcellulose by gavage for 16 days, 14 weeks, or 2 years, and male and female B6C3F$_1$ mice received oxymetholone in 0.5% methylcellulose by gavage for 16 days or 14 weeks. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and mouse peripheral blood erythrocytes.

16-Day Study in Rats

Groups of five male and five female F344/N rats were administered 0, 160, 315, 625, 1,250, or 2,500 mg oxymetholone/kg body weight in 0.5% methylcellulose by gavage for 16 days. All male rats survived to the end of the study; one 2,500 mg/kg female died on day 14. The mean body weights of all dosed groups of males were significantly less than those of the vehicle controls, while those of 160 and 315 mg/kg females were significantly greater.

16-Day Study in Mice

Groups of five male and five female B6C3F$_1$ mice were administered 0, 320, 630, 1,250, 2,500, or 5,000 mg/kg in 0.5% methylcellulose by gavage for 16 days. All mice survived to the end of the study. The final mean body weights of all dosed groups of females were greater than those of the vehicle controls.

14-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were administered 0, 80, 160, 315, 625, or 1,250 mg/kg in 0.5% methylcellulose by gavage for 14 weeks. One male rat each in the 625 and 1,250 mg/kg groups died before the end of the study. The mean body weights of males administered 160 mg/kg or greater were significantly less than those of the vehicle controls; in contrast, the mean body weights of all dosed groups of females were significantly greater.

A dose-related erythrocytosis, evidenced by increases in erythrocyte counts, total hemoglobin concentrations, and hematocrit values, occurred in dosed groups of rats at week 14. A dose-related hypocholesterolemia occurred at all time points in all dosed groups of rats. Dose- and time-related decreases in 5′-nucleotidase activity occurred in treated rats. There was a transient, treatment-related increase in the activity of alanine aminotransferase in males and females.

For male rats administered oxymetholone, cauda epididymis, epididymis, and testis weights and spermatid counts and total spermatid heads per testis were significantly less than those of the vehicle controls, and total spermatid heads per gram testis were significantly greater. Female rats in the 80 mg/kg group spent more time in diestrus and less time in estrus than did the vehicle controls.

Kidney weights of males and females and liver and uterus weights of females were increased compared to vehicle controls in rats that received 315 mg/kg or greater; thymus weights of males and females and sartorius muscle and testis weights of males were less. Compared to the vehicle controls, rats that received 160 mg/kg or greater had increased incidences of nonneoplastic lesions of the kidney and mammary gland, and the incidences of hydrometra of the uterus and dysgenesis of the ovary were increased in dosed groups of females. Female rats administered 315 mg/kg or greater had increased incidences of cytoplasmic vacuolization of the adrenal gland and myocardial degeneration of the heart. The severities of these lesions generally increased with increasing dose.

14-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were administered 0, 160, 320, 630, 1,250, or 2,500 mg/kg in 0.5% methylcellulose by gavage for 14 weeks. All mice administered oxymetholone survived until the end of the study. The mean body weights of all dosed groups were similar to those of the vehicle controls.

The percentages of motile sperm in 1,250 and 2,500 mg/kg males were significantly less than those of the vehicle controls. The estrous cycle lengths of 630, 1,250, and 2,500 mg/kg females were significantly longer, and females in the 1,250 and 2,500 mg/kg groups spent more time in diestrus and less time in estrus.

Kidney and liver weights of males and females were greater and thymus weights of females were less than those of the vehicle controls. All dosed females had hyperplasia of the clitoral gland, metaplasia of the parietal layer epithelium of the Bowman's capsule in the kidney, and cytoplasmic alteration of the submandibular gland; these lesions were not observed in the vehicle control group. The incidences of hypoplasia of the ovary in 320 mg/kg or greater females and of parotid gland atrophy in 1,250 and 2,500 mg/kg females were increased. The results of the 14-week oral gavage studies were generally similar in rats and mice, but rats were much more sensitive to oxymetholone. Because it was not likely that a long-term mouse study would provide significant additional toxicity information, the NTP decided to conduct a 2-year study in rats only.

2-Year Study in Rats

Groups of 90 male F344/N rats were administered 0, 3, 30, or 150 mg/kg in 0.5% methylcellulose by gavage, and 90 female F344/N rats were administered 0, 3, 30, or 100 mg/kg in 0.5% methylcellulose by

gavage for up to 104 weeks, with 9 or 10 rats per group evaluated at 3, 6, 12, or 18 months.

Survival and Body Weights

Survival of all dosed groups was similar to that of the vehicle controls. The mean body weights of the 30 mg/kg male group were generally within 10% of those of the vehicle controls, but those of the 150 mg/kg group were markedly decreased. Mean body weights of 3 and 30 mg/kg females were generally greater than those of the vehicle controls throughout the study.

Determinations of Oxymetholone in Plasma

The concentrations of oxymetholone in plasma of male and female rats receiving 3 mg/kg for 6, 12, or 18 months were generally below the limits of quantification; therefore, all plasma concentrations in the 3 mg/kg group are considered to be estimates (Table 8). The plasma concentrations at 30 mg/kg were approximately one order of magnitude greater than those of the estimates for males and females receiving 3 mg/kg. There were no dose-related differences in plasma concentrations in female rats receiving 30 or 100 mg/kg, but plasma concentrations in males were significantly elevated in the 150 mg/kg group. It was concluded that oxymetholone kinetics was saturated at 30 mg/kg in female but not male rats.

Pathology Findings

A wide spectrum of neoplasms and nonneoplastic lesions was seen in rats administered oxymetholone for 2 years. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in 100 mg/kg females as were the incidences of basophilic and clear cell foci in 150 mg/kg males and 100 mg/kg females compared to vehicle controls. The incidences of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) were significantly increased in 30 mg/kg females. The incidences of mineralization in the lung of 150 mg/kg males and 30 and 100 mg/kg females were significantly increased. The incidence of keratoacanthoma was increased in 30 mg/kg females, and the combined incidence of squamous cell papilloma, keratoacanthoma, basal cell adenoma, squamous cell carcinoma, or carcinoma of the sweat gland was significantly increased in 100 mg/kg females. The incidences of subcutaneous tissue fibroma and fibroma or fibrosarcoma (combined) were significantly increased in 3 mg/kg males.

At 2 years, the incidences of benign pheochromocytoma and benign or malignant pheochromocytoma (combined) of the adrenal gland in 150 mg/kg males and medullary hyperplasia in 100 mg/kg females were significantly increased. The incidences of cytoplasmic vacuolization of adrenal cortical cells were significantly increased in 30 and 150 mg/kg males at 18 months and 2 years and in 100 mg/kg females beginning at 12 months and in 30 mg/kg females at 2 years.

The incidences of renal tubule adenoma in 3 and 150 mg/kg males were slightly increased. An extended evaluation of the kidney was conducted, and additional incidences of renal tubule adenoma were observed in step sections in vehicle control and dosed male rats. The combined single- and step-section incidence of renal tubule adenoma was significantly increased in 3 mg/kg males. The incidences of nephropathy were significantly increased in 30 and 150 mg/kg males at 2 years and in 100 mg/kg females beginning at 3 months. The severities of nephropathy were significantly increased in dosed groups of males at 2 years and in 100 mg/kg females at 18 months and 2 years. The incidences of mineralization of the kidney were significantly increased in 150 mg/kg males at all time points.

The incidences of ovarian dysgenesis were significantly increased in 100 mg/kg females beginning at 3 months and in 30 mg/kg females beginning at 6 months, and severities increased with increasing dose. The incidences of chronic myocardial degeneration (cardiomyopathy) were significantly increased in 100 mg/kg females at 6 months and 2 years and the severity was increased at 2 years. The incidences of lobular hyperplasia were increased in 150 mg/kg males at 18 months and 2 years and in 30 and 100 mg/kg females at all time points. The incidences of seminiferous tubule degeneration were significantly increased in 30 and 150 mg/kg males at 2 years, and the incidences of mineralization of the testis were increased in 150 mg/kg males at 12 months and in 30 mg/kg males at 18 months and at 2 years.

Decreased incidences of neoplasms occurred in male and female rats. The incidence of uterine stromal polyp or stromal sarcoma (combined) was significantly decreased in 100 mg/kg females at 2 years. The incidences of mammary gland fibroadenoma and fibroadenoma or carcinoma (combined) were significantly decreased in all dosed groups of females. The incidences of pituitary gland pars distalis adenoma were significantly decreased in 30 and 100 mg/kg females at 2 years. The incidences of testicular interstitial cell adenoma were significantly decreased in 30 and 150 mg/kg males at 18 months and in all dosed groups at 12 months and 2 years. The incidences of mononuclear cell leukemia were significantly decreased in 30 and 150 mg/kg males and 100 mg/kg females at 2 years.

GENETIC TOXICOLOGY

Oxymetholone was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation. It did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9, and no increase in the frequency of micronucleated normochromatic erythrocytes was noted in peripheral blood samples from male or female mice treated for 14 weeks with oxymetholone.

CONCLUSIONS

Under the conditions of this 2-year gavage study, there was *equivocal evidence of carcinogenic activity** of oxymetholone in male F344/N rats based on increased incidences of subcutaneous tissue fibromas and fibromas or fibrosarcomas (combined) of the skin, variably increased incidences of benign and benign or malignant pheochromocytomas (combined) of the adrenal gland, and increased incidences of renal tubule adenomas. There was *clear evidence of carcinogenic activity* of oxymetholone in female F344/N rats based on increased incidences of hepatocellular neoplasms. Increased incidences of alveolar/bronchiolar neoplasms and skin neoplasms in female rats were also related to oxymetholone administration.

Decreased incidences of alveolar/bronchiolar neoplasms and testicular interstitial cell adenomas in males; uterine stromal polyps or stromal sarcomas (combined), mammary gland neoplasms, and pituitary gland pars distalis adenomas in females; and mononuclear cell leukemia in males and females were related to oxymetholone administration.

In addition, gavage administration of oxymetholone to male and female F344/N rats resulted in a spectrum of nonneoplastic effects frequently reported with administration of synthetic anabolic androgens.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Oxymetholone

	Male F344/N Rats	Female F344/N Rats
Doses in methylcellulose by gavage	0, 3, 30, and 150 mg/kg	0, 3, 30, and 100 mg/kg
Body weights	150 mg/kg group less than the vehicle control group	3 and 30 mg/kg groups generally greater than the vehicle control group
Survival rates	15/51, 15/50, 14/50, 20/50	25/50, 29/50, 30/50, 31/50
Nonneoplastic effects	Liver: basophilic focus (23/51, 29/50, 41/50, 38/49); clear cell focus (2/51, 2/50, 6/50, 12/49) Lung: mineralization (19/51, 25/50, 27/50, 28/47) Adrenal gland: cortex, cytoplasmic vacuolization (22/51, 23/50, 40/50, 33/49) Kidney: mineralization (6/51, 6/50, 9/50, 25/49); nephropathy (43/51, 47/50, 50/50, 48/49); severity of nephropathy (2.0, 2.6, 2.7, 2.7) Mammary gland: lobular hyperplasia (0/51, 0/48, 4/49, 35/50) Testes: degeneration (9/51, 9/50, 37/50, 28/49); mineralization (17/51, 10/50, 33/50, 19/49)	Liver: basophilic focus (39/50, 40/50, 37/50, 41/49); clear cell focus (5/50, 11/50, 6/50, 14/49) Lung: mineralization (15/50, 23/50, 33/50, 33/49) Adrenal gland: cortex, cytoplasmic vacuolization (4/50, 5/50, 21/50, 37/49) Kidney: nephropathy (32/50, 26/50, 38/50, 41/49); severity of nephropathy (1.3, 1.2, 1.2, 1.7) Ovary: dysgenesis (0/50, 1/49, 43/50, 49/49); severity of dysgenesis (, 1.0, 2.7, 3.4) Heart: myocardium, chronic degeneration (29/50, 34/50, 40/50, 45/49); severity of degeneration (1.3, 1.3, 1.8, 1.8)
Neoplastic effects	None	Liver: hepatocellular adenoma (1/50, 1/50, 1/50, 8/49); hepatocellular adenoma or carcinoma (1/50, 1/50, 1/50, 10/49) Lung: alveolar/bronchiolar adenoma (0/50, 0/50, 6/50, 1/49); alveolar/bronchiolar adenoma or carcinoma (0/50, 0/50, 7/50, 1/49) Skin: squamous cell papilloma, keratoacanthoma, basal cell adenoma, squamous cell carcinoma, or carcinoma (0/50, 0/50, 4/50, 5/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Oxymetholone

	Male F344/N Rats	Female F344/N Rats
Uncertain Findings	Skin: subcutaneous tissue, fibroma (0/51, 5/50, 2/50, 2/50); subcutaneous tissue, fibroma or fibrosarcoma (0/51, 7/50, 2/50, 2/50) Adrenal gland: benign pheochromocytoma (19/51, 21/50, 21/50, 29/49); benign or malignant pheochromocytoma (19/51, 25/50, 21/50, 29/49) Kidney: renal tubule adenoma (standard evaluation - 0/51, 1/50, 0/50, 2/49; standard and extended evaluations combined - 4/51, 13/50, 1/50, 6/49)	None
Decreased incidences	Testes: adenoma (33/51, 20/50, 0/50, 0/49) Mononuclear cell leukemia: (21/51, 15/50, 7/50, 4/50)	Uterus: stromal polyp or stromal sarcoma (5/50, 9/50, 2/50, 0/50) Mammary gland: fibroadenoma (21/50, 11/50, 1/50, 4/50); fibroadenoma or carcinoma (23/50, 11/50, 1/50, 4/50) Pituitary gland (pars distalis): adenoma (27/50, 26/50, 18/49, 14/50) Mononuclear cell leukemia: (12/50, 11/50, 11/50, 5/50)
Level of evidence of carcinogenic activity	Equivocal evidence	Clear evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Micronucleated normochromatic erythrocytes	
Mouse peripheral blood *in vivo*:	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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. 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. 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 cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report 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 five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to 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 chemical-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 chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-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. Such consideration 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:

- 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 to neoplastic 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 incidence 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);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- 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.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on oxymetholone on 30 October 1998 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 30 October 1998, the draft Technical Report on the toxicology and carcinogenesis studies of oxymetholone received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. W.C. Eastin, NIEHS, introduced the toxicology and carcinogenesis studies of oxymetholone by discussing the uses of the chemical and the rationale for the study, describing the experimental design in rats, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in male and female rats. Dr. Eastin also discussed the 16-day and 14-week studies in male and female $B6C3F_1$ mice. The proposed conclusions for the 2-year study were *equivocal evidence of carcinogenic activity* in male F344/N rats and *clear evidence of carcinogenic activity* in female F344/N rats.

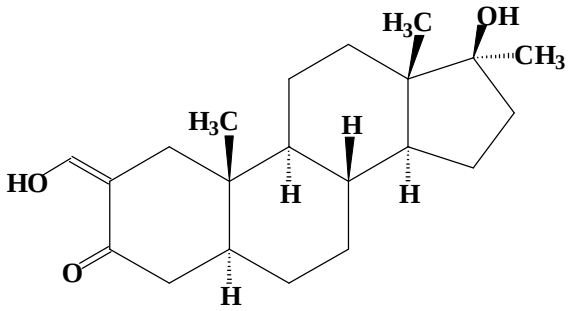
Dr. Fischer, a principal reviewer, was unable to attend the meeting but had submitted her review, which Dr. L.G. Hart, NIEHS, read into the record. Dr. Fischer agreed with the proposed conclusions. She thought the comparison of the rodent results with studies in humans was thorough and enhanced confidence in the conclusions. Dr. Fischer questioned whether the increased incidence of lung neoplasms in the 30 mg/kg group of females should be considered treatment related when there was no significant increase in these neoplasms in the 100 mg/kg group.

Dr. Bailer, the second principal reviewer, agreed with the proposed conclusions. He wondered if all rat data, including interim sacrifice data, should be routinely included in tests of tumorigenic trends. Dr. J.K. Haseman, NIEHS, responded that while statistical analyses that include the interim sacrifice data are done, they are usually not included in the report unless they affect the overall interpretation of the data. In addition, neoplasms are seldom observed at interim sacrifices. Dr. Bailer noted the statement that "there is a strong correlation between a chemical's electrophilicity, mutagenicity in *Salmonella*, and carcinogenicity in rodents" and wondered whether that is true for all chemical classes. Dr. Eastin said that point would be clarified and the statement would be modified if necessary.

Dr. Cullen, the third principal reviewer, agreed in principle with the proposed conclusions. He thought the lack of a dose-related response for hepatocellular neoplasms in female rats suggested *some evidence* rather than *clear evidence* of carcinogenic activity. Dr. Eastin commented that interpretation of neoplasm results is difficult with synthetic anabolic steroid analogues of testosterone, which has complicated and divergent biological effects. The conclusion for liver neoplasms was based on the rarity of these neoplasms, especially carcinomas, in female rats. Dr. Bailer observed that he would not say there is no dose response but rather that there is not a linear dose response. Dr. Cullen said that given the International Agency for Research on Cancer statement that there is limited evidence of human carcinogenicity for anabolic compounds and the paucity of data on carcinogenicity of oxymetholone in animals, it would have been useful to have more information on mice, and especially for mouse liver.

Dr. Bailer moved that the Technical Report on oxymetholone be accepted with the revisions discussed and the conclusions as written for male rats, *equivocal evidence of carcinogenic activity*, and for female rats, *clear evidence of carcinogenic activity*. Dr. Hecht seconded the motion. Dr. Cullen said that based on the definition of *clear evidence* and the lack of a clear dose response, he would offer an amendment to change the conclusion in female rats to *some evidence of carcinogenic activity*. Lacking a second, that amendment was tabled. Dr. Bailer's original motion was accepted with four yes votes to one no vote (Dr. Cullen).

INTRODUCTION



OXYMETHOLONE

CAS No. 434-07-1

Chemical Formula: $C_{21}H_{32}O_3$ Molecular Weight: 332.5

Synonyms: Adroidin; anadroyd; anasteron; anasteronal; anasterone; androstan-3-one, androstano[2,3-c]1,2,5-oxadiazol-17-ol, 17-methyl-, (5-α,17-β)-; becorel; 4,5-dihydro-2-hydroxymethylene-17-α-methyltestosterone; dynasten; HMD; 17β-hydroxy-2-(hydroxymethyl)-17-methyl-5-α-androstan-3-one; 17-hydroxy-2-(hydroxymethylene)-17-methyl-(5-α,17-β)-; 17-hydroxy-2-(hydroxymethylene)-17-methyl-5-α-17-β-androst-3-one; 17β-hydroxy-2-(hydroxymethylene)-17-α-methyl-5-α-androstan-3-one; 17β-hydroxy-2-(hydroxymethylene)-17-methyl-5α-androstan-3-one; 17-hydroxy-2-(hydroxymethylene)-17-methyl-5-α-17-β-androstan-3-one; 17β-hydroxy-2-hydroxymethylene-17α-methyl-3-androstanone; 2-hydroxymethylene-17-α-methyl-5-α-androstan-17-β-ol-3-one; 2-hydroxymethylene-17α-methyl dihydrotestosterone; 2-hydroxymethylene-17-α-methyl-17-β-hydroxy-3-androstanone; methabol; 17α-methyl-2-hydroxymethylene-17-hydroxy-5-α-androstan-3-one; oximetholonum; oximetolona; oxitosona-50; oxymethenolone; roboral; zenalosyn

Trade names: Adroyd; Anadrol; Anapolon; Anapolon 50; Nastenon; Pardroyd; Pavisoid; Plenastril; Protanabol; Synasteron

CHEMICAL AND PHYSICAL PROPERTIES

Oxymetholone is an odorless, white, fluffy powder that is insoluble in water but soluble in alcohol, chloroform, ether, and dioxane. The melting point ranges from 172° to 180° C, and the optical rotation is +38° (*Remington's*, 1985; *Merck*, 1989).

PRODUCTION, USE, AND HUMAN EXPOSURE

Oxymetholone is a synthetic androgen related structurally to testosterone. Because testosterone is promptly degraded by the liver when given orally or parenterally, a number of chemically modified compounds have been developed that retain androgenic activity but resist hepatic degradation. These involve modifications at the 17-C position, either esterification of the hydroxyl group with carboxylic acids or 17-C alkylation (as in oxymetholone). Various other additions to the ring structure have also been made, usually to enhance potency. Alkyl groups at the 17-C position cannot be removed metabolically, and these forms are biologically active (Wilson, 1996).

Synthetic androgens are used to treat a variety of conditions including hypogonadism and delayed puberty. Androgens are also used to correct hereditary angioneurotic edema, manage carcinoma of the breast, promote a positive nitrogen balance following injury or surgery, and stimulate erythropoiesis. Considerable amounts of androgens are consumed by athletes in attempts to improve athletic performance. Currently, the hydroxy ester or testosterone esters are the preferred agents for all uses except the treatment of hereditary angioneurotic edema, for which the alkylated androgens are

particularly effective (Wilson, 1996). Syntex Laboratories, Inc., the sole United States manufacturer, recommends oxymetholone only for the treatment of anemias. All actions of synthetic androgens are also produced by the natural androgens, primarily testosterone. Another pharmaceutical use for anabolic steroids, including oxymetholone, is to promote weight gain or treat weight loss in patients with advanced HIV infection (Berger *et al.*, 1996; Gold *et al.,* 1996; Hengge *et al.*, 1996).

It is not clear exactly when oxymetholone was first marketed, but it appears that the compound was first used in Japan in the 1960s and later in the United States. In 1972, the FDA permitted the use of oxymetholone to treat pituitary dwarfism and as an adjunctive therapy in osteoporosis pending further investigation. The FDA withdrew its approval for use of oxymetholone in the treatment of pituitary dwarfism in 1980 and in topically applied drug products for over-the-counter use in 1993 (21 CFR, Part 310). In 1983, the FDA allowed the continued use of oxymetholone for treatment of "certain anemias." Thus, the sanctioned uses of oxymetholone are limited. The recommended dosages for treatment of anemias differ for each patient but are usually in the range of 1 to 5 mg/kg body weight per day, with minimum therapies lasting 3 to 6 months (*PDR*, 1998). No production data or recent information on regulated use are available, but 21,000 prescriptions for oxymetholone (10 or 50 mg tablets) were written in 1979, and survey audits of hospitals and drugstores placed the amount of oxymetholone purchased on the illicit market at about 400 kg for that same year (NCI, 1985).

Since the 1950s, increasing numbers of athletes have experimented with anabolic drugs in efforts to increase strength (Wilson, 1996). Estimates in the 1980s indicate that 80% to 100% of national and international male bodybuilders, weightlifters, and participants in the shot put, discus, hammer, and javelin throws used anabolic steroids; football players and competitors in other sports used anabolic steroids to a lesser extent (Lamb, 1984). Dosages used by athletes are often much higher than the normal endogenous testosterone production of 4 to 10 mg/day. Documented dosages range from 10 or 15 mg/day to 300 mg/day, with anecdotal reports of up to 2 g/day. Generally, a variety of injectable and oral steroids are taken at dosages that increase, peak, and then taper off prior to competitions and potential drug tests.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

In disposition studies, [^{14}C]-oxymetholone was administered by gavage or intravenously to groups of F344/N male rats. Radioactivity peaked in the blood within 4 hours following a single oral gavage dose of 5 mg [^{14}C]-oxymetholone/kg body weight, indicating rapid intestinal absorption. Within 4 to 8 hours after dosing, the concentrations in the liver were 2 to 4 times the ^{14}C activity measured in blood. By 24 hours, approximately 15% of the administered dose was excreted in the urine and 61% in the feces, and by 72 hours, 17% and 80% of the total dose had been excreted in urine and feces, respectively. The rate and pattern of excretion were similar when rats were administered a single gavage dose of 50 mg [^{14}C]-oxymetholone/kg body weight. Repetitive dosing with 50 mg/kg resulted in a fivefold increase in blood concentrations of oxymetholone equivalents after 7 days, with no further increase thereafter. Approximately 35% of a 5 mg [^{14}C]-oxymetholone/kg body weight intravenous dose was excreted in bile over a 7-hour period, suggesting that fecal elimination was the result of biliary excretion. The major portion of ^{14}C activity in blood appeared to be bound to constituents in the plasma (Sanders and Matthews, 1991).

A small-scale, single-dose oxymetholone study was conducted to obtain toxicokinetic data for F344/N rats and B6C3F$_1$ mice (Appendix J). These studies were not considered definitive because of the small sample size (generally three animals/time point) and unbalanced design, but the results are mentioned here because they provide useful information. Oxymetholone was administered to male rats and mice by intravenous injection (20 mg/kg) and by gavage to male and female rats (30 and 120 mg/kg) and male mice (120 mg/kg). After dosing, plasma was sampled

periodically in male rats and mice but only at the 2-hour time point in female rats. The greatest plasma concentration for male rats and mice administered oxymetholone by intravenous injection occurred at the first sampling time, 5 minutes after administration. At this time point, the mean oxymetholone concentration in rat plasma was an order of magnitude greater than that in mouse plasma. Following a gavage dose, male rat plasma concentrations were greatest at 2 hours for both the 30 and 120 mg/kg doses. Plasma oxymetholone concentrations were recorded at 12 hours but were below the limit of detection at 24 hours in male rats. Bioavailability of the 120 mg/kg gavage dose was determined to be 17%. Male mice receiving 120 mg/kg by gavage appeared to have the highest plasma concentrations at 1 hour, and the concentrations were approximately one-fifth that of male or female rats at 2 hours.

Humans

Oxymetholone, marketed as a tablet, is absorbed after oral administration, but no quantitative investigations have appeared in the literature. Generally, after an anabolic steroid is administered orally to humans, blood concentrations rapidly increase within a few hours. Anabolic steroids and their metabolites are excreted in the urine and feces over a period of several days (van der Vies, 1993). Adhikary and Harkness (1971) and MacDonald *et al.* (1973) reported two urinary metabolites of oxymetholone in humans, and Bi *et al.* (1992a,b) have been able to determine additional metabolites in urine and have proposed an oxidative metabolic pathway. Schänzer (1996), in a review of the metabolism of anabolic androgenic steroids, described the primary pathway for the human metabolism of oxymetholone based on the literature (Figure 1).

TOXICITY

Experimental Animals

Oral administration of five different anabolic steroids (some having the 17α substitution and some not), including oxymetholone, to beagle dogs at doses of 10 mg/kg per day for 6 months resulted in the formation of concentric membrane whorls in hepatocytes. The membrane structures were thought to be smooth endoplasmic reticulum that had undergone either regeneration, degeneration, hypertrophy, or decreased turnover (Muraoka *et al.*, 1981). Plasma concentrations of cholesterol, phospholipids, and triglyceride were decreased by up to 50% of the control values, and alanine aminotransferase and aspartate aminotransferase activities were increased in some dogs and not in others with each drug.

Miyakae *et al.* (1974) administered oxymetholone by gavage (20 mg/kg) to albino rabbits daily for 3 weeks. The authors found significant and transient inhibition of bromosulfonphthalein clearance and increases in alanine aminotransferase and aspartate aminotransferase activities. Bromosulfonphthalein clearance effects were found only with steroids having the 10α alkyl substitution; these steroids are less readily metabolized by the liver.

In contrast to the differences in effects on bromosulfonphthalein retention seen with the 17α substitution versus nonsubstituted anabolic steroids in rabbits, similar degrees of hyperplasia, dysplasia, and hepatic neoplasms were seen in Balb/C mice fed 17α-substituted (methyl testosterone) and nonsubstituted (decadurabolin) androgens (150 μg/day) for 12 weeks and examined after 10 months. Males were somewhat more affected than females (Taylor *et al.*, 1982).

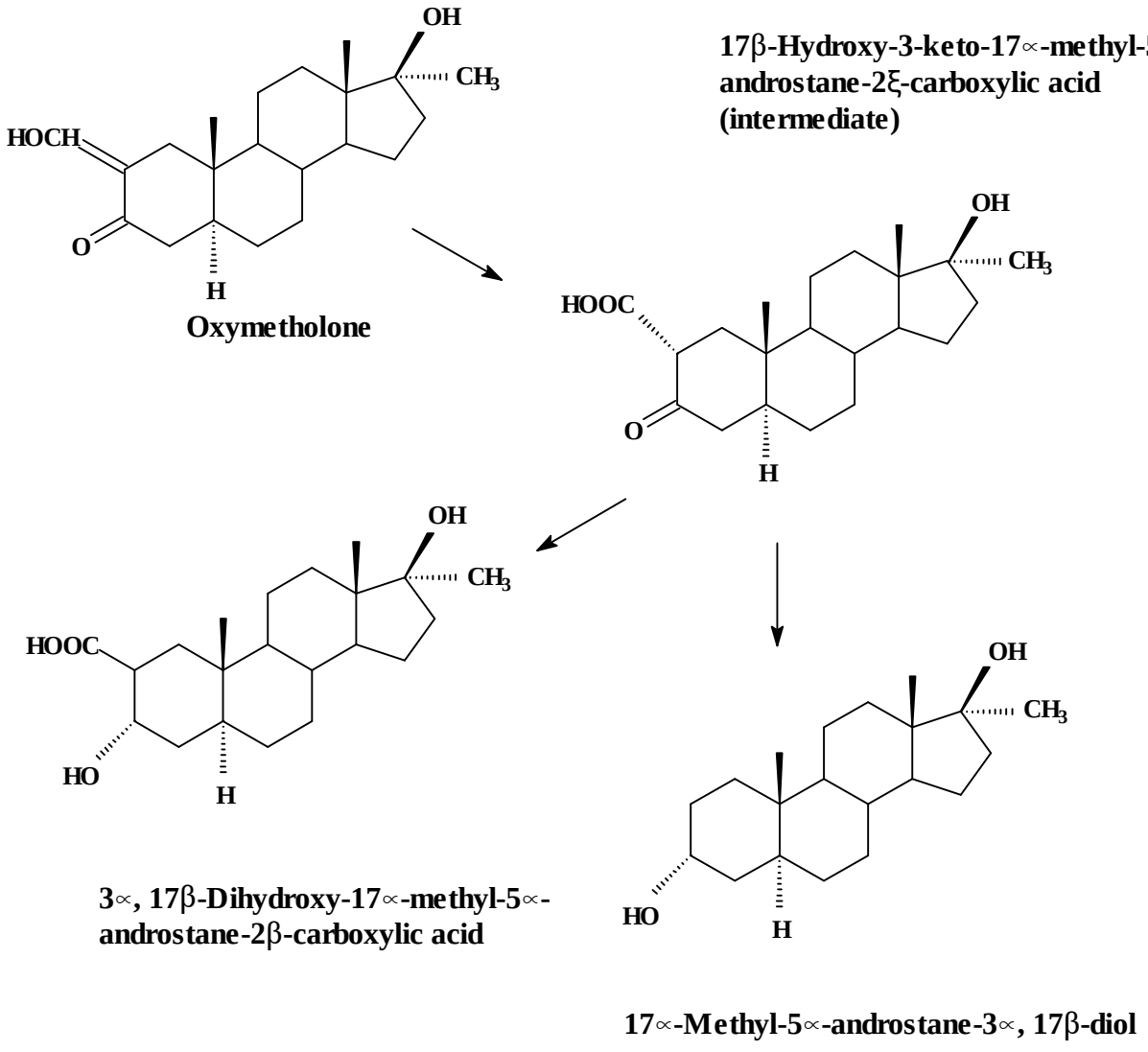


FIGURE 1
Primary Pathway for Human Metabolism of Oxymetholone (Schänzer, 1996)

Humans

Injections of human chorionic gonadotropin are sometimes used after finishing a steroid cycle to promote recovery of testicular function (Strauss *et al.*, 1983). Androgen administration tends to suppress pituitary secretion of luteinizing and follicle-stimulating hormones, which results in testicular atrophy and decreased production of natural testosterone. Sperm count is at times decreased, and men sometimes exhibit gynecomastia, which may be due to a direct inhibition by oxymetholone and other androgenic agents on 5α-reductase, the enzyme responsible for conversion of testosterone to the intracellularly active form, dihydrotestosterone (Villapando *et al.*, 1982).

While there is little doubt of the efficacy of androgen therapy in situations of natural androgen deficiency, there is little evidence that "supraphysiologic" doses have any real effect on athletic performance. Direct measurements of force production in rats and monkeys did not show improved performance with androgen dosing (Lamb, 1984). About half of the controlled human studies have shown very modest improvements in strength, and this contrasts sharply with the perception of greatly improved performance among athletes taking the drugs. Generally, no effects on lean body mass were seen, but body weight was increased slightly, primarily due to salt retention. Psychological factors and a placebo effect undoubtedly played a role in the athletes' perceptions; however, it is difficult to determine the significance of these factors because obvious changes in libido that occurred while the athletes were under anabolic steroid treatment have made double-blind drug trials somewhat less than blind. Also, increased libido may affect athletic performance. All of these affirm the lack of apparent real effect on performance in men; nevertheless, anabolic steroids continue to be used by male athletes at dosages reported to be as high as 3,200 mg/week (Evans, 1997). Women clearly show marked improvements in athletic performance while taking androgens as part of a general virilization process (Wilson, 1996).

It is fairly clear, based on studies of weight-training athletes, that psychological changes are a side effect of anabolic steroid use (Lin and Erinoff, 1990). For example, athletes taking large doses of various anabolic steroids including oxymetholone reported mood changes (Haupt and Rovere, 1984), depression, hostility, aggression, irritation, and paranoia (Perry *et al.*, 1990; Parrott *et al.*, 1994; Pope and Katz, 1994).

A number of specific biochemical effects in addition to those recognized as common responses to androgenic stimulation have been noted in athletes and others taking oxymetholone for various reasons. In male athletes who had taken low doses of oxymetholone (50 mg/day) intermittently during an 80-day period, the mean high-density lipoprotein cholesterol concentration (13.6 mg/100 mL serum) was found to be markedly lower than that in untrained or strength-trained men (44 to 46 mg/100 mL) (Costill *et al.*, 1984). No effects on blood pressure or urinalysis parameters were seen. Similar effects on high-density lipoprotein were seen in a larger study of anabolic steroid users, but the changes were found to have reversed 5 months after discontinuance of treatment (Lenders *et al.*, 1988). Marked hypertriglyceridemia and hypercholesterolemia occurred in a hemodialysis patient after 5 weeks of treatment with 100 mg oxymetholone per day. The condition improved upon discontinuation of the drug and reappeared upon subsequent rechallenge (Reeves *et al.*, 1976). Clinical observations have associated long-term, low-dose (1 to 5 mg/day) oxymetholone treatment for anemias with glucose intolerance and low concentrations of circulating immunoreactive insulin (Woodard *et al.*, 1981). High circulating concentrations of glucagon were observed in six patients taking 50 to 200 mg oxymetholone per day for prolonged periods (7 months to 7 years) for treatment of anemias (Williams *et al.*, 1986). Treatment of human volunteers with oxymetholone doses up to 30 mg/day resulted in marked elevations in serum thyroxine-binding prealbumin and cortisol-binding globulin and depression in thyroxine-binding globulin (Barbosa *et al.*, 1971).

Clinical reports have indicated an association between oxymetholone use and decreased tolerance to anticoagulants (Robinson *et al.,* 1971). Ekert *et al.* (1971) proposed that this effect is the result of a decrease in fibrinogen synthesis; decreased fibrinogen levels with no increase in fibrinogen degradation products were noted in seven of nine children administered oxymetholone to treat various anemias. No evidence of general liver toxicity was seen in these studies. While evidence for increased fibrinolysis was not seen in this study or in one by Walker *et al.*

(1975), both studies reported increased levels of activated plasminogen, or plasminogen activator, suggesting an increased fibrinolytic potential.

The most common serious adverse reaction associated with anabolic steroid therapy is hepatotoxicity; continued therapy may be associated with hepatic coma and death (*PDR*, 1998). Additional adverse effects include nausea, vomiting, anorexia, acne, suppression of gonadotropin secretion, virilization, gynecomastia and oligospermia in men, sodium retention, edema, cholestatic jaundice, decreases in several clotting factors, and hemorrhagic diathesis (*Remington's*, 1985).

A considerable number of clinical reports (Bagheri and Boyer, 1974; Groos *et al.*, 1974; Nadell and Kosek, 1977; McDonald and Speicher, 1978; Arnold and Kaplan, 1979) have associated use of androgenic steroids, in particular oxymetholone, with development of peliosis hepatis, an unusual disorder consisting of blood-filled spaces of various sizes within the hepatic parenchyma. This condition frequently leads to death from liver failure or hemorrhage but has been reported to resolve when steroids are withdrawn. Microscopically, the lesion is described as cavernous sinusoidal ectasia that is often located in the pericentral areas and associated with hyperplasia and enlargement of endothelial and/or Kupffer cells. Hepatocytes show only mild dystrophic changes in the form of polyploidy, prominent nucleoli, and decreased cytoplasmic basophilia. Dilated bile canaliculi in jaundiced patients is a fairly frequent finding (Young *et al.*, 1977). There is little evidence of hepatocellular regeneration or injury. Kosek and Smith (1980) observed these lesions in rats given oxymetholone. They proposed that the lesion results from a direct cytotoxic effect on the endothelial cells in the sinusoids and have observed these cells to be "injured" in rats in a manner similar to that seen in humans. In *in vitro* studies with human umbilical cord endothelial cell cultures, oxymetholone was found to be directly toxic to these cells at a concentration predicted to be reached in the blood of patients (Kosek and Smith, 1980).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

As an androgen, oxymetholone is active in the reproductive cycles in anticipated ways. Subcutaneous injection of oxymetholone in rats (1 to 4,000 μg/day) for 14 days depressed ovarian and uterine weights and ovulation at doses of 400 μg/day and greater (Boris *et al.*, 1972). Oxymetholone (5 mg/day) caused fetal resorptions when given to pregnant Holtzman rats following implantation (gestation days 7 to 12) (Naqvi and Warren, 1971). This action was blocked by administration of an equal amount of progesterone. Oxymetholone did not promote the capacity of microsomal hydroxylases to hydroxylate progesterone; thus, it was concluded that oxymetholone suppressed circulating levels of pituitary gonadotropins (none were measured). Lower doses (1 mg/day) given to pregnant Wistar rats from gestation days 17 to 20 caused virilization of female fetuses (Kawashima *et al.*, 1977).

Humans

The influence of high-dose anabolic steroid administration on endocrine and seminal parameters of 41 male bodybuilders was studied by comparison with 41 normal volunteers (nonsteroid users). Although only five of the normal volunteers had sperm counts below the lower normal limit of 20×10^6 sperm/mL, 24 of the bodybuilders showed subnormal values. Depending on the duration of anabolic steroid use and the period since the last drug intake before the investigation, percentages of motile and normally formed sperm were significantly reduced in bodybuilders compared with normal volunteers. In those bodybuilders who had stopped consumption of anabolic steroids more than 4 months previously, sperm numbers were in the normal range, suggesting that even after prolonged use of extremely high doses of anabolic steroids, sperm production may return to normal (Knuth *et al.*, 1989).

From a survey of noncompetitive athletes' steroid use in Great Britain, of the 97 men interviewed, 56% reported testicular atrophy, 52% gynecomastia. Of the 13 women interviewed, eight reported menstrual irregularities, eight fluid retention, four clitoral

enlargement, and three decreased breast size (Korkia and Stimson, 1997).

The luteolytic activity of oxymetholone was evaluated in 10 women. Administration early in the follicular phase of the menstrual cycle inhibited ovulation and prolonged the duration of the cycles in two of three volunteers, but treatment beginning on day 10 (three volunteers) did not prevent ovulation, although subsequent plasma progesterone concentrations were reduced. Treatment after ovulation (four volunteers) suppressed progesterone levels by 50% to 80% and shortened cycle length by 6 to 8 days (Cox, *et al.*, 1975). Ten female athletes who consistently used anabolic steroids noted clitoral enlargement and menstrual irregularities (Strauss *et al.*, 1985).

CARCINOGENICITY

Experimental Animals

Prostate cancer has been induced by implanting depots of testosterone propionate in silastic membranes in Lobund-Wistar rats that were previously induced with N-nitroso-N-methylurea or fed diets supplemented with 15% corn oil (Pollard and Luckert, 1986a,b). The development of clinically apparent prostate cancer is relatively uncommon in most strains of laboratory rats. In NTP studies, the incidence of adenoma or carcinoma (combined) is 0.6% in untreated controls and 0.7% in corn oil controls (Haseman *et al.*, 1985). Testosterone is considered a promoter of prostate cancer, and the role of androgens in prostate cancer has been previously recognized (Huggins and Hodges, 1972).

The International Agency for Research on Cancer (IARC) has determined that there is sufficient evidence to call testosterone carcinogenic in animals. In addition to the results cited above on prostate cancer in rats, neonatal treatment of female mice by subcutaneous testosterone injection induced hyperplastic epithelial lesions of the genital tract and increased the incidence of mammary gland neoplasms. Subcutaneous implants of testosterone proprionate produced cervical-uterine neoplasms in adult female mice. Numerous other studies (generally initiation/promotion designs) have indicated reduced incidences of mammary neoplasms (IARC, 1982).

The utility of a number of alternative systems is being evaluated as screens for toxicity (Robinson, 1998). Oxymetholone has been studied in the Tg.AC and $p53^{def}$ transgenic mouse models. The Tg.AC transgenic line was produced in FVB/N mice by pronuclear injection of a v-Ha-*ras* transgene linked to a fetal zeta-globin promoter and an SV40 polyadenylation/splice sequence. Tg.AC mice behave like genetically initiated mice, rapidly developing epidermal papillomas in response to topical tumor promoter or carcinogen treatment. A dose-response relationship has been observed with promoters and carcinogens. In addition, Tg.AC mice appear to respond to genotoxic as well as nongenotoxic carcinogens (Tennant *et al.*, 1995, 1996; Eastin *et al.*, 1998). Daily topical applications of oxymetholone at concentrations of 0, 1.2, 6.0, or 12.0 mg/kg to Tg.AC mice for 20 weeks produced a dose-related increase in the incidences of skin papillomas (3/25, 2/20, 5/20, 12/20) (Holden *et al.*, 1997).

The $p53^{def}$ mouse model has an alteration of the p53 tumor suppressor gene, a gene critical to cell cycle control and DNA repair and one often found to be mutated or lost in human and rodent tumors. Mice with a single copy of the wildtype p53 allele ($p53^{def}$) offer a single target for mutagens, a condition analogous to humans with some heritable forms of cancer. The heterozygous state should increase the probability for either loss of p53 tumor suppressor function or gain of transforming activity by requiring only a single mutation. The p53-heterozygous mice are viable and show a low background tumor incidence up to almost 12 months of age (Tennant *et al.*, 1995, 1996). Oxymetholone at concentrations of 0, 125, 625, or 1,250 mg/kg was administered daily by gavage to $p53^{def}$ mice for 26 weeks. Anabolic androgenic effects were observed, including increased body weight gains and clitoral and preputial gland enlargement in females, but there were no chemical-related neoplastic observations in this study (R. Stoll, personal communication).

Humans

There have been numerous reports of an association between the use of anabolic steroids, primarily oxymetholone, and liver neoplasms (Johnson *et al.*, 1972; Guy and Auslander, 1973; Henderson *et al.*, 1973; Ziegenfuss and Carabasi, 1973; Stromeyer

et al., 1979), including benign adenomas, hepatocellular carcinomas, and cholangiocarcinomas. Numerous cases have been observed when oxymetholone was used to treat Fanconi's anemia (Mulvihill *et al.*, 1975; Kew *et al.*, 1976), with one report of hepatocellular carcinoma developing in a 6-year-old girl after only 2 months of oxymetholone therapy (Mokrohisky *et al.*, 1977). This led to the suggestion that the neoplasms might actually be related to the anemia rather than to the steroid (IARC, 1977); however, subsequent reports have clearly shown liver neoplasms in patients taking oxymetholone for other conditions (Montgomery *et al.*, 1980; Zevin *et al.*, 1981; Westaby *et al.*, 1983). There is still uncertainty over the true malignant nature of many of the neoplasms reported to be carcinomas in the earlier studies, and more recent reports indicate that a considerable number of these neoplasms regress or at least do not progress rapidly once steroid therapy is stopped (McCaughan *et al.*, 1985).

Other neoplasms may also be related to androgen therapy. Sale and Lerner (1977) reported a case of a patient with aplastic anemia treated for 6 years with several androgenic steroids who developed hepatomas, multiple pancreatic islet cell neoplasms, and a renal medullary interstitial cell neoplasm. Prostate cancer has been reported in men as young as 40 years old who had received androgen therapy for impotence (Guinan *et al.*, 1997) or for bodybuilding (Roberts and Essenhigh, 1986).

Oxymetholone is effective in reversing anemias of various etiologies, including a regenerative or aplastic anemia (Allen *et al.*, 1968; Hast *et al.*, 1976; Low-Beer and Scott, 1976), sickle cell anemia (Alexanian and Nadell, 1975), and anemias resulting from various neoplastic diseases (Pengelly, 1973; Presant and Safdar, 1973). The mechanism is widely thought to be related to either stimulation of increased erythropoietin synthesis or to a synergistic effect with erythropoietin. Increased erythropoietin excretion was noted by Alexanian and Nadell (1975) in their studies on sickle cell anemia patients given from 60 to 270 mg/day, but increased plasma levels were not noted in another patient given an undisclosed dose (Napier *et al.*, 1976). Other possible effects of oxymetholone could include enhancement of the differentiation of erythropoietin responsive cells or ofthe colony-forming unit erythroid stem cells of the erythroblast system (Hirota, 1981). One possible consequence of this type of action on the bone marrow is a stimulation of abnormal stem cells to produce leukemia. Isolated reports of an association of oxymetholone treatment with acute myeloblastic leukemia have appeared (Delamore and Geary, 1971; Li *et al.*, 1971). DNA synthesis rates in cultured acute myeloblastic cells *in vitro* were not affected by inclusion of oxymetholone in the culture media (Ribas-Mundo *et al.*, 1976).

GENETIC TOXICITY

There is only one published study describing the mutagenic activity of oxymetholone. Oxymetholone was tested for mutagenicity in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535, with and without liver S9 metabolic activation enzymes; results in all four strains were negative (Zeiger *et al.*, 1992).

STUDY RATIONALE

Oxymetholone was nominated by the National Institute of Environmental Health Sciences and the National Cancer Institute based on its extensive illicit pharmaceutical use and the limited evidence that it is a potential human carcinogen (IARC, 1977, 1982; NTP, 1998). There were no data available to evaluate the carcinogenicity in experimental animals to support the "limited evidence" conclusion from human case studies (IARC, 1982). Fourteen-day studies were conducted using dosed feed. Oxymetholone in feed was poorly accepted by rats and mice; this was likely due to a palatability problem. Therefore, 16-day and 14-week studies in which oxymetholone was administered by gavage in 0.5% methylcellulose to male and female F344/N rats and B6C3F$_1$ mice and a 2-year study in which oxymetholone was administered by gavage in 0.5% methylcellulose to F344/N rats were conducted to determine the toxicity and carcinogenicity of oxymetholone.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Oxymetholone

Oxymetholone was obtained from Syntex Corporation (Republic of Panama) in one lot (S090189). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix G). Reports on analyses performed in support of the oxymetholone studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white fluffy powder, was identified as oxymetholone by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy, melting point, and optical rotation value. The purity of lot S090189 was determined with elemental analyses, weight loss on drying, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for oxymetholone. Weight loss on drying indicated 0.09% water. TLC by two systems indicated a major spot and no impurities. HPLC revealed a major peak and no impurities with areas of 0.1% or greater relative to the major peak area. Major peak comparisons of lot S090189 to a dried United States Pharmacopeia (USP) reference standard by HPLC indicated a purity of 102% ± 1% for lot S090189. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using HPLC. These studies indicated that oxymetholone was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature in amber glass jars. Stability was monitored during the 16-day, 14-week, and 2-year studies using HPLC. No degradation of the bulk chemical was detected.

Methylcellulose

Methylcellulose was obtained from Fisher Scientific Company (Pittsburgh, PA) in two lots (876672 and 946150) and from Sigma Chemical Corporation (St. Louis, MO) in one lot (48F0090). Lot 876672 was used in all studies and lots 946150 and 48F0090 were used in the 2-year study. Identity, purity, and stability analyses of lot 876672 were conducted by the analytical chemistry laboratory during the 16-day and 14-week studies. The identity of all lots was confirmed by the study laboratory during the 2-year study (Appendix G).

The chemical, a white powder, was identified as methylcellulose by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy and USP XXI analyses for the apparent viscosity, weight loss on drying, residue on ignition, arsenic content, heavy metal content, and percent methoxy content. The purity of lot 876672 was determined by Karl Fischer water analysis, elemental analyses, functional group titration, and HPLC. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for methylcellulose based on 1.8° of substitution and corrected for 1.94% water (indicated by Karl Fischer water analysis). In addition, elemental analyses indicated 0.058% sodium. Karl Fischer water analysis indicated 1.94% ± 0.03% water. Functional group titration indicated a methoxy group content of 30.62% ± 0.08%; this value is consistent with the theoretical value, assuming 1.8° of substitution (30.4%). The complete battery of USP tests for methylcellulose indicated the following results: the apparent viscosity was 3,749 to 4,060 cP; the weight loss on drying was 1.9% ± 0.3%; the residue on ignition was less than 0.3%; the tests for arsenic and heavy metals were passed; and the methoxy group contents were 30.3% ± 0.2% for lot 876672 and 28.3% ± 0.0% for the USP reference material. The chemical met the USP specifications for methylcellulose for all analyses. HPLC revealed a major peak and no impurities with areas of 0.1% or greater relative to the major peak area. Cumulative analytical data indicated

that lot 876672 of methylcellulose was suitable for use as a dosing vehicle.

Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography. These studies indicated that methylcellulose was stable as a bulk chemical for 3 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored protected from light at room temperature. Stability and purity were monitored during the 2-year study by comparing the methoxy group content to a frozen reference sample of lot 876672. No degradation of the bulk chemical was detected.

Preparation and Analysis of Dose Formulations

The vehicle was prepared by mixing methylcellulose with heated, deionized water and then diluting with water to form a 0.5% solution, which was allowed to cool. Oxymetholone was mixed with the dosing vehicle to form a paste, which was then added to the remaining vehicle and stirred until a homogenous solution was obtained (Table G1). The dose formulations were stored at 5° C in amber glass jars during the 16-day studies and at room temperature in amber glass jars for up to 35 days in the 14-week and 2-year studies. Homogeneity and stability studies of the 31.25 and 500 mg/mL (16-day studies), 15.75 and 250 mg/mL (14-week studies), and 0.6 and 30 mg/mL (2-year study) dose formulations were performed by the analytical chemistry laboratory using HPLC. Homogeneity was confirmed, and the stability of the dose formulations was confirmed for 28 days (16-day studies) or 35 days (14-week and 2-year studies) at up to room temperature when stored protected from light. Formulations were also stable for at least 3 hours when stored open to air and light. Resuspendability of the 500 mg/mL formulation after storage for 28 days at 5° C or at room temperature was also confirmed by HPLC.

Periodic analyses of the dose formulations of oxymetholone were conducted at the study laboratory using HPLC. Dose formulations were analyzed once during the 16-day studies (Table G2), every 4 to 8 weeks during the 14-week studies (Table G3), and approximately every 8 weeks during the 2-year study (Table G4). Four of the five dose formulations analyzed and used during the 16-day studies were within 10% of the target concentration. One dose formulation which was 116% of the target concentration was considered to be acceptable for the 16-day studies and was used for dosing. Five of the ten animal room samples were within 10% of the target concentration. All dose formulations used during the 14-week studies were within 10% of the target concentration. Of the animal room samples, 70% (21/30) were within 10% of the target concentration. All 56 of the dose formulations analyzed during the 2-year study were within 10% of the target concentration. Of the animal room samples, 70% (14/20) were within 10% of the target concentration. Variations in postadministration values during all the studies were thought to be caused by difficulties in resuspension of the formulations.

16-Day Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 14 days and were 6 weeks old on the first day of the studies. Groups of five male and five female rats received oxymetholone in 0.5% methylcellulose by gavage at doses of 0, 160, 315, 625, 1,250, or 2,500 mg/kg and groups of five male and five female mice received oxymetholone in 0.5% methylcellulose by gavage at doses of 0, 320, 630, 1,250, 2,500, or 5,000 mg/kg. Feed and water were available *ad libitum*. Rats and female mice were housed five per cage, and male mice were housed individually. Clinical findings were recorded twice daily for rats and mice. The animals were weighed initially, on day 8, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

14-Week Studies

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to oxymetholone and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY).

On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 12 (rats) or 15 (mice) days and were approximately 7 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix I).

Groups of 10 male and 10 female rats received oxymetholone in 0.5% methylcellulose by gavage at doses of 0, 80, 160, 315, 625, or 1,250 mg/kg. Groups of 10 male and 10 female mice received oxymetholone in 0.5% methylcellulose by gavage at doses of 0, 160, 320, 630, 1,250, or 2,500 mg/kg. Feed and water were available *ad libitum*. Rats and female mice were housed five per cage and male mice were housed individually. Clinical findings were recorded and the animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

On days 5 and 19 and at the end of the study, blood was collected from the retroorbital sinus of clinical pathology study rats for hematology and clinical chemistry analyses. Blood was collected from the posterior vena cava of core study rats at the end of the study for auxiliary coagulation tests. Blood samples for hematology analyses were placed into microcollection tubes containing potassium EDTA. Erythrocyte, platelet, and leukocyte counts, hematocrit values, mean cell hemoglobin, and mean cell hemoglobin concentration were determined using a Serono-Baker System 9000 hematology analyzer (Serono-Baker Diagnostics, Allentown, PA). Hemoglobin concentration was determined photometrically using a cyanmethemoglobin procedure. Differential leukocyte counts were determined microscopically from slides stained with modified Wright-Giemsa stain. Reticulocyte counts were determined from new methylene blue-stained smears by a Miller disc. For clinical chemistry analyses, samples were collected into microcollection serum separator tubes, and the serum samples were analyzed using a Hitachi 704® chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) using commercially available reagents. Samples for coagulation studies were placed in tubes containing sodium citrate. Activated partial thromboplastin time was determined using a Coag-a-Mate-X2 automated photo-optical clot detection system (Organon Teknika, Turnhout, Belgium) and Organon Teknika Automated® or APTT® reagents. Prothrombin time was measured using a Coag-a-Mate automated photo-optical clot detection system and Organon Teknika Automated® reagents. Fibrinogen concentration was determined using a BBL Fibrometer® with a modified thrombin clotting time procedure. The parameters measured are listed in Table 1.

At the end of the 14-week studies, samples were collected for sperm motility and vaginal cytology evaluations on core study rats exposed to 0, 80, 315, or 1,250 mg/kg and mice exposed to 0, 630, 1,250, or 2,500 mg/kg. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count, motility, and concentration. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing

10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer. A necropsy was performed on all core study animals. The heart, right kidney, liver, lung, right testis, thymus, and uterus were weighed. The sartorius and gastrocnemius muscles from the right hind legs of rats were removed, weighed, dried overnight in an oven at 47° C, and reweighed to determine the effects on increasing or decreasing muscle mass (Lamb, 1984). Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on vehicle control and 1,250 mg/kg rats and vehicle control and 2,500 mg/kg mice. Table 1 lists the tissues and organs routinely examined.

Cell proliferation in the liver and kidney of rats and mice was evaluated by immunohistochemical staining for proliferating cell nuclear antigen. Unstained paraffin sections from five randomly selected male and female control rats and mice, 1,250 mg/kg rats, and 2,500 mg/kg mice were immunostained and the nuclei scored according to the methods of Foley *et al.* (1991). At least 2,000 hepatocytes and 3,000 renal tubule epithelial cells per animal were scored in a total of 10 random fields, and the proliferating index was calculated by dividing the number of labeled nuclei by the number of total cells counted.

2-Year Study

Study Design

Groups of 90 male and 90 female rats received oxymetholone in 0.5% methylcellulose by gavage at doses of 0, 3, 30, or 150 mg/kg for males and 0, 3, 30, or 100 mg/kg for females. Interim evaluations of 10 male and 10 female rats from each group were conducted at 3, 6, 12, and 18 months.

Ten male and 10 female rats per group were designated for interim plasma toxicokinetic determinations at 6, 12, and 18 months. Blood was collected via cardiac puncture into heparinized tubes, and plasma was separated by centrifugation and immediately frozen.

A standard operating procedure for analysis of oxymetholone in plasma was developed and validated for the concentration range of 0.1 to 10 mg/L. Oxymetholone was extracted with a mixture of dimethyl formamide and acetonitrile. Following precipitation of the proteins and centrifugation, the supernatant was transferred and dried with sodium sulfate. The clear extract was then evaporated to dryness and derivatized with methanolic phosphoric acid at 90° C. Plasma samples were analyzed using reverse-phase HPLC with ultraviolet detection to measure the concentrations of oxymetholone extracted from the plasma. Danazol was used as the internal standard. HPLC was performed on a Zorbax TMS column using ultraviolet detection (285 nm) and a mobile phase of acetonitrile:water:ammonium dihydrogen phosphate (550:500:5.75 v/v/wt). The flow rate was 1.2 mL/minute. Recoveries of oxymetholone and the internal standard averaged 63.2% and 84.1%, respectively. The linear regression equation relating the peak height ratio of the standards to their respective concentrations in mg/L plasma was computed without blank values. The spiked plasma standard data were plotted to evaluate linearity. The regression equation and the peak height ratio determined for each spiked plasma standard were used to calculate the concentration of test compound for each spiked standard. Stability of the plasma was determined; stability was confirmed for 3 days.

Source and Specification of Animals

Male and female F344/N rats were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year study. Rats were quarantined for 13 or 14 days before the beginning of the study. Five male and five female rats were randomly selected for parasite evaluation and gross observation of disease. Rats were approximately 7 weeks old at the beginning of the study. The health of the animals was monitored during the study according to the protocols of the NTP Sentinel Animal Program (Appendix I).

Animal Maintenance

Male rats were housed three per cage, and female rats were housed five per cage. Feed and water were available *ad libitum*. Cages were changed twice per week, and racks were rotated every 2 weeks. Further

details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix H.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the study.

A complete necropsy and microscopic examination were performed on all rats. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. At the 3-, 6-, 12-, and 18-month interim evaluations, qualitative morphologic examination was performed on one ovary and quantitation of follicles was conducted on the contralateral organ according to the methods of Pederson and Peters (1968). For extended evaluation of renal proliferative lesions, kidneys were sectioned at 1-mm intervals, and four additional sections were obtained from each kidney. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. 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 evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the adrenal gland, bone (males), heart, kidney, liver, lung (females), mammary gland, ovary, pituitary gland, testis, and uterus.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Oxymetholone

16-Day Studies	14-Week Studies	2-Year Study
Study Laboratory		
Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	F344/N rats
Animal Source		
Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Farms (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies		
14 days	Rats: 12 days Mice: 15 days	13 days (males) or 14 days (females)
Average Age When Studies Began		
6 weeks	7 weeks	7 weeks
Date of First Dose		
Rats: 3 December 1991 Mice: 4 December 1991	Rats: 10 May 1992 (clinical pathology study males), 11 May 1992 (core study males and clinical pathology study females), or 12 May 1992 (core study females) Mice: 13 May 1992 (males) 19 May 1992 (females)	21 April 1993 (males) 22 April 1993 (females)
Duration of Dosing		
16 days (5 days/week)	14 weeks (5 days/week)	104 weeks (5 days/week)
Date of Last Dose		
Rats: 18 December 1991 Mice: 19 December 1991	Rats: 10 August 1992 (males) 11 August 1992 (females) Mice: 12 August 1992 (males) 18 August 1992 (females)	18 April 1995 (males) and 18-19 April 1995 (females)
Necropsy Dates		
	Rats: 11 August 1992 (males) 12 August 1992 (females) Mice: 13 August 1992 (males) 19 August 1992 (females)	3-Month interim evaluation: 21 July 1993 (males) and 22 July 1993 (females) 6-Month interim evaluation: 21 October 1993 (males) and 22 October 1993 (females) 12-Month interim evaluation: 21 April 1994 (males) and 22 April 1994 (females) 18-Month interim evaluation: 20 October 1994 (males) and 21 October 1994 (females) Terminal sacrifice: 18 April 1995 (males) and 19-20 April 1995 (females)

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Oxymetholone

16-Day Studies	14-Week Studies	2-Year Study
Average Age at Necropsy	20 weeks	3-Month interim evaluation: 20 weeks 6-Month interim evaluation: 33 weeks 12-Month interim evaluation: 59 weeks 18-Month interim evaluation: 85 weeks Terminal sacrifice: 111 weeks
Size of Study Groups 5 males and 5 females	10 males and 10 females	Interim evaluations: 10 males and 10 females per evaluation Terminal sacrifice: 50 males and 50 females
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 16-day studies	Same as 16-day studies
Animals per Cage Rats and female mice: 5 Male mice: 1	Rats and female mice: 5 Male mice: 1	3 (males) or 5 (females)
Method of Animal Identification Tail tattoo	Tail tattoo	Tail tattoo
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed twice per week.	Same as 16-day studies	Same as 16-day studies
Water Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Cages Polycarbonate (Lab Products, Inc., Maywood, NJ), changed twice per week for multiply housed animals and once per week for individually housed animals	Same as 16-day studies	Same as 16-day studies
Bedding Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice per week for multiply housed animals and once per week for individually housed animals	Same as 16-day studies	Same as 16-day studies
Cage Filters Spun-Bonded DuPont 2024 polyester (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks	Same as 16-day studies	Same as 16-day studies
Racks Stainless steel (Lab Products, Maywood, NJ), changed every 2 weeks.	Same as 16-day studies	Same as 16-day studies

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Oxymetholone

16-Day Studies	14-Week Studies	2-Year Study
Animal Room Environment		
Temperature: 22.2°-23.3° C Relative humidity: 46%±9% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 22.2°-26.1° C for rats or 20.6°-22.8° C for mice Relative humidity: 47%±7% for rats or 44%±7% for mice Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 19.4°-26.1° C Relative humidity: 46%±20% Room fluorescent light: 12 hours/day Room air changes: 10/hour
Doses		
Rats: 0, 160, 315, 625, 1,250, or 2,500 mg/kg body weight in 0.5% methylcellulose by gavage at a volume of 5 mL/kg body weight Mice: 0, 320, 630, 1,250, 2,500, or 5,000 mg/kg body weight in 0.5% methylcellulose at a volume of 10 mL/kg body weight	Rats: 0, 80, 160, 315, 625, or 1,250 mg/kg body weight in 0.5% methylcellulose by gavage at a volume of 5 mL/kg body weight Mice: 0, 160, 320, 630, 1,250, or 2,500 mg/kg body weight in 0.5% methylcellulose at a volume of 10 mL/kg body weight	0, 3, 30, or 150 mg/kg (males) or 0, 3, 30, or 100 mg/kg (females) body weight in 0.5% methylcellulose by gavage at a volume of 5 mL/kg body weight
Type and Frequency of Observation		
Observed twice daily; animals were weighed initially, on day 8, and at the end of the studies; clinical findings were recorded twice daily.	Observed twice daily; animals were weighed and clinical findings were recorded initially, weekly, and at the end of the studies.	Observed twice daily; animals were weighed and clinical findings were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the study.
Method of Sacrifice		
CO_2 asphyxiation	Same as 16-day studies	Same as 16-day studies
Necropsy		
None	Necropsy was performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, thymus, and uterus. In addition, the sartorius and gastrocnemius muscles from the right hind legs of rats were removed, weighed, dried overnight, and reweighed.	Necropsy was performed on all animals.
Clinical Pathology		
None	On days 5 and 19 and at the end of the study blood was collected from the retroorbital sinus of clinical pathology study rats for hematology and clinical chemistry. At the end of the study, blood was collected from the posterior vena cava of core study rats for auxiliary coagulation tests. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and nucleated erythrocyte counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; platelet count; leukocyte counts and differentials; activated partial thromboplastin time; thromboplastin time; and fibrinogen concentration ***Clinical chemistry:*** creatinine, total protein, albumin, cholesterol, and triglyceride concentrations; alanine aminotransferase, creatine kinase, sorbitol dehydrogenase, and 5′-nucleotidase activities; and bile salt concentration	None

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Oxymetholone

16-Day Studies	14-Week Studies	2-Year Study
Histopathology		
None	Complete histopathology was performed on 0 and 1,250 mg/kg rats and 0 and 2,500 mg/kg mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, epididymis, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (with adjacent skin), nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The following target organs were identified in rats: adrenal gland, heart, kidney, mammary gland, ovary, and uterus. The following target organs were identified in mice: clitoral gland, kidney, ovary, and salivary gland.	Complete histopathology was performed on all rats. In addition to gross lesions and tissue masses, the following tissues were examined in all groups of rats: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.
Sperm Motility and Vaginal Cytology		
None	At the end of the studies, sperm samples were collected from all male rats in the 0, 80, 315, and 1,250 mg/kg dose groups and from male mice in the 0, 630, 1,250, and 2,500 mg/kg dose groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per gram testis, spermatid heads per testis, spermatid count, and sperm motility and concentration. The left epididymis, cauda epididymis, and testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all female rats in the 0, 80, 315, and 1,250 mg/kg groups and all female mice in the 0, 630, 1,250, and 2,500 mg/kg groups for vaginal cytology evaluations. The following parameters were evaluated: relative frequency of estrous stages and estrous cycle length.	None
Toxicokinetics		
None	None	At the 6-, 12-, and 18-month interim evaluations, blood was collected via cardiac puncture from 10 male and 10 female anesthetized rats for determinations of oxymetholone concentrations in plasma.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Oxymetholone

16-Day Studies	14-Week Studies	2-Year Study
Proliferating Cell Nuclear Antigen Analyses		
None	Cell proliferation in the liver and kidney of rats and mice was evaluated by immunohistochemical staining for proliferating cell nuclear antigen. Unstained paraffin sections from five randomly selected male and female vehicle control rats and mice, 1,250 mg/kg rats, and 2,500 mg/kg mice were immunostained and the nuclei scored according to the methods of Foley *et al*. (1991). At least 2,000 hepatocytes and 3,000 renal tubule epithelial cells per animal were scored in a total of 10 random fields, and the proliferating index was calculated by dividing the number of labeled nuclei by the number of cells counted.	None

STATISTICAL METHODS

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 found dead of other than natural causes or missexed were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, and B5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3 and B3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3 and B3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of $k=3$ was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and $B6C3F_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1-P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (e.g., P=0.99 is presented as P=0.01N). For neoplasms and nonneoplastic lesions detected at the interim evaluations, the Fisher exact test (Gart *et al.*, 1979), a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Tissue and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across dose levels (analogous nonparametric procedures gave similar results). A Student's *t*-test was used to test for statistically significant differences in the proliferation index between vehicle controls and dosed animals.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year study were submitted to the NTP Archives, this study was audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of oxymetholone was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated erythrocytes in peripheral blood of mice. The protocols for these studies and the results are given in Appendix C.

The genetic toxicity studies of oxymetholone are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the molecular structure and the effects of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats

and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

RATS

16-DAY STUDY

All male rats survived to the end of the study; one 2,500 mg/kg female was found dead on day 14 (Table 2). The final mean body weights and body weight gains of all dosed groups of males were significantly less than those of the vehicle controls. The final mean body weights and body weight gains of 160 and 315 mg/kg females were significantly greater than those of the vehicle controls. No clinical findings that could be attributed to oxymetholone administration were observed.

TABLE 2
Survival and Body Weights of Rats in the 16-Day Gavage Study of Oxymetholone

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	149 ± 3	237 ± 3	88 ± 2	
160	5/5	151 ± 2	220 ± 1**	70 ± 1**	93
315	5/5	149 ± 2	205 ± 4**	56 ± 2**	86
625	5/5	151 ± 1	197 ± 5**	47 ± 5**	83
1,250	5/5	146 ± 4	187 ± 6**	41 ± 4**	79
2,500	5/5	149 ± 3	186 ± 3**	38 ± 4**	79
Female					
0	5/5	121 ± 3	155 ± 3	35 ± 2	
160	5/5	118 ± 2	174 ± 4**	56 ± 3**	112
315	5/5	118 ± 1	169 ± 2*	51 ± 3**	108
625	5/5	118 ± 1	163 ± 4	45 ± 3	105
1,250	5/5	117 ± 1	150 ± 4	32 ± 4	96
2,500	4/5[c]	117 ± 2	148 ± 3	33 ± 2	96

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Day of death: 14

14-WEEK STUDY

One male rat each in the 625 and 1,250 mg/kg groups died before the end of the study (Table 3). One 1,250 mg/kg female died due to gavage error on day 2. Mean body weight gains of dosed males were reduced in a dose-related manner with mean body weights 2% to 12% less than that of the vehicle controls at week 3 and progressing to 6% to 25% less than that of the vehicle controls by week 14 (Figure 2). The final mean body weights of male rats that received 160 mg/kg or greater were significantly less than that of the vehicle controls (Table 3). In contrast, mean body weight gains of all groups of treated female rats were significantly greater than that of the vehicle controls. However, the rate of mean body weight gain was inversely proportional to the oxymetholone concentrations. Mean body weights of treated females were 10% to 17% greater than the vehicle controls by week 3 and 11% to 31% greater by week 14 (Figure 2). Final mean body weights of all groups of treated females were significantly greater than that of the vehicle controls. No clinical findings that could be attributed to oxymetholone administration were observed.

TABLE 3
Survival and Body Weights of Rats in the 14-Week Gavage Study of Oxymetholone

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	151 ± 8	373 ± 4	222 ± 8	
80	10/10	153 ± 8	349 ± 8	196 ± 9*	94
160	10/10	148 ± 8	326 ± 8**	178 ± 7**	88
315	10/10	151 ± 7	305 ± 5**	154 ± 4**	82
625	9/10[c]	150 ± 8	279 ± 9**	141 ± 5**	75
1,250	9/10[d]	151 ± 8	280 ± 5**	128 ± 5**	75
Female					
0	10/10	111 ± 3	197 ± 3	86 ± 4	
80	10/10	114 ± 3	258 ± 3**	145 ± 4**	141
160	10/10	115 ± 3	252 ± 7**	147 ± 6**	128
315	10/10	114 ± 3	232 ± 4**	119 ± 4**	118
625	10/10	114 ± 3	222 ± 5**	109 ± 3**	114
1,250	9/10[e]	114 ± 3	218 ± 5**	104 ± 3*	111

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Day of death: 93 (after last day of dosing but before necropsy)
[d] Day of death: 62
[e] Day of death: 2 (accidental death)

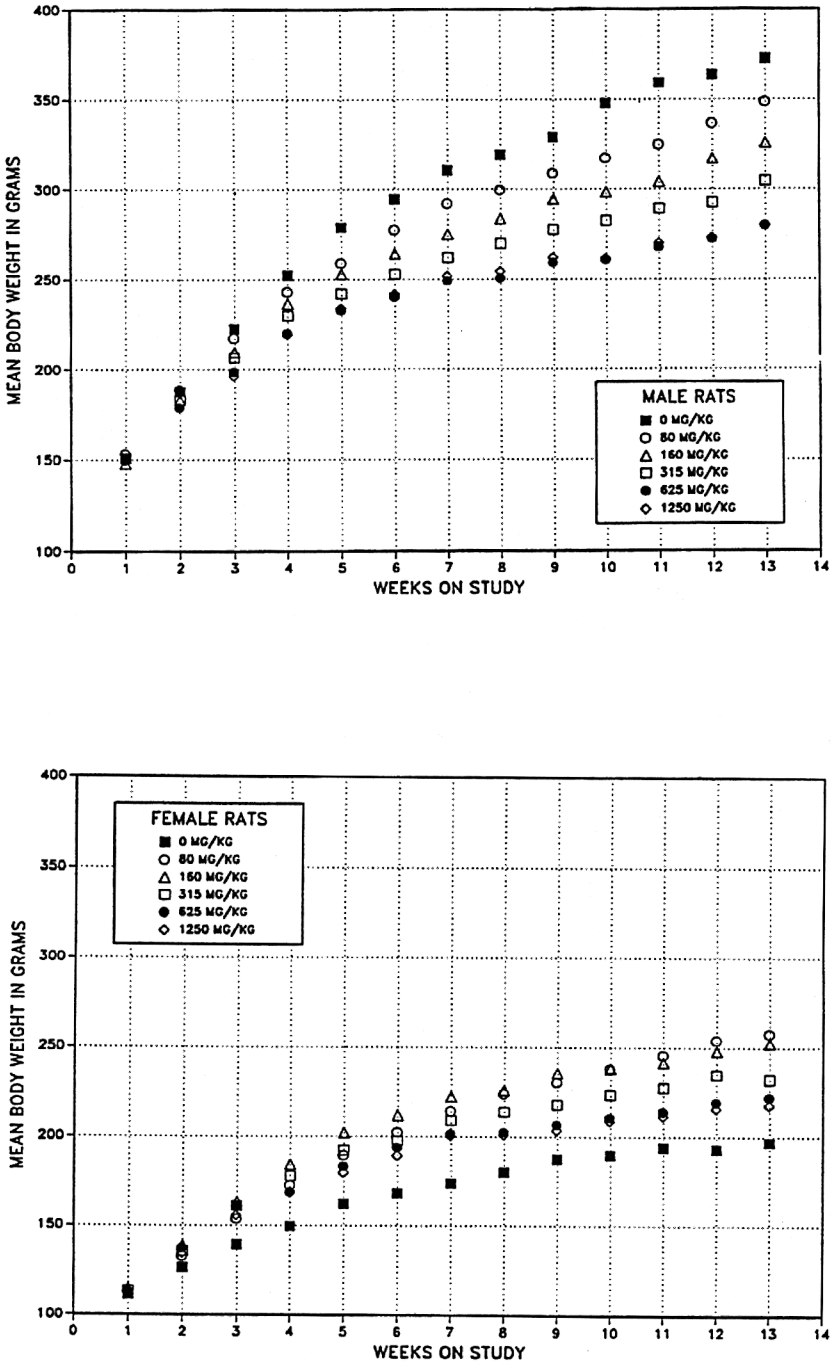


FIGURE 2
Growth Curves for Male and Female Rats Administered Oxymetholone by Gavage for 14 Weeks

The hematology and clinical chemistry data are listed in Table D1. A treatment-related erythrocytosis, evidenced by increases in erythrocyte counts, total hemoglobin concentrations, and hematocrit values, occurred in all dosed female rats at week 14. Erythrocytosis also occurred in all treated males at 14 weeks, but only erythrocyte counts were elevated. At week 14, the erythrocytes of the treated male and female rats were characterized as microcytic due to decreased mean cell volumes. Decreased mean cell hemoglobin values occurred concurrently with the decreased mean cell volumes and reflected the decreased erythrocyte size. At week 14, there also were decreases in the mean cell hemoglobin concentrations in females receiving 160 mg/kg or greater. In contrast to the increased erythrocyte counts, there were transient decreases in reticulocyte counts on day 19 in male rats receiving 160 mg/kg or greater and in females receiving 625 or 1,250 mg/kg.

On day 5, increases in leukocyte counts, characterized by increased numbers of segmented neutrophils and lymphocytes, occurred in females that received 160 mg/kg or greater and males that received 315 mg/kg or greater. The increased segmented neutrophil counts persisted throughout the study. The leukocytosis, however, was transient and by week 14, leukocyte counts for female rats were similar to vehicle controls and decreased in males that received 160 mg/kg or greater. In the males, decreased leukocyte counts were characterized by decreased lymphocyte counts. At week 14, there were minimal increases in the thromboplastin times in all treated females and activated partial thromboplastin times in females receiving 625 mg/kg or greater; increases in the coagulation variables did not occur in treated males.

A dose-related hypocholesterolemia, demonstrated by decreased serum cholesterol concentrations, occurred at all time points for all dosed groups of male and female rats. The severity of hypocholesterolemia also increased with time. Mild to marked increases in triglyceride concentrations also occurred in dosed rats, but there was no consistent time or dose relationship for the increases.

Decreased creatinine concentrations also occurred in male and female rats in response to oxymetholone treatment. With time, the decreases became more severe and more dose groups were affected; by week 14, males receiving 160 mg/kg or greater and all dosed groups of females were affected. Treatment-related decreases in total protein concentrations occurred in 625 and 1,250 mg/kg females at all time points. At week 14, decreased total protein concentrations also occurred in the 315 mg/kg females and in 625 and 1,250 mg/kg males. Albumin concentrations were unaffected.

5′-Nucleotidase, a plasma membrane brush border enzyme, is used as a marker of cholestatic disease. Dose- and time-related decreases in 5′-nucleotidase activity occurred in treated rats. In rats receiving 625 or 1,250 mg/kg oxymetholone, 5′-nucleotidase activity was less than that of vehicle controls by day 5 and decreased further between days 5 and 19, after which there was no further change. 5′-Nucleotidase activities in rats receiving 160 or 315 mg/kg oxymetholone were less than those of the vehicle controls by day 19 and decreased further by week 14, at which time 5′-nucleotidase activity in 80 mg/kg rats was also less than vehicle controls.

There was a transient, treatment-related increase in the activities of alanine aminotransferase in males and females. On day 5, males and females that received 160 mg/kg or greater had increased activities and on day 19, all treated groups of females demonstrated increased alanine aminotransferase activities. However, the increased alanine aminotransferase activities were no longer present on day 19 in males or in males or females at week 14.

Compared to vehicle controls, kidney weights of males and females and liver and uterus weights of females were increased in rats that received 315 mg/kg or greater; thymus weights of males and females and sartorius muscle and testis weights of males were less (Tables E1 and E2). The absolute wet sartorius muscle weights of 625 and 1,250 mg/kg males and the absolute dry sartorius muscle weights of 315, 625, and 1,250 mg/kg males were significantly less than those of the vehicle controls (Table E2). The absolute wet gastrocnemius muscle weights of 80 and 160 mg/kg females were significantly greater than those of the vehicle controls; however, the relative wet gastrocnemius muscle weight of 160 mg/kg females was significantly less than those of the vehicle controls.

Pathology examinations of rats administered oxymetholone for 14 weeks revealed effects in the kidney, mammary gland, uterus, ovary, adrenal gland, and heart (Table 4).

Microscopic effects in the kidney consisted of increased incidences of renal tubule regeneration in males and females and renal tubule mineralization in males compared to the vehicle controls (Table 4). Regeneration was a minimal to moderate change in all treated males, minimal in females dosed with 160 mg/kg or greater, and characterized primarily by foci of tubules interpreted to be regenerative due to cytoplasmic basophilia and increased nuclear/cytoplasmic ratio. In more severe instances, there was piling up of the epithelial cells lining the tubule and variation in nuclear size in addition to mild inflammatory changes in the interstitium. In some foci, the basement membrane was thickened, and there were luminal protein casts. This spectrum of changes is similar to that of chronic nephropathy, a common spontaneous degenerative change in F344/N rats, particularly in males. However, because regeneration and not degeneration was considered the primary change at the higher doses, this diagnosis was made instead of nephropathy. At the lower doses, regeneration was diagnosed when the number of regenerative foci exceeded that seen in the vehicle controls with spontaneous nephropathy. Mineralization was another kidney effect found in all groups of dosed males and consisted of basophilic concretions within tubules at the cortico-medullary junction. Renal tubule mineralization is normally present in vehicle control female rats, and neither the incidence nor severity was increased in treated females.

Morphologic changes of the mammary gland were treatment-related effects in male and female rats. In young control F344/N rats, mammary tissue is sexually dimorphic. In males, the mammary gland tissue is more abundant than in females and is composed of solid lobules of eosinophilic cells without obvious alveolar or ductal differentiation (Plate 1a), whereas in females, it is composed of scattered tubules with little alveolar component (Plate 2a). In oxymetholone-treated males, there was clear differentiation into alveolar and ductal structures lined by cuboidal epithelial cells and containing luminal secretory material (Plate 1b). This effect, diagnosed as dilatation, was present in males administered 160 mg/kg or greater. In treated females, a change diagnosed as hyperplasia occurred in all dosed groups and was characterized by an increased amount of solid and alveolar tissue containing secretory material (Plate 2b). These treatment-related effects in males and females, in which the morphology of the mammary gland was more similar to that of the opposite gender, were attributed to a hormonal effect on this sexually dimorphic tissue.

In female rats, the uterus and ovaries were also identified as target organs. Gross observations of enlarged, fluid-filled uteri and increased uterine weights corresponded microscopically to luminal dilatation consistent with hydrometra in females that received 160 mg/kg or greater. An unusual morphologic change of the ovary in treated females consisted of shrunken organs composed of atretic follicles and prominent dark-staining interstitial cells (Plates 3a and 3b). There were reduced numbers of developing follicles or corpora lutea, indicating disrupted follicle maturation and luteogenesis. Collectively, these ovarian changes were diagnosed as dysgenesis and were found in all groups of oxymetholone-treated females (Table 4).

Cytoplasmic vacuolization of adrenal cortical cells occurred in male and female rats; incidences in 315 mg/kg and greater females were significantly increased (Table 4). In vehicle controls, a granular or microvesicular appearance of the cytoplasm of cortical cells was observed, primarily in the zona fasciculata in males. Larger, clear cytoplasmic vacuoles were found in these cells in rats administered 315 mg/kg or greater.

Myocardial degeneration (cardiomyopathy), evidenced by scattered interstitial foci of chronic mononuclear inflammatory cell infiltration, may be present in vehicle control F344/N rats at this age, especially males. The incidence and severity of this change was increased in female rats exposed to oxymetholone as evidenced by increased numbers and extent of inflammatory foci (Table 4). The severity of cardiomyopathy was slightly increased in male rats.

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Rats in the 14-Week Gavage Study of Oxymetholone

	Vehicle Control		80 mg/kg		160 mg/kg		315 mg/kg		625 mg/kg		1,250 mg/kg	
Male												
Kidney[a]	10		10		10		10		10		9	
Renal Tubule, Regeneration, Diffuse[b]	0		10**	(1.1)[c]	10**	(1.1)	10**	(1.9)	10**	(2.2)	9**	(3.2)
Renal Tubule, Mineralization	0		1	(1.0)	10**	(1.3)	10**	(2.0)	10**	(2.5)	9**	(2.9)
Mammary Gland	9		9		7		8		10		8	
Dilatation	0		0		7**	(1.6)	8**	(2.6)	10**	(2.4)	8**	(2.9)
Adrenal Gland	10		10		10		10		10		9	
Cytoplasmic Vacuolization	9	(1.0)	6	(1.0)	10	(1.0)	10	(1.4)	10	(1.6)	9	(3.0)
Heart	10		10		10		10		10		9	
Myocardium, Degeneration, Chronic	10	(1.3)	8	(1.6)	10	(1.4)	10	(1.3)	9	(1.8)	9	(1.8)
Female												
Kidney	10		10		10		10		10		10	
Renal Tubule, Regeneration, Diffuse	0		1	(1.0)	8**	(1.0)	9**	(1.0)	9**	(1.0)	10**	(1.1)
Renal Tubule, Mineralization	10	(1.2)	10	(1.0)	10	(1.7)	10	(1.5)	10	(1.3)	9	(1.3)
Mammary Gland	10		8		8		9		8		10	
Hyperplasia	0		5**	(1.6)	8**	(1.6)	9**	(1.8)	8**	(1.8)	9**	(2.0)
Uterus	10		10		10		10		10		10	
Hydrometra	1	(2.0)	2	(1.0)	9**	(1.8)	10**	(3.0)	10**	(2.9)	9**	(2.9)
Ovary	10		10		10		10		10		10	
Dysgenesis	0		10**	(1.0)	10**	(2.0)	10**	(2.0)	10**	(3.5)	9**	(4.0)
Adrenal Gland	10		10		10		10		10		10	
Cytoplasmic Vacuolization	0		0		0		8**	(1.1)	10**	(2.1)	9**	(2.1)
Heart	10		10		10		10		10		10	
Myocardium, Degeneration, Chronic	3	(1.0)	6	(1.0)	7	(1.0)	9**	(1.7)	9**	(1.4)	9**	(1.7)

** Significantly different ($P \leq 0.01$) from the vehicle control group by the Fisher exact test
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Quantitation of proliferating cell nuclear antigen (PCNA) indices in the liver and kidney of vehicle control and 1,250 mg/kg rats was performed. The only significant increase noted was in the labeling index of renal tubule cells from male rats exposed to 1,250 mg/kg oxymetholone (data not shown).

For dosed male rats, left cauda epididymis, left epididymis, and left testis weights and spermatid counts and total spermatid heads per testis were significantly less than those of the vehicle controls (Table F1). The number of spermatid heads per gram testis was significantly greater than that of the vehicle controls for dosed males. Females in the 80 mg/kg group spent more time in diestrus and less time in estrus than vehicle control females (Table F2).

Dose Selection Rationale: Doses for male rats were set at 0, 3, 30, and 150 mg/kg for the 2-year study based on the significant reduction in the rate of body weight gain observed in groups that received 315 mg/kg or greater, an increase in kidney weights, and increased severities of regeneration and renal tubule mineralization in groups that received 315 mg/kg or greater. The final mean body weight of 160 mg/kg males was 12% less than that of the vehicle controls; however, none of the other treatment-related effects were considered to be life-threatening. Therefore, the high dose was set slightly below this concentration. The mid-dose concentration for the 2-year study was set below the lowest dose concentration used in the 14-week study because of the slight treatment-related effect on body weight gain in the 80 mg/kg group and the presence of minimal renal tubule regeneration. The low dose of 3 mg/kg was selected to be in the range commonly used in humans (*PDR,* 1998).

Doses for female rats were set at 0, 3, 30, and 100 mg/kg for the 2-year study based on increased incidences and severities of dysgenesis of the ovary at doses of 160 mg/kg or greater and the effects of increased incidences of mammary gland hyperplasia and uterine hydrometra. There were significant increases in the body weights of all dosed groups. However, the increased rate of body weight gain was inversely related to steroid concentration; i.e., the 80 mg/kg group mean body weight gain was greatest and the 1,250 mg/kg group was least, suggesting that the anabolic effect on body weight gain was less effective at doses of 160 mg/kg and greater. Although there was an expected significant increase in body weights of females that received 80 mg/kg or greater, there were no other treatment-related effects that would preclude the use of this dose. A high dose of 100 mg/kg was selected for the 2-year study; the two lower doses were the same as those for males.

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves (Figure 3). Survival of all dosed groups was similar to that of the vehicle controls.

Body Weights and Clinical Findings

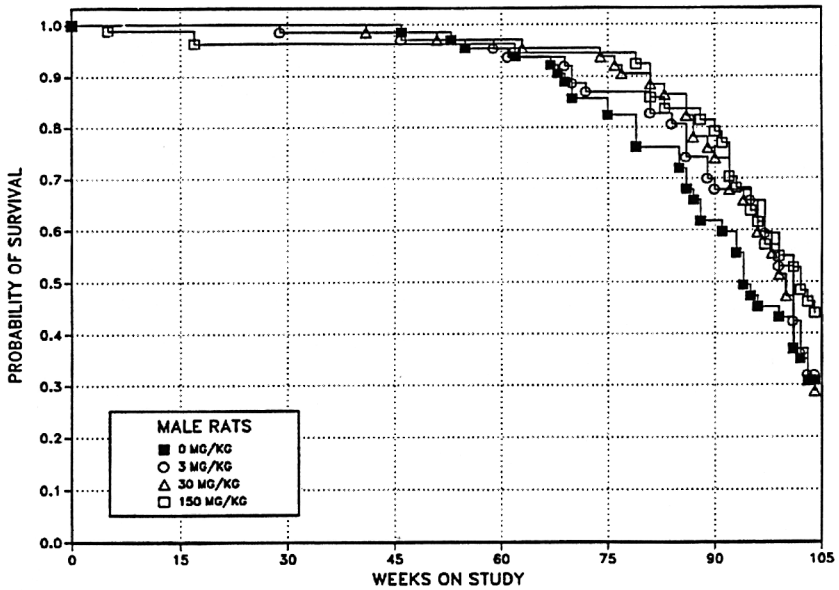
Mean body weights of males that received 30 or 150 mg/kg were generally less than those of the vehicle controls throughout the study, while mean body weights of males that received 3 mg/kg were generally similar to those of the vehicle controls (Figure 4 and Table 6). Mean body weights of females that received 3 or 30 mg/kg were generally greater than those of the vehicle controls throughout the study. Female rats that received 100 mg/kg also had mean body weights that were greater than controls during the first year of the study, but were similar during the second year of the study (Figure 4 and Table 7). Clinical findings related to oxymetholone treatment were associated with a reduction in body weight gain.

TABLE 5
Survival of Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Male				
Animals initially in study	90	90	90	90
3-Month interim evaluation[a]	10	10	10	9
6-Month interim evaluation[a]	10	10	10	10
12-Month interim evaluation[a]	9	10	10	10
18-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	0	1	0	3
Missexed[a]	0	0	0	1
Moribund	24	22	25	15
Natural deaths	12	12	11	12
Animals surviving to study termination	15	15	14	20
Percent probability of survival at end of study[b]	29	31	28	43
Mean survival (days)[c]	582	604	627	576
Survival analysis[d]	P=0.150N	P=0.631N	P=0.670N	P=0.141N

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Female				
Animals initially in study	90	90	90	90
3-Month interim evaluation[a]	10	10	10	10
6-Month interim evaluation[a]	10	10	10	10
12-Month interim evaluation[a]	10	10	10	10
18-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	1	0	1	1
Moribund	9	11	10	10
Natural deaths	15	10	9	8
Animals surviving to study termination	25	29	30	31
Percent probability of survival at end of study	51	58	61	63
Mean survival (days)	601	608	599	603
Survival analysis	P=0.365N	P=0.545N	P=0.392N	P=0.296N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dose group is indicated by **N**.



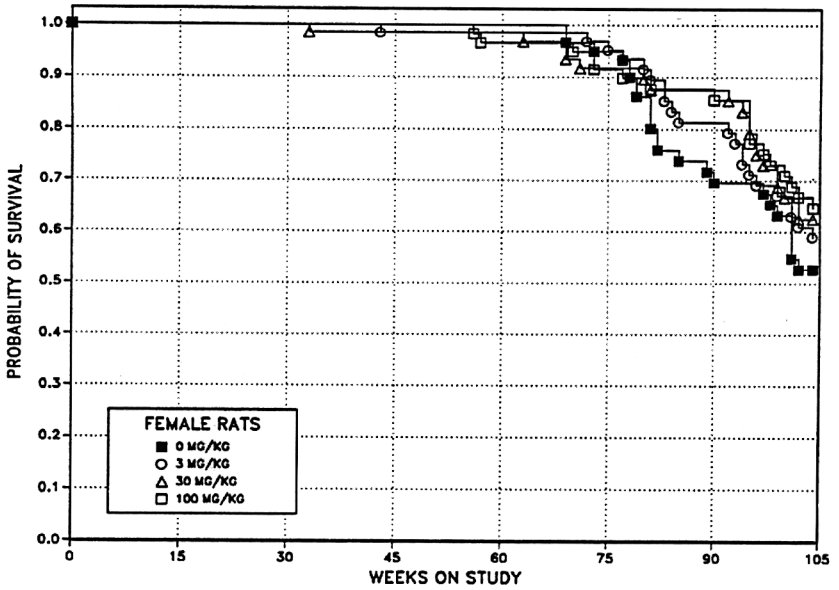


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Rats Administered Oxymetholone by Gavage for 2 Years

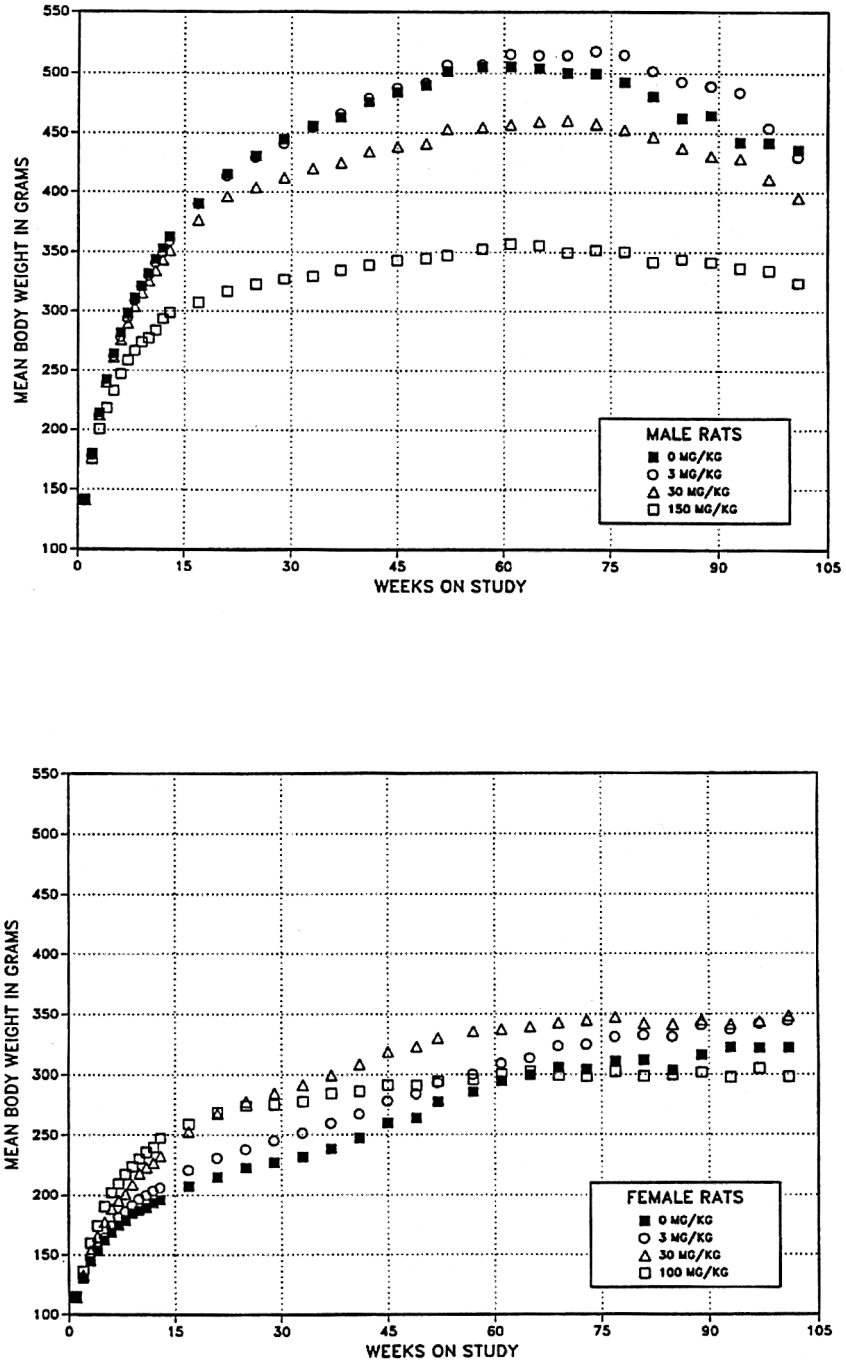


FIGURE 4
Growth Curves for Male and Female Rats Administered Oxymetholone by Gavage for 2 years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Oxymetholone

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	3 mg/kg Av. Wt. (g)	3 mg/kg Wt. (% of controls)	3 mg/kg No. of Survivors	30 mg/kg Av. Wt. (g)	30 mg/kg Wt. (% of controls)	30 mg/kg No. of Survivors	150 mg/kg Av. Wt. (g)	150 mg/kg Wt. (% of controls)	150 mg/kg No. of Survivors
1	142	90	140	99	90	141	100	90	141	100	89
2	180	90	178	99	90	179	100	90	176	98	89
3	214	90	212	99	90	212	99	90	201	94	89
4	242	90	240	99	90	240	99	90	218	90	89
5	264	90	262	99	90	261	99	90	233	88	89
6	282	90	278	99	90	276	98	90	247	88	88
7	298	90	294	99	90	290	97	90	259	87	88
8	311	90	309	99	90	304	98	90	267	86	88
9	321	90	321	100	90	315	98	90	274	85	88
10	332	90	330	99	90	326	98	90	277	84	88
11	344	90	341	99	90	334	97	90	284	83	88
12	353	90	349	99	90	343	97	90	294	83	88
13	363	90	359	99	90	351	97	90	299	82	87
17[a]	390	80	390	100	80	377	97	80	307	79	78
21	415	80	414	100	80	396	95	80	317	76	75
25	431	80	429	100	79	404	94	80	323	75	74
29[a]	445	70	441	99	69	412	93	70	327	74	64
33	456	70	455	100	68	420	92	70	330	72	64
37	463	70	466	101	68	425	92	70	335	72	64
41	476	70	479	101	68	435	91	70	339	71	64
45	484	70	488	101	68	439	91	69	343	71	64
49	490	69	492	100	67	441	90	69	345	70	64
52	501	69	507	101	67	453	90	68	347	69	64
57[a]	505	58	507	100	57	455	90	58	353	70	54
61	506	58	516	102	56	457	90	58	357	71	54
65	504	57	515	102	55	460	91	57	356	71	53
69	500	55	515	103	55	461	92	57	350	70	53
73	500	52	518	104	51	458	92	57	352	70	53
77	493	50	515	105	51	453	92	55	351	71	53
81[a]	481	37	502	104	41	447	93	44	342	71	42
85	462	37	493	107	38	438	95	42	344	74	38
89	465	30	489	105	35	431	93	38	341	74	37
93	443	29	484	109	32	429	97	33	337	76	32
97	442	22	455	103	31	412	93	29	334	76	28
101	436	21	430	99	25	396	91	23	324	74	25
Mean for weeks											
1-13	280		278	99		275	98		244	87	
14-52	455		456	100		420	92		331	73	
53-101	478		495	104		441	92		345	72	

[a] Interim evaluation occurred during weeks 14, 27, 53, and 79.

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Oxymetholone

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	3 mg/kg Av. Wt. (g)	3 mg/kg Wt. (% of controls)	3 mg/kg No. of Survivors	30 mg/kg Av. Wt. (g)	30 mg/kg Wt. (% of controls)	30 mg/kg No. of Survivors	100 mg/kg Av. Wt. (g)	100 mg/kg Wt. (% of controls)	100 mg/kg No. of Survivors
1	114	90	114	100	90	114	100	90	115	101	90
2	130	90	132	101	90	133	102	90	136	105	90
3	145	90	147	102	90	153	106	90	160	111	90
4	153	90	156	102	90	165	108	90	174	114	90
5	162	90	165	102	90	178	110	90	190	118	90
6	169	90	174	103	90	188	112	90	202	120	90
7	175	90	182	104	90	195	112	90	210	120	90
8	179	90	186	104	90	201	113	90	217	122	90
9	185	90	191	104	90	209	113	90	224	121	90
10	187	90	197	105	90	218	117	90	230	123	90
11	189	90	200	106	90	223	118	90	236	125	90
12	193	90	204	105	90	227	118	90	240	124	90
13	196	90	206	105	90	232	119	90	247	126	90
17[a]	207	80	221	107	80	253	122	80	259	125	80
21	215	80	231	107	80	268	125	79	269	125	80
25	223	80	238	107	80	278	125	79	274	123	80
29[a]	227	70	245	108	70	285	125	69	275	121	69
33	232	70	252	109	70	292	126	69	278	120	69
37	238	70	260	109	70	299	126	68	285	119	69
41	247	70	267	108	70	308	125	68	286	116	69
45	260	70	278	107	69	319	123	68	291	112	69
49	264	70	284	108	69	323	122	68	291	110	69
52	278	70	293	106	69	330	119	68	295	106	69
57[a]	286	60	300	105	59	335	117	58	296	104	58
61	295	60	309	105	59	337	114	58	300	102	57
65	300	60	314	105	59	339	113	57	302	101	57
69	306	60	324	106	59	343	112	57	299	98	57
73	304	58	325	107	58	345	113	54	299	98	56
77	311	57	331	107	57	348	112	54	303	97	54
81[a]	312	41	333	107	45	342	110	43	299	96	43
85	303	36	331	109	41	341	113	42	300	99	42
89	316	35	341	108	40	345	109	42	302	96	42
93	322	33	337	105	39	342	106	41	298	92	41
97	322	33	342	106	34	344	107	36	305	95	37
101	322	30	344	107	33	348	108	32	298	93	34
Mean for weeks											
1-13	167		173	104		187	112		199	119	
14-52	239		257	108		296	124		280	117	
53-101	308		328	106		342	111		300	97	

[a] Interim evaluation occurred during weeks 14, 27, 53, and 79.

Determinations of Oxymetholone in Plasma

The concentrations of oxymetholone in the plasma of male and female rats receiving 3 mg/kg for 6, 12, or 18 months were generally below the limits of quantitation; therefore, all plasma concentrations in the 3 mg/kg group are considered to be estimates (Table 8). The plasma concentrations at 30 mg/kg were approximately an order of magnitude greater than those of the estimates for rats receiving 3 mg/kg at all time points in females, and at 6 months in males. At the 12 and 18 month sampling times, plasma concentrations in males receiving 30 mg/kg were three to four times greater than that of the 3 mg/kg group. Plasma oxymetholone concentrations were quantifiable, although variable, at 30 and 150 mg/kg in male rats and 30 and 100 mg/kg in female rats. There were no dose-related differences in plasma concentrations in female rats receiving 30 or 100 mg/kg at any time point. For males, plasma oxymetholone concentrations were significantly ($P<0.05$) elevated in the 150 mg/kg group at each time point compared to plasma concentrations in the 30 mg/kg group. However, these increases were not proportional to the differences in dose, and high-dose male rats were gavaged with a higher concentration (150 mg/kg) of oxymetholone than were high-dose females (100 mg/kg). It was concluded that oxymetholone kinetics was saturated at 30 mg/kg in female but not male rats.

TABLE 8
Plasma Concentrations of Oxymetholone in Rats in the 2-Year Gavage Study of Oxymetholone[a]

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Male				
n	10	10	10	10
Month 6	0.00 ± 0.00	0.0130 ± 0.0199[b]	0.200 ± 0.074	0.320 ± 0.041
Month 12	0.00 ± 0.00	0.0391 ± 0.0103	0.158 ± 0.070	0.220 ± 0.053
Month 18	0.00 ± 0.00	0.0550 ± 0.0293	0.171 ± 0.081	0.305 ± 0.102
	Vehicle Control	**3 mg/kg**	**30 mg/kg**	**100 mg/kg**
Female				
n	10	10	10	10
Month 6	0.00 ± 0.00	0.0251 ± 0.0794[c]	0.309 ± 0.109	0.288 ± 0.066
Month 12	0.00 ± 0.00	0.0177 ± 0.0067	0.188 ± 0.031	0.221 ± 0.054[d]
Month 18	0.00 ± 0.00	0.0372 ± 0.0231[e]	0.421 ± 0.158	0.444 ± 0.132

[a] Data are given in μg/mL as mean ± standard deviation. Samples were collected approximately 20 minutes after gavage dosing. The samples were stored at -20 °C then shipped overnight to Cedra Corporation (Austin, TX) for analyses. All 3 mg/kg plasma oxymetholone values were below the limit of quantitation; therefore, all values should be considered only as estimates.
[b] No measurable peak was detected for five animals; the value for one animal was below the limit of detection.
[c] No measurable peak was detected for nine animals.
[d] n=9
[e] Values for two animals were below the limit of detection and were regarded as zero in the subsequent statistical analysis.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the liver, lung, skin, adrenal gland, kidney, ovary, heart, uterus, mammary gland, pituitary gland, and testes and incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Liver: The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in 100 mg/kg females compared to the vehicle controls at 2 years, and the incidences exceeded the historical control ranges from methylcellulose gavage, drinking water, and feed studies (Tables 9, B3, and B4a). Hepatocellular carcinomas have not been observed in female rats in the current NTP historical control database. Hepatocellular adenomas in 100 mg/kg females were nodules from 0.3 to 1 cm in diameter. Microscopically, the adenomas had sharp borders separating them from the surrounding parenchyma and were composed of hepatocytes altered in size and/or staining characteristics (Plate 4). Hepatocellular carcinomas were larger than adenomas and microscopically were multilobular and composed of more anaplastic cells arranged in trabecular cords. The incidences of basophilic foci in 30 mg/kg males at 18 months and in 30 and 150 mg/kg males and 100 mg/kg females at 2 years, clear cell foci in 150 mg/kg males and 100 mg/kg females at 2 years, and mixed cell foci in 30 mg/kg females at 2 years were significantly greater than those in the vehicle controls (Tables 9, A5, and B5). Foci were microscopic lesions composed of tinctorially altered hepatocytes that blended with the adjacent parenchyma. Foci are common spontaneous lesions in aging male and female F344/N rats. Although induction of some types of foci is considered to be an indicator of hepatocarcinogenic potential, the significance of the increased incidences in the current study is unclear.

The incidences of bile duct hyperplasia in all dosed groups of males at 18 months and in 150 mg/kg males at 2 years were significantly decreased. Bile duct hyperplasia is a common lesion in aging F344/N rats, particularly in males. The decreased incidence of this lesion in the males in the current study may be related to a feminizing effect of oxymetholone. Cytoplasmic vacuolization of hepatocytes was observed in 30 mg/kg females at 12 and 18 months. Affected single cells were scattered within the lobule in a centrilobular to random pattern.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Male				
6-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Bile Duct, Hyperplasia[a]	3 (1.0)[b]	0	0	0
12-Month Interim Evaluation				
Number Examined Microscopically	9	10	9	10
Basophilic Focus	0	2	2	0
Clear Cell Focus	0	0	0	1
Bile Duct, Hyperplasia	3 (1.0)	5 (1.0)	3 (1.0)	0
18-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Basophilic Focus	4	8	9*	8
Clear Cell Focus	2	0	2	2
Bile Duct, Hyperplasia	10 (1.1)	6* (1.2)	6* (1.7)	0**
2-Year Study				
Number Examined Microscopically	51	50	50	49
Basophilic Focus	23	29	41**	38**
Clear Cell Focus	2	2	6	12**
Bile Duct, Hyperplasia	29 (1.4)	27 (1.1)	24 (1.2)	0**
Hepatocellular Adenoma	1	1	1	0
Hepatocellular Carcinoma	0	1	0	0
Hepatocellular Adenoma or Carcinoma[c]	1	2	1	0

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Female				
6-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Basophilic Focus	0	1	0	0
Centrilobular, Vacuolization Cytoplasmic	0	0	1 (1.0)	0
12-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Basophilic Focus	4	8	2	7
Clear Cell Focus	0	0	1	1
Centrilobular, Vacuolization Cytoplasmic	0	0	7** (1.3)	0
Bile Duct, Hyperplasia	0	0	1 (1.0)	0

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Female (continued)				
18-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Basophilic Focus	7	10	10	9
Clear Cell Focus	0	1	0	3
Mixed Cell Focus	0	0	2	0
Centrilobular, Vacuolization Cytoplasmic	0	0	9** (1.0)	1 (1.0)
Bile Duct, Hyperplasia	0	0	0	1 (1.0)
Hepatocellular Adenoma	0	0	0	1
2-Year Study				
Number Examined Microscopically	50	50	50	49
Basophilic Focus	37	40	37	41*
Clear Cell Focus	5	11	6	14*
Mixed Cell Focus	2	7	9*	7
Centrilobular, Vacuolization Cytoplasmic	7 (3.0)	8 (2.3)	6 (1.5)	3 (1.3)
Bile Duct, Hyperplasia	1 (2.0)	3 (1.7)	6 (1.0)	0
Hepatocellular Adenoma[d]				
Overall rate[e]	1/50 (2%)	1/50 (2%)	1/50 (2%)	8/49 (16%)
Adjusted rate[f]	2.5%	2.4%	2.4%	19.2%
Terminal rate[g]	1/25 (4%)	1/29 (3%)	1/30 (3%)	7/31 (23%)
First incidence (days)	728 (T)	728 (T)	728 (T)	659
Poly-3 test[h]	P<0.001	P=0.748N	P=0.749N	P=0.018
Hepatocellular Carcinoma	0	0	0	2
Hepatocellular Adenoma or Carcinoma[d]				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	10/49 (20%)
Adjusted rate	2.5%	2.4%	2.4%	24.0%
Terminal rate	1/25 (4%)	1/29 (3%)	1/30 (3%)	9/31 (29%)
First incidence (days)	728 (T)	728 (T)	728 (T)	659
Poly-3 test	P<0.001	P=0.748N	P=0.749N	P=0.005

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test (interim evaluations) or the Poly-3 test (2-year study)
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year NTP gavage (methylcellulose vehicle controls) or drinking water or feed studies (undosed controls) (mean ± standard deviation): methylcellulose, 7/50 (14%); drinking water, 6/330 (1.9% ± 1.3%), range, 0%-4%; feed, 26/902 (2.9% ± 3.5%), range, 0%-10%
[d] Historical incidence: methylcellulose, 1/50 (2%); drinking water, 5/330 (1.4% ± 1.1%), range, 0%-3%; feed, 4/901 (0.4% ± 1.1%), range, 0%-4%
[e] Number of animals with neoplasm per number of animals with liver examined microscopically
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dose group is indicated by **N**.

Lung: At 2 years, the incidences of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) in the 30 mg/kg females were significantly increased and exceeded the historical control ranges for methylcellulose gavage, drinking water, and feed studies (Tables 10, B3, and B4b). The highest incidence previously observed in female historical control groups for feed studies was 3/50 (6%). Additionally, an alveolar/bronchiolar adenoma was observed in each of the 30 and 100 mg/kg groups of females at 18 months. However, hyperplasia is generally considered to be a precursor lesion to adenoma in the lungs of F344/N rats but was not significantly increased in treated females. Despite the absence of increased incidences of lung neoplasms in 100 mg/kg females, the increased incidence in the 30 mg/kg group was considered to be related to treatment with oxymetholone. Adenomas in female rats were typically small, 1.5- to 2-mm nodules within the pulmonary parenchyma and were composed of cuboidal cells with uniform morphology that filled contiguous alveolar spaces (Plate 5). One of the adenomas had somewhat unusual morphology of atypical epithelial cells that lined the alveoli, which were separated by a thick fibrous stroma. The single lung carcinoma observed in one 30 mg/kg female was a 1-cm mass with irregular borders and composed of more atypical cells forming papillary growth patterns.

Although the incidences of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) were significantly decreased in 30 mg/kg males at 2 years (Tables 10 and A3), the incidences in the concurrent vehicle control males exceeded the historical control ranges for methylcellulose gavage and drinking water studies (Table A4b). Moreover, as is commonly observed in historical control groups, the incidence in 30 mg/kg males was zero. Therefore, the significant decrease seen in this group was not considered to be chemical related.

The incidences of mineralization in 30 mg/kg males at 18 months and in 150 mg/kg males and 30 and 100 mg/kg females at 2 years were significantly increased (Tables A5 and B5). Mineralization was a minimal change that appeared as irregular crystalline concretions in the walls of larger blood vessels.

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Male				
2-Year Study				
Number Examined Microscopically	51	50	50	47
Mineralization[a]	19 (1.1)[b]	25 (1.2)	27 (1.2)	28* (1.2)
Alveolar Epithelium, Hyperplasia	1 (2.0)	1 (1.0)	3 (1.7)	2 (1.5)
Alveolar/bronchiolar Adenoma[c]				
Overall rate[d]	4/51 (8%)	1/50 (2%)	0/50 (0%)	3/47 (6%)
Adjusted rate[e]	11.1%	2.7%	0.0%	8.5%
Terminal rate[f]	2/15 (13%)	0/15 (0%)	0/14 (0%)	3/20 (15%)
First incidence (days)	549	720	—[h]	728 (T)
Poly-3 test[g]	P=0.401	P=0.170N	P=0.050N	P=0.514N
Alveolar/bronchiolar Carcinoma	1	0	0	0
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	5/51 (10%)	1/50 (2%)	0/50 (0%)	3/47 (6%)
Adjusted rate	13.8%	2.7%	0.0%	8.5%
Terminal rate	2/15 (13%)	0/15 (0%)	0/14 (0%)	3/20 (15%)
First incidence (days)	549	720	—	728 (T)
Poly-3 test	P=0.505	P=0.095N	P=0.024N	P=0.370N

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Female				
18-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Alveolar/bronchiolar Adenoma	0	0	1	1
2-Year Study				
Number Examined Microscopically	50	50	50	49
Mineralization	15 (1.0)	23 (1.0)	33** (1.0)	33** (1.0)
Alveolar Epithelium, Hyperplasia	4 (1.8)	10 (1.2)	4 (2.0)	9 (1.8)
Alveolar/bronchiolar Adenoma[j]				
Overall rate	0/50 (0%)	0/50 (0%)	6/50 (12%)	1/49 (2%)
Adjusted rate	0.0%	0.0%	14.1%	2.4%
Terminal rate	0/25 (0%)	0/29 (0%)	5/30 (17%)	1/31 (3%)
First incidence (days)	—	—	441	728 (T)
Poly-3 test	P=0.471	—[k]	P=0.019	P=0.508
Alveolar/bronchiolar Carcinoma	0	0	1	0
Alveolar/bronchiolar Adenoma or Carcinoma[l]				
Overall rate	0/50 (0%)	0/50 (0%)	7/50 (14%)	1/49 (2%)
Adjusted rate	0.0%	0.0%	16.5%	2.4%
Terminal rate	0/25 (0%)	0/29 (0%)	6/30 (20%)	1/31 (3%)
First incidence (days)	—	—	441	728 (T)
Poly-3 test	P=0.488	—	P=0.009	P=0.508

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test (interim evaluations) or the Poly-3 test (2-year study)
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year NTP gavage (methylcellulose vehicle controls) or drinking water or feed studies (undosed controls) (mean ± standard deviation): methylcellulose, 0/50; drinking water, 3/331 (1.0% ± 1.1%), range, 0%-2%; feed, 22/902 (2.5% ± 3.3%), range, 0%-14%
[d] Number of animals with neoplasm per number of animals with lung examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dose group is indicated by **N**.
[h] Not applicable; no neoplasm in animal group
[i] Historical incidence: methylcellulose, 0/50; drinking water, 3/331 (1.0% ± 1.1%), range, 0%-2%; feed, 29/902 (3.2% ± 3.6%), range, 0%-16%
[j] Historical incidence: methylcellulose, 0/50; drinking water, 5/330 (1.4% ± 1.1%), range, 0%-3%; feed, 13/900 (1.4% ± 1.8%), range, 0%-6%
[k] Value of statistic cannot be computed.
[l] Historical incidence: methylcellulose, 1/50 (2%); drinking water, 5/330 (1.4% ± 1.1%), range, 0%-3%; feed, 17/900 (1.9% ± 1.9%), range, 0%-6%

Skin: The incidence of combined epithelial neoplasms of the skin (squamous cell papilloma, keratoacanthoma, basal cell adenoma, squamous cell carcinoma, or carcinoma of the sweat gland) was significantly increased in 100 mg/kg females at 2 years, and the incidence exceeded the historical control range from methylcellulose gavage, drinking water, and feed studies (Tables 11 and B4c). The incidence of keratoacanthoma was also increased in 30 mg/kg females (Table 11). Spontaneous skin neoplasms of epithelial origin (epidermal and adnexal tumors) are considerably more common in male F344/N rats than in female rats. This gender difference implies that sex steroids may play a role in the development of these neoplasms, and, therefore, masculinization of females by oxymetholone may provide a biologic basis for the skin neoplasm effect in females. In the 3 mg/kg male rats, the incidences of subcutaneous tissue fibroma and fibroma or fibrosarcoma (combined) were significantly increased at 2 years (Tables 11, A3, and A4c); however, the combined fibroma and fibrosarcoma incidence in the concurrent vehicle control group (0%) was below the average historical control incidence for feed studies. The combined fibroma and fibrosarcoma incidence of 14% in 3 mg/kg males exceeded the historical control range for feed studies and may have been related to administration of oxymetholone.

A number of nonneoplastic effects were observed in female rats as a result of treatment with oxymetholone. In addition, there were decreased incidences of neoplasms, normally observed in aged rats, that were considered to be caused by oxymetholone treatment.

TABLE 11
Incidences of Neoplasms of the Skin in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Male				
Subcutaneous Tissue, Fibroma[a]				
Overall rate[b]	0/51 (0%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rate[c]	0.0%	13.3%	5.2%	5.3%
Terminal rate[d]	0/15 (0%)	2/15 (13%)	1/14 (7%)	0/20 (0%)
First incidence (days)	—[f]	479	707	434
Poly-3 test[e]	P=0.523N	P=0.035	P=0.259	P=0.251
Subcutaneous Tissue, Fibroma or Fibrosarcoma[g]				
Overall rate	0/51 (0%)	7/50 (14%)	2/50 (4%)	2/50 (4%)
Adjusted rate	0.0%	18.2%	5.2%	5.3%
Terminal rate	0/15 (0%)	2/15 (13%)	1/14 (7%)	0/20 (0%)
First incidence (days)	—	479	707	434
Poly-3 test	P=0.338N	P=0.010	P=0.259	P=0.251

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Female				
Number Necropsied	50	50	50	50
Squamous Cell Papilloma[h]	0	0	0	2
Keratoacanthoma	0	0	4	0
Basal Cell Adenoma	0	0	0	1
Squamous Cell Carcinoma	0	0	0	1
Sweat Gland, Carcinoma	0	0	0	1
Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, Squamous Cell Carcinoma, or Carcinoma[i]				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	5/50 (10%)
Adjusted rate	0.0%	0.0%	9.6%	11.9%
Terminal rate	0/25 (0%)	0/29 (0%)	4/30 (13%)	4/31 (13%)
First incidence (days)	—	—	728 (T)	725
Poly-3 test	P=0.008	—[j]	P=0.066	P=0.035

(T)Terminal sacrifice
[a] Historical incidence for 2-year NTP gavage (methylcellulose vehicle controls) or drinking water or feed studies (undosed controls) (mean ± standard deviation): methylcellulose, 1/50; drinking water, 8/331 (2.7% ± 3.5%), range, 0%-8%; feed, 50/904 (5.6% ± 3.1%), range, 0%-10%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend is indicated by **N**.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence: methylcellulose, 1/50; drinking water, 13/331 (4.2% ± 2.8%), range, 1%-8%; feed, 59/904 (6.5% ± 3.0%), range, 2%-10%
[h] Number of animals with neoplasm
[i] Historical incidence: methylcellulose, 0/50; drinking water, 5/330 (1.5% ± 1.5%), range, 0%-4%; feed, 17/901 (1.9% ± 2.0%), range, 0%-8%
[j] Value of statistic cannot be computed.

Adrenal Gland: At 2 years, the incidences of benign pheochromocytoma and benign or malignant pheochromocytoma (combined) in 150 mg/kg males were significantly increased (Tables 12 and A3). When the pheochromocytomas from the 12- and 18-month interim evaluations are included in the statistical analysis, both the trend (P=0.021) and the 150 mg/kg group incidence (P=0.022) remain statistically significant. The incidence of benign or malignant pheochromocytoma (combined) in 150 mg/kg males exceeded the historical control ranges for benign, malignant, or complex pheochromocytoma (combined) in methylcellulose gavage, drinking water, and feed studies (Tables 12 and A4d). In addition, of the 29 males in the 150 mg/kg group that had pheochromocytomas, 19 had bilateral neoplasms as compared to only three bilateral neoplasms in the 19 vehicle controls with pheochromocytoma. However, there was no increase in the incidence of medullary hyperplasia, generally considered to be a precursor lesion to pheochromocytoma, in treated males. Moreover, adrenal medullary proliferative lesions occur at a high and variable rate in male F344/N rats. Therefore, it is uncertain if the increase in the incidence of pheochromocytoma in 150 mg/kg males is related to administration of oxymetholone. Benign pheochromocytomas in males were well delineated nodules within the adrenal medulla, often impinging into the cortex, and were composed of basophilic medullary cells in solid or trabecular patterns. In one male in each of the 30 and 150 mg/kg groups, malignant pheochromocytomas were diagnosed based on marked enlargement of the adrenal gland, effacement of the cortex, and penetration to the capsule by neoplastic cells and extensive associated hemorrhage and necrosis. The incidence of pheochromocytoma in 100 mg/kg females exceeded the historical control ranges for benign, malignant, or complex pheochromocytoma (combined) in methylcellulose gavage, drinking water, and feed studies (Table B4d). However, the incidence did not significantly exceed that of the concurrent vehicle control group. Four females with pheochromocytomas in the 100 mg/kg group had bilateral neoplasms. The incidence of medullary hyperplasia was increased in 100 mg/kg females at 2 years; however, there was no dose response. This marginal increase was not considered to be treatment related. The incidences of cytoplasmic vacuolization of cortical cells were significantly increased in 30 and 150 mg/kg males at 18 months and 2 years and in 100 mg/kg females at 12 and 18 months and in 30 and 100 mg/kg females at 2 years. The incidence of angiectasis (dilatation of capillaries and sinusoids) was significantly decreased in 100 mg/kg females at 2 years.

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Gland in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Male				
12-Month Interim Evaluation				
Number Examined Microscopically	9	10	10	10
Medulla, Benign Pheochromocytoma[a]	1	0	0	0
18-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Cortex, Cytoplasmic Vacuolization	4 (1.0)[b]	8 (1.3)	10** (1.8)	10** (1.0)
Medulla, Hyperplasia	3 (2.0)	1 (1.0)	2 (1.5)	0
Medulla, Benign Pheochromocytoma	1	0	1	1
Medulla, Malignant Pheochromocytoma	1	0	0	0
2-Year Study				
Number Examined Microscopically	51	50	50	49
Cortex, Cytoplasmic Vacuolization	22 (1.4)	23 (1.5)	40** (1.9)	33** (1.8)
Medulla, Hyperplasia	15 (2.7)	17 (2.4)	20 (2.5)	15 (2.6)
Medulla, Benign Pheochromocytoma, Bilateral	3	11*	9	19**
Medulla, Benign Pheochromocytoma (includes bilateral)	19	25	21	29**
Medulla, Malignant Pheochromocytoma	0	0	1	1
Medulla, Benign or Malignant Pheochromocytoma[c]				
Overall rate[d]	19/51 (37%)	25/50 (50%)	21/50 (42%)	29/49 (59%)
Adjusted rate[e]	49.4%	62.9%	51.0%	75.5%
Terminal rate[f]	9/15 (60%)	8/15 (53%)	9/14 (64%)	18/20 (90%)
First incidence (days)	519	485	564	577
Poly-3 test[g]	P=0.015	P=0.147	P=0.534	P=0.009

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Gland in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Female				
18-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Cortex, Angiectasis	0	3 (2.0)	0	0
Cortex, Cytoplasmic Vacuolization	0	0	1 (1.0)	9** (1.4)
Medulla, Hyperplasia	0	0	1 (2.0)	0
Medulla, Benign Pheochromocytoma	1	0	0	0
2-Year Study				
Number Examined Microscopically	50	50	50	49
Cortex, Angiectasis	21 (2.0)	26 (2.1)	15 (1.3)	3** (1.7)
Cortex, Cytoplasmic Vacuolization	4 (2.0)	5 (2.2)	21** (1.4)	37** (1.2)
Medulla, Hyperplasia	5 (2.6)	1 (2.0)	3 (1.7)	13* (2.2)
Medulla, Bilateral Benign Pheochromocytoma	0	0	0	4
Medulla, Benign Pheochromocytoma	7	4	2	10
Medulla, Malignant Pheochromocytoma	0	1	0	0
Medulla, Benign or Malignant Pheochromocytoma[h]				
Overall rate	7/50 (14%)	5/50 (10%)	2/50 (4%)	10/49 (20%)
Adjusted rate	17.2%	11.7%	4.7%	24.2%
Terminal rate	2/25 (8%)	2/29 (7%)	0/30 (0%)	10/31 (32%)
First incidence (days)	589	579	561	728 (T)
Poly-3 test	P=0.082	P=0.340N	P=0.066N	P=0.307

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test (interim evaluations) or the Poly-3 test (2-year study)
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for benign, malignant, or complex pheochromocytoma (combined) for 2-year NTP gavage (methylcellulose vehicle controls) or drinking water or feed studies (undosed controls) (mean ± standard deviation): methylcellulose, 25/50 (50%); drinking water, 106/329 (32.2% ± 9.0%), range, 24%-49%; feed, 252/896 (28.2% ± 8.4%), range, 14%-46%
[d] Number of animals with neoplasm per number of animals with adrenal gland examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dose group is indicated by **N**.
[h] Historical incidence for benign, malignant, or complex pheochromocytoma (combined): methylcellulose, 1/50 (2%); drinking water, 25/329 (7.6% ± 3.5%), range, 4%-14%; feed, 34/896 (3.8% ± 1.9%), range, 0%-6%

Kidney: The incidences of nephropathy were significantly increased in 30 and 150 mg/kg males at 2 years and in 100 mg/kg females at 3, 6, and 12 months and at 2 years (Tables 13, A3, and B3). The severities of nephropathy were significantly increased in dosed groups of males at 2 years and in 100 mg/kg females at 18 months and at 2 years. The diagnosis of nephropathy encompassed a spectrum of morphologic changes including, in its least severe form, scattered foci of basophilic regenerative tubules, and with increasing severity, tubular protein casts, interstitial inflammation and fibrosis, and more extensive tubular regeneration and atrophy. Incidences of fibrous osteodystrophy, an extrarenal lesion indicative of enhanced nephropathy, were increased in males (vehicle control, 2/51; 3 mg/kg, 8/49; 30 mg/kg, 13/50; 150 mg/kg, 15/50; Table A5). The incidences of renal mineralization were significantly increased in 150 mg/kg males at all time points. Minimal to mild mineralization appeared as basophilic concretions in the lumens of tubules at the corticomedullary junction. In more severe instances, which tended to occur with more severe nephropathy, mineral deposits occurred in the walls and lumens or cortical convoluted tubules.

Adenoma of the renal tubule occurred in one male rat administered 3 mg/kg and two male rats administered 150 mg/kg, and the incidence of renal tubule adenoma in 150 mg/kg male rats was greater than the historical control range for drinking water studies (Tables 13, A1, and A4e). Based on these findings, which are suggestive of a neoplastic effect on the renal tubule, an extended evaluation of the kidney was conducted by the preparation of step sections. Extended evaluations of kidneys from all vehicle control and dosed males and from vehicle control and 100 mg/kg females were performed. Additional incidences of renal tubule hyperplasia and adenoma were observed in step sections from vehicle control and dosed male rats. Hyperplasia consisted of tubules with normal or slightly enlarged diameters lined by thickened, stratified epithelial cells. Renal tubule adenomas were composed of epithelial cells forming more solid nodules that were several tubules in diameter. The incidence of renal tubule adenoma in the combined original and step sections from 3 mg/kg male rats (13/50, 26%) was significantly increased relative to the vehicle controls (4/51, 8%) and exceeded historical incidences from previous NTP extended kidney evaluations of control male F344/N rats (average, 4.5%; range, 0%-16%). Therefore, although incidences of renal tubule adenoma were not significantly increased in the 30 and 150 mg/kg males, the increased incidence in 3 mg/kg males may have been related to administration of oxymetholone. In contrast to males, only a single additional proliferative lesion (hyperplasia in a vehicle control female) was found in the extended evaluation of kidneys from female rats.

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control		3 mg/kg		30 mg/kg		150 mg/kg	
Male								
3-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		9	
Mineralization[a]	0		2	(1.0)[b]	2	(1.0)	8**	(1.1)
Nephropathy	8	(1.0)	7	(1.0)	9	(1.0)	8	(1.3)
6-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Mineralization	2	(1.0)	0		1	(1.0)	9**	(1.0)
Nephropathy	8	(1.0)	7	(1.0)	9	(1.1)	10	(1.2)
12-Month Interim Evaluation								
Number Examined Microscopically	9		10		10		10	
Mineralization	1	(1.0)	0		0		9**	(1.1)
Nephropathy	9	(1.9)	10	(1.3)	10	(1.4)	10	(1.7)
18-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Mineralization	0		0		0		4*	(1.0)
Nephropathy	10	(2.0)	10	(2.3)	9	(2.1)	10	(1.8)
2-Year Study								
Number Examined Microscopically	51		50		50		49	
Single Sections (Standard Evaluation)								
Mineralization	6	(1.7)	6	(1.8)	9	(2.2)	25**	(1.5)
Nephropathy	43	(2.0)	47	(2.6)**	50*	(2.7)**	48*	(2.7)**
Renal Tubule Hyperplasia	3	(2.7)	2	(4.0)	3	(1.7)	1	(2.0)
Renal Tubule Adenoma[c]	0		1		0		2	
Step Sections (Extended Evaluation)								
Renal Tubule Hyperplasia	10	(2.6)	11	(2.4)	11	(3.0)	3	(2.0)
Renal Tubule Adenoma	4		12		1		5	
Single Sections and Step Sections (Combined)								
Renal Tubule Hyperplasia	12	(2.7)	13	(2.6)	14	(2.7)	4*	(2.0)
Renal Tubule Adenoma	4		13*		1		6	

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control		3 mg/kg		30 mg/kg		100 mg/kg	
Female								
3-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Mineralization	10	(1.0)	9	(1.0)	9	(1.0)	10	(1.0)
Nephropathy	0		0		0		8**	(1.0)
6-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Mineralization	10	(1.1)	10	(1.0)	10	(1.0)	9	(1.0)
Nephropathy	0		1	(1.0)	2	(1.0)	7**	(1.0)
12-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Mineralization	9	(1.0)	10	(1.0)	10	(1.0)	10	(1.0)
Nephropathy	5	(1.0)	6	(1.0)	9	(1.0)	10*	(1.0)
18-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Mineralization	8	(1.0)	9	(1.0)	10	(1.0)	9	(1.0)
Nephropathy	8	(1.0)	4	(1.0)	9	(1.2)	10	(1.5)*
2-Year Study								
Single Sections (Standard Evaluation)								
Number Examined Microscopically	50		50		50		49	
Mineralization	27	(1.0)	31	(1.0)	35	(1.1)	36	(1.0)
Nephropathy	32	(1.3)	26	(1.2)	38	(1.2)	41*	(1.7)**
Renal Tubule Adenoma	0		0		0		1	
Step Sections (Extended Evaluation)								
Number Examined Microscopically	50						49	
Renal Tubule Hyperplasia	1						0	
Single Sections and Step Sections (Combined)								
Number Examined Microscopically	50						49	
Renal Tubule Hyperplasia	1						0	
Renal Tubule Adenoma	0						1	

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test (interim evaluation incidences), the Poly-3 test (2-year study incidences), or the Mann-Whitney U test (severities)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year NTP gavage (methylcellulose vehicle controls) or drinking water or feed studies (undosed controls) (mean ± standard deviation): methylcellulose, 3/50 (6%); drinking water, 2/327 (0.7% ± 1.0%), range, 0%-2%; feed, 7/902 (0.8% ± 1.2%), range, 0%-4%

Ovary: Female rats administered oxymetholone had prominent morphologic changes of the ovary similar to those observed in the 14-week study. Large areas of ovarian tissue were replaced by atypical dark-staining sex cord/stromal cells arranged in well-organized nests surrounding small vessels or atretic follicles and particularly prominent in hilar areas (Plates 6a and 6b). The atypical cells resembled interstitial cells by virtue of their location, but with distinctive features of minimal to no visible cytoplasm and round nuclei with prominent stippled chromatin. Few growing follicles and corpora lutea were present in affected ovaries, suggesting disrupted follicle maturation and luteogenesis. Follicle counts performed on the ovaries of interim-sacrifice animals also demonstrated increased numbers of immature primary follicles in treated females. These ovarian effects were collectively diagnosed as dysgenesis; the incidences of dysgenesis were significantly increased in 100 mg/kg females beginning at 3 months and in 30 mg/kg females beginning at 6 months (Tables 14 and B5).

TABLE 14
Incidences of Dysgenesis of the Ovary in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
3-Month Interim Evaluation				
Number Examined Microscopically	10	10	9	9
Dysgenesis[a]	0	0	0	9** (2.1)[b]
6-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Dysgenesis	0	0	10** (2.2)	10** (2.4)
12-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Dysgenesis	0	0	10** (1.7)	10** (3.0)
18-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Dysgenesis	0	0	8** (2.4)	10** (3.3)
2-Year Study				
Number Examined Microscopically	50	49	50	49
Dysgenesis	0	1 (1.0)	43** (2.7)	49** (3.4)

** Significantly different ($P \leq 0.01$) from the vehicle control group by the Fisher exact test (interim evaluations) or the Poly-3 test (2-year study)
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Heart: The incidences of chronic myocardial degeneration (cardiomyopathy) were significantly increased in 100 mg/kg females at 6 months and in 30 and 100 mg/kg females at 2 years (Tables 15 and B5). Myocardial degeneration was characterized by focal areas of myofiber loss and replacement by interstitial fibrosis and mononuclear inflammatory cell infiltration, most commonly in the left ventricle and papillary muscle. Increased severity of this lesion in dosed female rats was evidenced by more extensive and widespread involvement of the heart in affected animals.

TABLE 15
Incidences of Chronic Myocardial Degeneration of the Heart in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
3-Month Interim Evaluation	1/10[a] (1.0)[b]	6/10* (1.0)	3/10 (1.0)	4/10 (1.0)
6-Month Interim Evaluation	5/10 (1.0)	5/10 (1.0)	7/10 (1.3)	10/10** (1.0)
12-Month Interim Evaluation	7/10 (1.0)	8/10 (1.0)	9/10 (1.2)	9/10 (1.2)
18-Month Interim Evaluation	6/10 (1.0)	7/10 (1.1)	8/10 (1.3)	9/10 (1.6)
2-Year Study	29/50 (1.3)	34/50 (1.3)	40/50 (1.8)	45/49** (1.8)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test (interim evaluations) or the Poly-3 test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion/number examined microscopically
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Uterus: The incidence of stromal polyp or stromal sarcoma (combined) was significantly decreased in 100 mg/kg females at 2 years (5/50, 9/50, 2/50, 0/50; Table B3). The incidences in the 30 and 100 mg/kg groups were less than the incidences in historical controls in methylcellulose gavage and drinking water studies (Table B4e); the incidence in the 100 mg/kg group was also less than the range from historical feed studies.

Mammary Gland: The incidences of mammary gland fibroadenoma and fibroadenoma or carcinoma (combined) were significantly decreased in all dosed groups of females (Tables 16 and B3). The incidences of fibroadenoma or carcinoma (combined) in all dosed groups of females were less than the historical control range for fibroadenoma, adenoma, or carcinoma (combined) in methylcellulose gavage, drinking water, and feed studies (Tables 16 and B4f). Reduced multiplicity of mammary gland fibroadenomas in females was another treatment effect in this tissue. Nonneoplastic effects were present in the mammary gland of both male and female rats. At earlier time points, these effects were identical to those seen in the 14-week study and were characterized by morphologic changes of the sexually dimorphic mammary gland tissue. In males, the change was diagnosed as dilatation and consisted of more prominent tubulo-alveolar differentiation similar to that observed in control females. This occurred primarily in 150 mg/kg males at 3, 6, and 12 months. This change also became apparent in some aging vehicle control males at 18 months and in most vehicle control males at 2 years. At these later time points, the most remarkable treatment-related change in the mammary gland of males was an overall increase in the amount of tubulo-alveolar glandular tissue present in the section as compared to that of the vehicle controls, a change diagnosed as lobular hyperplasia. Luminal secretory material was present in these hyperplastic lesions. At the early time points in females, a mammary gland effect associated with treatment consisted of increased amounts of tubulo-alveolar gland tissue relative to vehicle controls,

morphologically similar to the effect seen in the 14-week study and diagnosed similarly as lobular hyperplasia. The incidences of lobular hyperplasia were significantly increased in 100 mg/kg females at 3 months and in 30 and 100 mg/kg females at 6, 12, and 18 months. Cytologically the increased alveolar component in treated females resembled the mammary gland tissue in vehicle control males. At the 18-month interim evaluation, although vehicle control females had more abundant and variable amounts of alveolar lobules, hyperplasia was still evident in treated females as an overall increase in the amount of glandular tissue. At 2 years, however, there was a variably abundant amount of glandular tissue in vehicle control females, and increases in the amount present in treated animals were not apparent.

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control		3 mg/kg		30 mg/kg		150 mg/kg	
Male								
3-Month Interim Evaluation								
Number Examined Microscopically	10		10		9		9	
Dilatation[a]	0		0		0		8**	(1.6)[b]
6-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Dilatation	0		0		0		9**	(1.9)
12-Month Interim Evaluation								
Number Examined Microscopically	8		9		10		10	
Dilatation	4	(1.8)	1	(2.0)	5	(1.2)	10*	(2.0)
18-Month Interim Evaluation								
Number Examined Microscopically	10		10		10		10	
Dilatation	2	(1.5)	3	(1.7)	1	(1.0)	7*	(1.4)
Lobular, Hyperplasia	0		0		0		6**	(1.5)
2-Year Study								
Number Examined Microscopically	51		48		49		50	
Dilatation	31	(1.5)	24	(1.5)	23	(1.7)	23	(1.6)
Lobular, Hyperplasia	0		0		4	(1.0)	35**	(1.4)

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland in Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Female				
3-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Lobular, Hyperplasia	0	0	2 (1.0)	9** (1.0)
6-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Lobular, Hyperplasia	0	0	10** (1.0)	10** (1.0)
12-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Lobular, Hyperplasia	0	0	10** (1.3)	8** (1.8)
18-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Lobular, Hyperplasia	1 (2.0)	0	9** (1.3)	9** (1.6)
Fibroadenoma	3	1	1	1
Carcinoma	1	0	0	0
2-Year Study				
Number Examined Microscopically	50	50	49	50
Lobular, Hyperplasia	0	1 (3.0)	0	1 (4.0)
Fibroadenoma, multiple	6	0	0	0
Fibroadenoma, includes multiple				
Overall rate[c]	21/50 (42%)	11/50 (22%)	1/50 (2%)	4/50 (8%)
Adjusted rate[d]	48.9%	25.9%	2.4%	9.1%
Terminal rate[e]	12/25 (48%)	8/29 (28%)	0/30 (0%)	0/31 (0%)
First incidence (days)	506	652	693	387
Poly-3 test[f]	P<0.001N	P=0.020N	P<0.001N	P<0.001N
Carcinoma	3	0	0	0
Fibroadenoma or Carcinoma[g]				
Overall rate	23/50 (46%)	11/50 (22%)	1/50 (2%)	4/50 (8%)
Adjusted rate	53.6%	25.9%	2.4%	9.1%
Terminal rate	14/25 (56%)	8/29 (28%)	0/30 (0%)	0/31 (0%)
First incidence (days)	506	652	693	387
Poly-3 test	P<0.001N	P=0.006N	P<0.001N	P<0.001N

* Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test (interim evaluations) or the Poly-3 test (2-year study)
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with neoplasm per number of animals necropsied
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.
[g] Historical incidence for mammary gland fibroadenoma, adenoma, or carcinoma (combined) for 2-year NTP studies with gavage (methylcellulose vehicle controls) or drinking water or feed studies (undosed controls) (mean ± standard deviation): methylcellulose, 37/50 (74%); drinking water, 132/330 (41.3% ± 12.8%), range, 28%-60%; feed, 418/901 (46.4% ± 12.1%), range, 24%-64%

Pituitary Gland: The incidences of pars distalis adenoma were significantly decreased in 30 and 100 mg/kg females at 2 years, and the incidences occurred with a negative trend (27/50, 26/50, 18/49, 14/50; Table B3). The incidence of pars distalis adenoma was significantly increased in 30 mg/kg males at the 18-month interim evaluation (2/10, 6/10, 9/10, 5/9; Table A1); however, at 2 years, the incidence occurred with a negative trend (30/51, 32/50, 30/50, 19/49; Table A3). When the data from the interim evaluations and the 2-year study are evaluated collectively, the decreasing trends in the incidences of pituitary gland neoplasms are significant for males (P=0.014) and females (P=0.003). A decreased incidence of adenoma of the pars distalis was observed in the 150 mg/kg male rats. An association between decreased body weights and decreased incidences of several neoplasm types, including adenoma of the pituitary gland pars distalis in the F344/N rat, has been demonstrated (Haseman, 1995). It is likely that the decreased incidence in the 150 mg/kg males is related to the significant decrease in mean body weight that also occurred only in that group. However, there was a dose-related decrease in the incidence of this neoplasm in females. The incidence in the vehicle control group is similar to the historical control incidence in dosed-feed studies (49%), and mean body weights of treated females were not decreased. Therefore, the decreased incidence of adenoma of the pars distalis in females may be related to the effects of the anabolic steroid.

Testes: The incidences of interstitial cell adenoma were significantly decreased in 30 and 150 mg/kg males at 18 months and in all dosed groups at 12 months and at 2 years (Tables 17 and A1). At 2 years, the incidences of interstitial cell adenoma occurred with a negative trend and in all groups, including the vehicle control group, were less than the historical control ranges for methylcellulose gavage and feed studies (Table A4f). The incidences of interstitial cell hyperplasia were also significantly decreased in 30 and 150 mg/kg males at 12 months and at 2 years. Interstitial cell hyperplasia and adenoma are common lesions in F344/N rats and represent a biologic continuum evidenced morphologically by aggregates of polygonal interstitial cells ranging in size from the diameter of a seminiferous tubule (hyperplasia) to large multilobulated masses several centimeters in diameter. In contrast to the 65% incidence in the vehicle control group, no adenoma or hyperplasia was observed in the 30 or 150 mg/kg males. The incidences of seminiferous tubule degeneration were significantly increased in 30 and 150 mg/kg males at 2 years. Degeneration is a common spontaneous change in aging F344/N rats, characterized by focal to diffuse loss of spermatogenic cells within the tubules, luminal cell debris, and the presence of multinucleated giant cells. Because the interstitial cell neoplasms may complicate the diagnosis of degeneration by compressing the adjacent cells, the difference in the incidence of degeneration between the vehicle controls and treated rats in this study at 2 years may have been confounded by the marked difference in neoplasm incidence between the groups. Moreover, the severities of degeneration were not increased in treated males at 2 years, and no effect was seen at earlier time points. Therefore, it is unclear whether the increased incidence of degeneration observed is a true chemical-related effect. The incidences of mineralization were increased in 150 mg/kg males at 12 months and in 30 mg/kg males at 18 months and at 2 years. Mineralization in the testis was seen as scattered large basophilic concretions within the lumen of seminiferous tubules.

Mononuclear Cell Leukemia: The incidences of mononuclear cell leukemia were significantly decreased in 30 and 150 mg/kg males (21/50, 15/50, 7/50, 4/50) and 100 mg/kg females (12/50, 11/50, 11/50, 5/50) at 2 years, and the incidences in males and females occurred with a negative trend (Tables A3 and B3). The incidences in all groups, including the vehicle controls, were less than those of historical water gavage vehicle controls [males: 33/50 (66%); females: 20/50 (40%)] and historical methylcellulose gavage vehicle controls [males: 26/50 (52%); females: 17/50 (34%)].

TABLE 17
Incidences of Neoplasms and Nonneoplastic Lesions of the Testes in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
12-Month Interim Evaluation				
Number Examined Microscopically	9	10	10	10
Seminiferous Tubule, Degeneration[a]	0	0	0	1 (1.0)[b]
Seminiferous Tubule, Mineralization	0	2 (1.0)	3 (1.0)	6** (1.0)
Interstitial Cell, Hyperplasia	8 (2.4)	7 (1.7)	0**	0**
Interstitial Cell, Adenoma	4	0*	0*	0*
18-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Seminiferous Tubule, Degeneration	2 (3.0)	1 (3.0)	2 (1.5)	3 (1.3)
Seminiferous Tubule, Mineralization	3 (1.0)	1 (1.0)	7* (1.1)	4 (1.0)
Interstitial Cell, Hyperplasia	3 (2.0)	4 (3.0)	0	0
Interstitial Cell, Adenoma	9	5	0**	0**
2-Year Study				
Number Examined Microscopically	51	50	50	49
Seminiferous Tubule, Degeneration	9 (2.0)	9 (2.4)	37** (2.1)	28** (1.3)
Seminiferous Tubule, Mineralization	17 (1.7)	10 (1.3)	33** (1.3)	19 (1.2)
Interstitial Cell, Hyperplasia	16 (1.8)	22 (2.1)	0**	0**
Interstitial Cell, Adenoma[c]				
Overall rate[d]	33/51 (65%)	20/50 (40%)	0/50 (0%)	0/49 (0%)
Adjusted rate[e]	81.4%	51.1%	0.0%	0.0%
Terminal rate[f]	14/15 (93%)	8/15 (53%)	0/14 (0%)	0/20 (0%)
First incidence (days)	497	485	—[h]	—
Poly-3 test[g]	P<0.001N	P<0.001N	P<0.001N	P<0.001N

* Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test (interim evaluations) or the Poly-3 test (2-year study)
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year NTP gavage (methylcellulose vehicle controls) or drinking water or feed studies (undosed controls) (mean ± standard deviation): methylcellulose, 46/50 (92%); drinking water, 264/329 (79.6% ± 11.0%), range, 65%-92%; feed, 802/903 (88.8% ± 6.0%), range, 74%-96%
[d] Number of animals with neoplasm per number of animals with testis examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.
[h] Not applicable; no neoplasms in animal group

MICE

16-Day Study

All mice survived to the end of the study (Table 18). The final mean body weights and body weight gains of all dosed groups of females were generally greater than those of the vehicle controls. No clinical findings that could be attributed to oxymetholone administration were observed.

Table 18
Survival and Body Weights of Mice in the 16-Day Gavage Study of Oxymetholone

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	5/5	24.9 ± 0.3	27.0 ± 0.3	2.1 ± 0.4	
320	5/5	25.1 ± 0.3	27.6 ± 0.4	2.4 ± 0.2	102
630	5/5	25.3 ± 0.4	27.6 ± 0.8	2.4 ± 0.6	102
1,250	5/5	25.2 ± 0.4	27.9 ± 0.3	2.7 ± 0.4	103
2,500	5/5	25.2 ± 0.3	28.6 ± 0.5	3.4 ± 0.3	106
5,000	5/5	24.7 ± 0.3	28.1 ± 0.5	3.3 ± 0.5	104
Female					
0	5/5	19.3 ± 0.2	21.8 ± 0.1	2.5 ± 0.2	
320	5/5	20.2 ± 0.3	23.6 ± 0.2**	3.4 ± 0.3	108
630	5/5	19.5 ± 0.2	24.4 ± 0.5**	4.9 ± 0.5**	112
1,250	5/5	20.0 ± 0.2	24.6 ± 0.5**	4.7 ± 0.4**	113
2,500	5/5	20.0 ± 0.3	24.8 ± 0.3**	4.8 ± 0.1**	114
5,000	5/5	19.8 ± 0.5	24.9 ± 0.4**	5.2 ± 0.3**	114

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' or Dunnett's test
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

14-Week Study

All dosed mice survived until the end of the study (Table 19). The final mean body weights and body weight gains of all dosed groups were similar to those of the vehicle controls (Table 19 and Figure 5). No clinical findings that could be attributed to oxymetholone administration were observed.

Table 19
Survival and Body Weights of Mice in the 14-Week Gavage Study of Oxymetholone

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	25.3 ± 0.4	37.3 ± 1.1	12.0 ± 0.8	
160	10/10	25.0 ± 0.4	39.3 ± 0.9	14.3 ± 0.8	106
320	10/10	25.5 ± 0.4	39.8 ± 1.2	14.4 ± 1.0	107
630	10/10	25.3 ± 0.3	39.2 ± 0.9	13.9 ± 0.8	105
1,250	10/10	25.5 ± 0.4	38.2 ± 1.4	12.7 ± 1.2	102
2,500	10/10	25.4 ± 0.4	37.3 ± 0.9	11.9 ± 0.8	100
Female					
0	10/10	21.4 ± 0.2	31.0 ± 1.3	9.5 ± 1.1	
160	10/10	21.6 ± 0.1	32.9 ± 1.0	11.2 ± 1.0	106
320	10/10	21.0 ± 0.2	31.9 ± 0.8	10.9 ± 0.6	103
630	10/10	21.4 ± 0.2	31.2 ± 0.7	9.8 ± 0.6	101
1,250	10/10	21.7 ± 0.3	31.7 ± 0.6	10.0 ± 0.6	102
2,500	10/10	20.9 ± 0.2	30.4 ± 0.6	9.5 ± 0.6	98

[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the vehicle control group are not significant by Williams' or Dunnett's test.

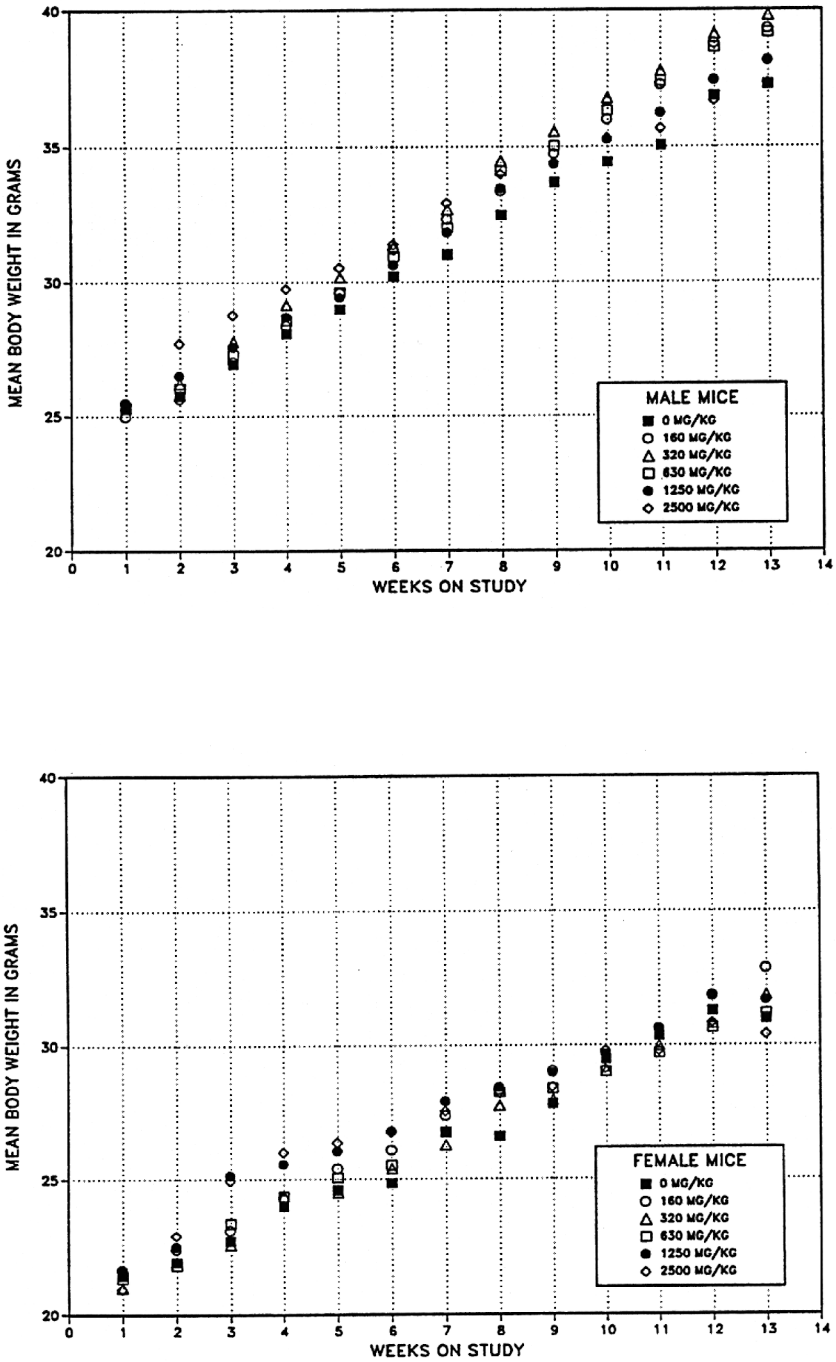


FIGURE 5
Growth Curves for Male and Female Mice Administered Oxymetholone by Gavage for 14 Weeks

The kidney weights of 1,250 and 2,500 mg/kg males and of all dosed groups of females and the liver weights of 2,500 mg/kg males and 320, 630, 1,250, and 2,500 mg/kg females were significantly greater than those of the vehicle controls (Table E3). The thymus weights of 1,250 and 2,500 mg/kg females and uterus weights of 160, 320, and 630 mg/kg females were significantly less.

Pathologic effects related to oxymetholone administration to mice for 14 weeks were found only in the ovary, clitoral gland, kidney, and salivary gland of females (Table 20). Hypoplasia of the ovary, observed in females administered 320 mg/kg or greater, was characterized by organs that were smaller in size than those of the vehicle controls and that had reduced numbers of corpora lutea and a paucity of interstitial gland tissue (Plates 7a and 7b). In contrast to the ovarian changes in rats (dysgenesis), follicular maturation in mice appeared normal, and there were no atypical interstitial cells. The morphology of the ovaries in dosed mice was interpreted to reflect the failure of follicles to develop into corpora lutea, presumably due to lack of proper hormonal stimulation for follicular growth and ovulation. Thus, this change was termed hypoplasia instead of atrophy, a term applied to aged ovaries with changes consistent with regression such as decreased numbers of both corpora lutea and follicles, as well as an increased relative amount of interstitial tissue. Clitoral gland enlargement was observed grossly in all dosed groups and histologically was characterized by an increased amount of gland tissue (hyperplasia) and prominent ectasia of the ducts (Plates 8a and 8b). Because the ectatic duct system of treated females resembled that of normal vehicle control males, this was considered to be a masculinizing effect of oxymetholone in mice. A morphologic change in the kidney glomeruli in all treated female mice was also considered to be the result of an androgenic effect of oxymetholone. This change was diagnosed as metaplasia of Bowman's epithelium and consisted of a transformation of the normally squamous parietal epithelial cells of Bowman's capsule into cuboidal cells (Plates 9a and 9b) that are normally seen in male mice. Another morphologic change thought to be an androgenic effect was cytologic alteration of the submandibular salivary gland in all treated females. This alteration consisted of an increased number of eosinophilic granules within the granular duct cells resulting in an appearance of this sexually dimorphic tissue more similar to that in males. In 1,250 and 2,500 mg/kg females, another salivary gland change was atrophy of the parotid gland, characterized by decreased size and increased basophilia of the acinar secretory cells.

Quantitation of PCNA labeling indices in the liver and kidney of vehicle control and 2,500 mg/kg mice was performed. No significant changes were noted in the labeling index of renal tubule cells.

The percentages of motile sperm in 1,250 and 2,500 mg/kg males were significantly less than that in the vehicle controls (Table F3), and the estrous cycle lengths of 630, 1,250, and 2,500 mg/kg females were significantly longer (Table F4). Females in the 1,250 and 2,500 mg/kg groups spent more time in diestrus and less time in estrus than did vehicle control females.

Rationale for Not Conducting a 2-Year Study in Mice: In the 14-week study, mice were considerably less sensitive than rats to the effects of oxymetholone treatment although they received twice the dose. There were no deaths or treatment-related clinical findings, and the final mean body weights were similar to those of the vehicle controls. Liver and kidney weights were increased in 1,250 and 2,500 mg/kg male and female mice, but there were no gross lesions, and no life-threatening lesions were observed microscopically. The conclusion, after a review of the histopathology, was that mice could likely tolerate doses up to 2,500 mg/kg in a 2-year study, approximately 1,000 times greater than normal human doses. The International Agency for Research on Cancer has classified oxymetholone as having limited evidence of carcinogenicity in humans based on case reports; however, there were no data available to assess carcinogenicity in animals. In the current 14-week studies, only female mice showed treatment-related effects, and these were similar to those observed in female rats. Because male and female rats were much more sensitive to treatment than mice, it was decided that a mouse study would not provide any significant additional toxicity information, and a 2-year carcinogenicity study in mice was not conducted.

TABLE 20
Incidences of Selected Nonneoplastic Lesions in Female Mice in the 14-Week Gavage Study of Oxymetholone

	Vehicle Control	160 mg/kg	320 mg/kg	630 mg/kg	1,250 mg/kg	2,500 mg/kg
Ovary[a]	10	10	10	10	10	10
Hypoplasia[b]	0	0	10** (1.0)[c]	10** (1.0)	10** (1.4)	10** (3.0)
Clitoral Gland	9	10	10	10	10	10
Hyperplasia	0	10** (3.0)	10** (3.0)	10** (3.0)	10** (3.0)	10** (3.0)
Kidney	10	10	10	10	10	10
Bowman's Capsule Parietal Layer, Metaplasia	0	10** (1.0)	10** (1.0)	10** (1.0)	10** (2.0)	10** (1.8)
Salivary Gland	10	10	10	10	10	10
Parotid Gland, Atrophy	0	0	0	0	4* (1.0)	9** (1.8)
Submandibular Gland, Cytoplasmic Alteration	0	10** (1.0)	10** (1.8)	10** (2.0)	10** (2.0)	10** (2.0)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

GENETIC TOXICOLOGY

In tests conducted by the NTP with oxymetholone, no indication of mutagenicity was observed. Oxymetholone was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535 when tested in a preincubation protocol with and without Aroclor 1254-induced rat or hamster liver S9 (Table C1; Zeiger *et al.*, 1992). Toxicity was not a limiting factor in concentration of oxymetholone tested, but formation of a precipitate was noted at concentrations of 3,333 μg/plate and greater. In tests with cultured Chinese hamster ovary cells, no induction of chromosomal aberrations was observed, with or without S9 activation (Table C2). No cell cycle delay was noted in treated cultures, but lethality occurred at concentrations above 22 μg/mL. *In vivo*, no significant increases in the frequency of micronucleated normochromatic erythrocytes were observed in blood obtained from male and female mice at the termination of the 14-week study (Table C3).

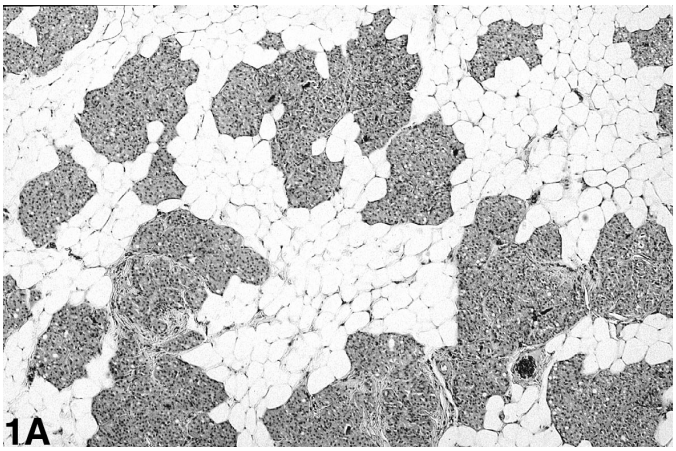


Plate 1A
Mammary gland of a control male F344 rat from the 13-week study of oxymetholone, composed of abundant, solid lobules of cells without distinct ductular differentiation.

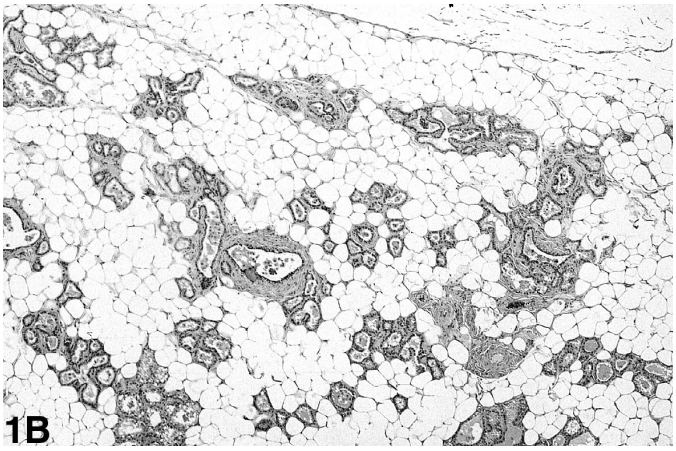


Plate 1B
Mammary gland of a male F344 rat treated with oxymetholone for 13 weeks. In contrast to the control, there is prominent tubulo-alveolar differentiation with distinct lumina.

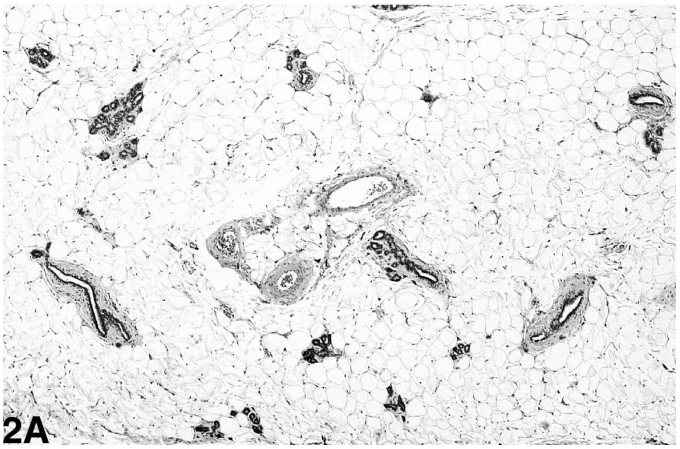


Plate 2A
Mammary gland of a control female F344 rat from the 13-week study of oxymetholone, composed of widely scattered tubular structures and little alveolar tissue.

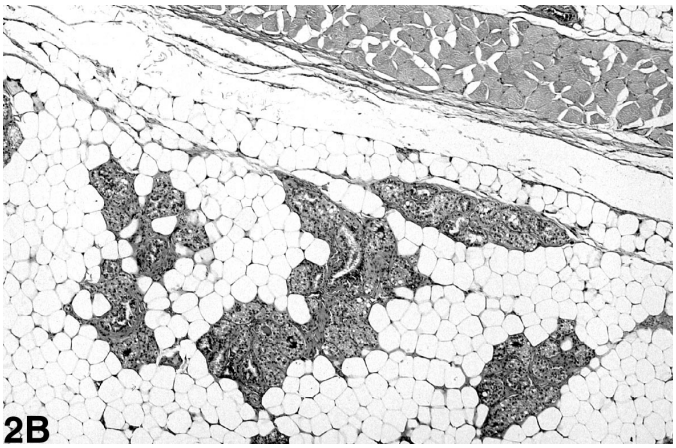


Plate 2B
Mammary gland of a female F344 rat treated with oxymetholone for 13 weeks. There is increased amount of solid glandular tissue, more similar to that seen in control males (Plate 1a).

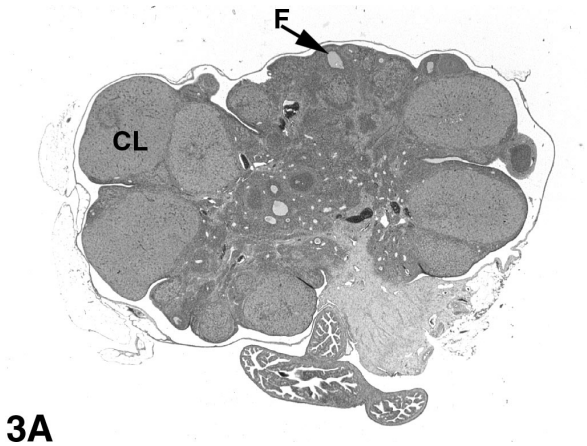


Plate 3A
Ovary of a control F344 rat from the 13-week study of oxymetholone, with follicle (F) and numerous corpora lutea (CL).

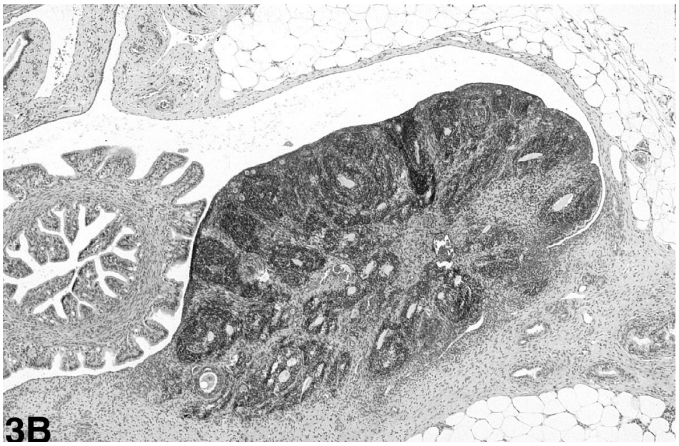


Plate 3B
Ovary of a F344 rat treated with oxymetholone for 13 weeks. There are numerous atretic follicles surrounded by clusters of dark staining interstitial cells. (see also Figure 10B)

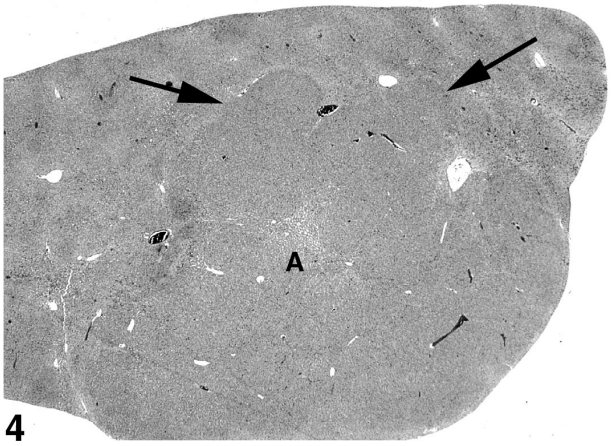


Plate 4
Liver of a female F344 rat treated with oxymetholone for 2 years. Note the lobulated hepatocellular adenoma (A) with well demarcated borders between the darker staining tumor cells and the normal parenchyma (arrows).

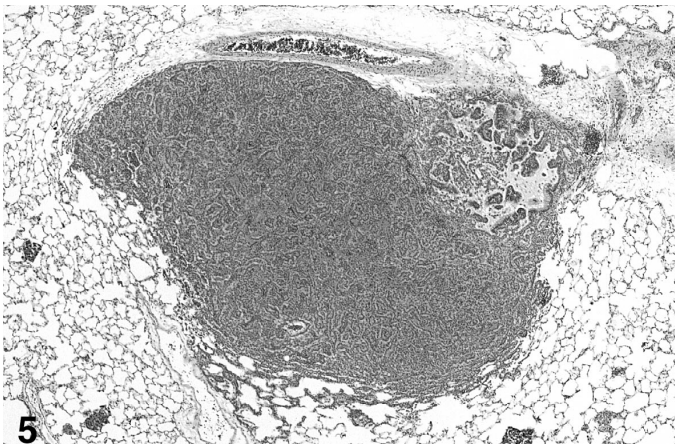


Plate 5
Lung of a female F344 rat treated with oxymetholone for 2 years. The normal alveolar parenchyma is replaced by a solid alveolar/bronchiolar adenoma.

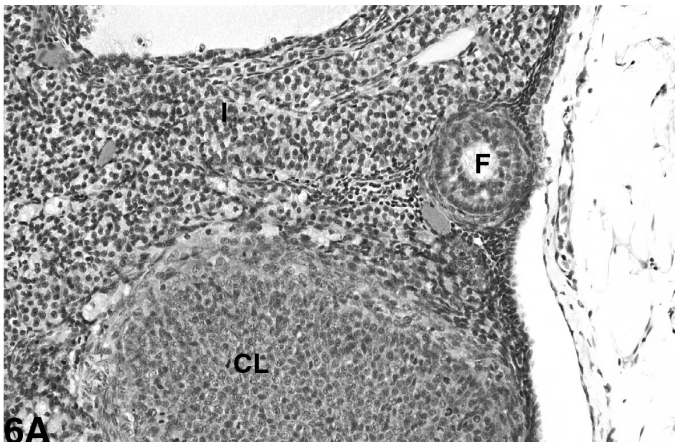


Plate 6A
Ovary of a control F344 rat from the 2-year study of oxymetholone, with follicle (F), corpus luteum (CL), and vacuolated interstitial cells (I).

Plate 6B
Ovary of a F344 rat treated with oxymetholone for 2 years. Much of the organ is replaced by dark staining interstitial cells that form organized nests around small blood vessels or atretic follicles.

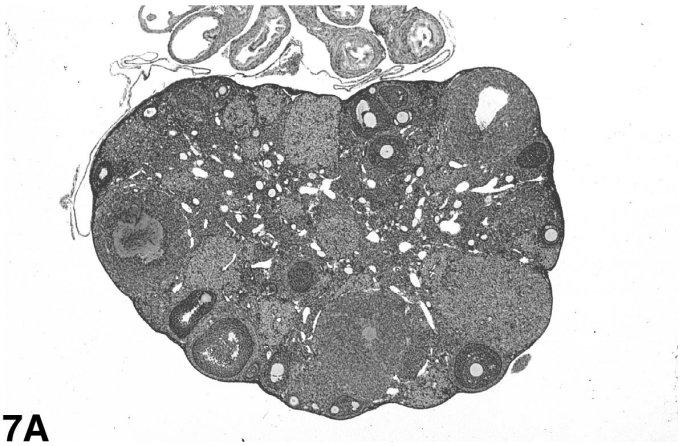


Plate 7A
Ovary of a control B6C3F$_1$ mouse from the 13-week study of oxymetholone, with numerous follicles and corpora lutea in various stages of development.

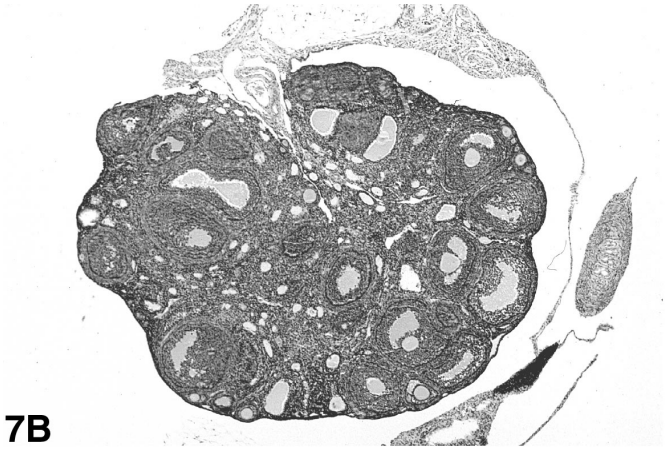


Plate 7B
Ovary of a B6C3F$_1$ mouse treated with oxymetholone for 13 weeks. There are numerous follicles but the number of corpora lutea is markedly reduced.

Plate 8A
Clitoral gland of a control B6C3F$_1$ mouse from the 13-week study of oxymetholone, with modified sebaceous acinar tissue surrounding the central excretory duct.

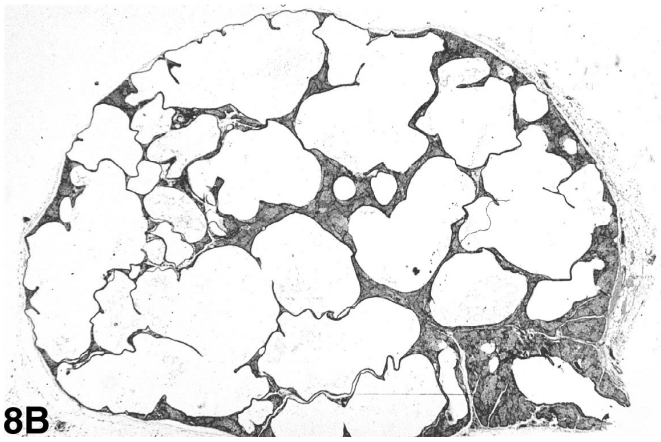


Plate 8B
Clitoral gland of a B6C3F$_1$ mouse treated with oxymetholone for 13 weeks. The gland is enlarged and there is prominent ectasia of the duct system.

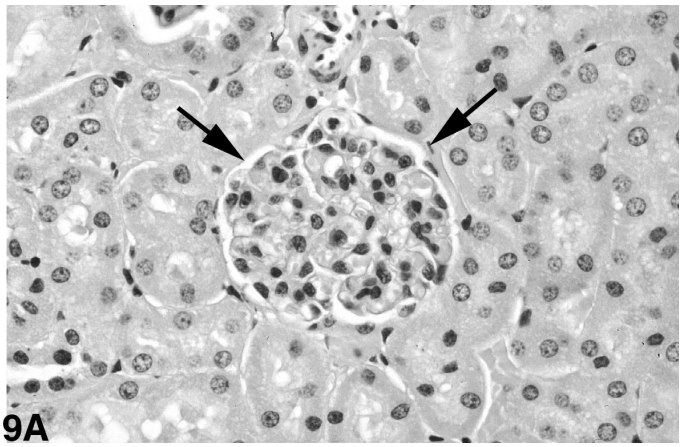


Plate 9A
Kidney of a control female B6C3F$_1$ mouse from the 13-week study of oxymetholone. Bowman's space is lined by an inapparent, flattened squamous epithelium (arrows).

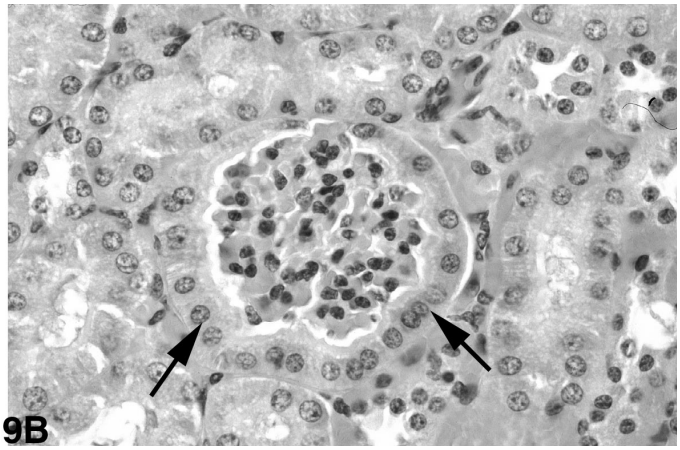


Plate 9B
Kidney of a female B6C3F$_1$ mouse treated with oxymetholone for 13 weeks. The lining of Bowman's capsule is replaced by metaplastic cuboidal epithelium (arrows) resembling that found in control males.

DISCUSSION AND CONCLUSIONS

Testosterone functions are generally classified as anabolic and androgenic. Anabolic actions include those related to tissue-building, and androgenic actions include those related to masculinization. These actions are determined not by the nature of the steroid but by the number of receptor sites and types of metabolizing enzymes of the specific target cell. Replacement therapy with androgens is indicated in a variety of conditions, including growth disorders, anemia and other blood disorders, cancer, and catabolic and debilitating states. However, because testosterone is quickly degraded when administered orally due to the first-pass metabolism in the liver, synthetic steroids have been made more effective by modifying the testosterone molecule. Alkyl substitution in the 17α position of testosterone decreases the rate of liver metabolism and allows the modified testosterone to be active when taken orally (Lin and Erinoff, 1990). Oxymetholone is methylated at the 17α position; the 5α-reduction (of the testosterone molecule) gives the chemical a greater myotropic effect and seems to prevent aromatization, and the hydroxymethylene group at the C-2 position appears to be important for steroid-protein interactions (MacDonald *et al.,* 1973).

While these synthetic anabolic androgens may improve the efficacy of treating a specific disorder, androgenic effects may occur, especially with misuse of the chemical. For example, it is well known that changes in plasma testosterone affect the pituitary secretions of luteinizing hormone and follicle stimulating hormone (Wierman and Wang, 1990), and exogenous synthetic anabolic androgens would be expected to affect the pituitary-gonadal axis in a similar manner. High levels of synthetic androgens, taken for their anabolic or erythropoietic effects, would also suppress luteinizing hormone, which regulates testosterone synthesis by the Leydig cells and estradiol and progesterone synthesis by the ovary, and follicle stimulating hormone, which promotes spermatogenesis in seminiferous tubules and ovarian follicle development. Commonly reported adverse side effects include mood changes, such as depression, hostility, aggression, irritation, and paranoia in athletes using anabolic steroids (Wilson, 1996). In men, steroid use produces testicular atrophy and gynecomastia, and acne has been reported in athletes (*PDR*, 1998) and nonathletes (Korkia and Stimson, 1997). In women, athletic performance has been reported to improve as a part of the virilization process. However, in women, anabolic steroids also cause acne, growth of facial hair, coarsening of the voice, and menstrual irregularity and may cause male pattern baldness, increased body hair, prominent musculature, and hypertrophy of the clitoris (*PDR,* 1998). The history of synthetic androgens and the adverse effects of anabolic steroids have been the subjects of several reviews (Hickson *et al.*, 1989; Graham and Kennedy, 1990; Lin and Erinoff, 1990; Kennedy, 1992; Yesalis and Bahrke, 1995).

Oxymetholone is approved for the treatment of anemia and has been used successfully to increase weight gain in patients with HIV-related wasting (Hengge *et al.*, 1996; *PDR*, 1998). However, because its actions are more anabolic than androgenic, oxymetholone is one of the synthetic anabolic steroids often used illicitly, and at pharmacologic doses, by athletes hoping to improve performance (Strauss *et al.*, 1983; Lamb, 1984; Perry *et al.*, 1990). Because of this use, anabolic steroids were added to the list of prohibited substances by the International Olympic Committee in 1975, and the urine of Olympic athletes is now tested for oxymetholone (IOC, 1995).

The studies reported here were conducted to obtain toxicology and carcinogenesis data in rodents exposed to oxymetholone not only at the recommended therapeutic dose but also at the very high doses reportedly used by athletes. The work of Sanders and Matthews (1991, 1999) on the disposition of radiolabeled oxymetholone indicates that the organs with the highest radioactivity were the liver, kidney, skin, adrenal gland, spleen, and testis, and all except the spleen showed anabolic effects in the current studies. The results of these studies generally support those results commonly reported in the literature regarding the effects of synthetic anabolic androgens, i.e., erythropoiesis, masculinization of females, and feminization of males.

In the 14-week rat study, the effect of oxymetholone on the hematopoietic system was greater in females than in males, which supports the existing literature. This gender difference in rats is attributed to the difference in androgen metabolism. The testosterone molecule appears to require a 17β-hydroxy and 5α-dihydro modification for erythropoietic stimulation (reviewed by Shahidi, 1973). The changes in the hematology parameters (increased erythrocyte counts and hematocrit and hemoglobin concentrations) are consistent with a secondary polycythemia related to an increased production of erythropoietin, stimulated by the oxymetholone treatment. It has been reported that anabolic/androgenic steroids increase both renal and nonrenal erythropoietin production (Shahidi, 1973). The decreased mean cell volumes, most prominent in female rats, suggest that the erythrocytes being produced are smaller than normal. Smaller erythrocytes could be related to the increased erythropoietin-stimulated erythrocyte production, resulting in a mild iron deficiency. The animals were young at the beginning of this study, and young animals have relatively poor iron stores. The increased erythrocyte production could have depleted the existing iron stores in the hematopoietic system, resulting in the production of smaller erythrocytes. The decrease that occurred in the mean cell hemoglobin concentrations would be consistent with the production of smaller erythrocytes. The increases in platelet counts, although inconsistent, could also be related to increased bone marrow stimulation by erythropoietin.

Several changes were observed in the coagulation evaluations in the 14-week studies in rats. Although most changes were not considered significant, a treatment-related increase in thromboplastin time occurred in all dosed female rats. This change suggests an altered synthesis and degradation of clotting factor VII. A similar change was not observed in dosed male rats.

In the current studies, high doses of oxymetholone had a positive effect on body weight gain in female rats and a negative effect on body weight gain in male rats, consistent with prior literature. Woodward (1993) reported that ovariectomized rats had an accelerated growth rate compared to intact females, and testosterone implants increased the growth rate significantly. In male rats, orchiectomy caused subnormal body weight gain, and testosterone increased the body weight to normal levels. However, exogenous testosterone had no effect on growth in intact males.

In the 14-week studies, oxymetholone caused atrophy of the testis and ovary in rats and mice, decreased spermatid counts in rats, and changes in the estrous cycle in mice. In intact male Long-Evans rats injected daily with oxymetholone (0.12, 1.2, or 12.0 mg/kg) or the corn oil vehicle for 12 weeks, there was no effect on body weight. Serum testosterone concentrations were significantly lower in the high-dose group compared with the other groups. Seminal vesicle weights were less in the mid- and high-dose groups, and testis weight was less in the high-dose group compared to the other dose groups. There was a significant reduction in the number of males showing sexual behavior in the high-dose group (Clark *et al.*, 1997). Male Sprague-Dawley rats were treated with the anabolic steroid oxandrolone beginning at 2 days after weaning (23 days of age) and continuing to 60 days of age. Testis, prostate gland, and seminal vesicle weights were all decreased compared to untreated animals. Testicular testosterone production was inhibited, and serum follicle stimulating hormone and luteinizing hormone levels were significantly less than those of controls. There was an arrest of advanced spermatids and a severe depletion of Leydig cells in the interstitial compartment (Grokett *et al.*, 1992).

Weightlifters received testosterone enanthate intramuscularly for 3 weeks, followed by a 4-week washout period. Serum testosterone concentrations were increased, and serum luteinizing hormone and follicle stimulating hormone levels were decreased (Zmuda *et al.*, 1993). About 60% of bodybuilders taking up to 40 times the clinical doses of anabolic steroids had subnormal sperm counts, and percentages of motile and normally formed sperm were significantly decreased compared with volunteers not using steroids. A variety of anabolic androgens were being used, and it was not possible to identify the effects of each one individually. As a group, the athletes taking anabolic androgens showed significantly reduced serum values for luteinizing hormone and follicle stimulating hormone compared with athletes who had stopped taking the steroids. Serum concentrations of estradiol, but not testosterone or dihydrotestosterone, were elevated in steroid users (Knuth *et al.*, 1989). The morphology of the ovaries from rats administered oxymetholone (30 or 100 mg/kg for 2 years or

1,250 mg/kg for 14 weeks) is unique in the history of NTP chronic bioassays and, consequently, questions arose concerning the appropriate diagnosis and pathogenesis of the lesions. The sum of the data, including follicle counts, combined with the known androgenic effects of oxymetholone, supports the conclusion that the lesions represent arrested follicular development, aberrant follicular atresia, and atypical interstitial/stromal cell growth and differentiation. Therefore, the term "ovarian dysgenesis" appears to be the most appropriate description for the ovarian morphology and the pathogenesis of the lesion. A similar ovarian appearance, termed "follicular dystrophy," was reported after testosterone treatment of hypophysectomized rats (Payne *et al.*, 1956).

The origin of the stromal cells remains unclear with respect to whether these cells represent atrophy of interstitial cells or failure of the sex cord/stromal cells to differentiate into interstitial cells. All interstitial cells arise from a population of unspecialized mesenchymal cells in the stroma compartment, and purportedly these mesenchymal cells have stem cell abilities to both proliferate and differentiate (Erickson *et al.*, 1985). Fully developed interstitial cells exhibit specialized ultrastructural properties of steroid-producing cells, including smooth endoplasmic reticulum, mitochondria with tubular cristae, and lipid droplets. The histological and ultrastructural features of the atypical stromal cells in the oxymetholone-treated rat ovaries more closely resemble stem cells, and few cytoplasmic organelles contain no lipid. Thus, these cells may represent stem cells that have failed to differentiate due to exogenous androgens.

At a dose selected to mimic human abuse levels (12 mg/kg), oxymetholone disrupted cyclical display of sexual receptivity and vaginal estrus in rats. Short-term exposure did not affect body weight (Clark *et al.*, 1998). This anabolic steroid has been reported to disrupt the menstrual cycle in humans (Cox *et al.*, 1975). Female athletes who consistently used anabolic steroids noted a deepening of the voice, increased facial hair, increased aggressiveness, clitoral enlargement, and menstrual irregularities (Strauss *et al.*, 1985).

Changes in clinical chemistry parameters, e.g., concentrations of liver enzymes and plasma lipids, have been commonly associated with abuse of anabolic steroids, reflecting the toxicity of this class of compounds to organ systems (Hickson *et al.*, 1989; Graham and Kennedy, 1990; Kennedy, 1992). In the 14-week oxymetholone gavage studies, serum concentrations of cholesterol were decreased in essentially all treated male and female rats in a dose-related manner; the decrease was more pronounced over time. Exogenous androgens have been reported to cause significant decreases in high-density lipoprotein concentrations in humans (Zmuda *et al.*, 1993; Kouri *et al.*, 1996), and 17-alkylated synthetic androgens appear to cause a greater reduction (Thompson *et al.*, 1989). The mechanism for the hypocholesterolemia in the rats in the current study was not evident. Cholesterol is the precursor in the synthesis of testosterone in the testis and estrogen and progesterone in the ovary (Hall, 1994; vom Saal *et al.*, 1994). In addition, the liver is a known target tissue of androgens and the major site of cholesterol biosynthesis in the rat (Bartley, 1989). It is not clear if the liver is a secondary source of cholesterol for gonadal steroid synthesis, but a decrease in normal steroid production may be related to the decrease in circulating levels of cholesterol. One example might be an effect on the activity of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase (the rate limiting enzyme of cholesterol synthesis) in the liver, i.e., decreased HMG-CoA reductase production, production of biologically inactive enzyme, or increased degradation or inhibition would affect circulating levels of cholesterol. Considering that high-density lipoprotein carries about 60% of the circulating cholesterol in the rat, a decrease in high-density lipoprotein levels may play a part in the total cholesterol decrease.

Depression of serum 5′-nucleotidase activity occurred in all treated male and female rats at 14 weeks. Decreased activity of 5′-nucleotidase also occurred in most male and female dosed groups on days 5 and 19. 5′-Nucleotidase is a plasma membrane brush border enzyme found in many tissues, including the biliary epithelium of the hepatobiliary tree. Like alkaline phosphatase, 5′-nucleotidase is used as a marker of cholestatic disease, and increased serum activity occurs due to the detergent activity of bile acids. In normal rats, it has been suggested that serum activities of 5′-nucleotidase and alkaline phosphatase are derived from tissues (e.g., intestine) other than liver, and serum activities of these enzymes can decrease in instances when there is decreased feed intake (Jenkins

and Robinson, 1975). In humans, androgens have been reported to cause jaundice, cholestatic hepatitis, and toxic hepatitis (Ishak and Zimmerman, 1987; Wilson, 1996).

Liver weights were increased in dosed female rats and in male rats administered 625 or 1,250 mg/kg in the 14-week studies, suggesting increased metabolic activity. Of the synthetic anabolic steroids available for clinical use, the 17α-alkylated agents have been associated with liver toxicity (Ishak and Zimmerman, 1987; Hickson *et al.*, 1989). In men, other clinical chemistry alterations have included increases in serum aspartate aminotransferase and alkaline phosphatase activities and bilirubin concentration (Kennedy, 1992). Increases in these serum enzyme activities suggest hepatocellular damage with leakage of cytosolic enzyme into the circulation. Hepatocellular damage would support the very mild increases in serum alanine aminotransferase activities that occurred in the treated female rats on days 5 and 19. This change did not occur in male rats treated for 14 weeks. However, the serum enzyme activity changes noted above in men were reported after longer-term treatment (months) (Lenders *et al.*, 1988). In fact, at the end of the 14-week studies, serum activity of alanine aminotransferase slightly decreased in the 160, 315, 625, and 1,250 mg/kg male rat groups. Additionally, the changes that occurred in alanine aminotransferase activity were not supported by similar changes in sorbitol dehydrogenase, so it is doubtful that the changes in the alanine aminotransferase activity are clinically significant. Primary hepatocyte cultures from 60-day-old Sprague-Dawley rats exposed to oxymetholone showed significant increased lactate dehydrogenase levels and glutathione depletion, interpreted by the authors as indicating a toxic effect (Welder *et al.*, 1995).

The interpretation of the results of this 2-year rat study was more complex than for other chemicals tested in the NTP because oxymetholone was modeled after the normal circulating hormone, testosterone. Testosterone affects directly and indirectly many different tissues in the body and specific responses may be related to the number of receptors in the individual target organs, the metabolism, and the effect of a primary response on other physiological systems. It is known that these conditions are not the same in all organs and are not the same in males and females. Because of its important role in reproductive physiology and because of medical problems associated with a hormonal imbalance, the effects of testosterone have been and continue to be widely studied and a considerable body of knowledge exists. Because testosterone itself cannot be orally administered, synthetic anabolic steroids have been created for therapeutic use. Oxymetholone was created by chemically modifying the testosterone molecule to overcome problems with testosterone bioavailability and to emphasize the anabolic effects of testosterone. However, it is not possible to eliminate the androgenic effects altogether. In the current oxymetholone studies, it is apparent from the atrophied testes and ovaries that the production of gonadal androgens and estrogens has been abolished or greatly reduced, and the anabolic androgenic effects of circulating levels of oxymetholone and its metabolites would predominate. An overall observed effect was a feminization of males and a masculinization of females. These observations have also been reported for male and female athletes taking large doses of synthetic steroids (Hickson *et al.*, 1989; Graham and Kennedy, 1990; Kennedy, 1992). What is not as well known with synthetic anabolic androgens is how they will affect the normal hormone physiologic interactions compared with the way unmodified testosterone does, especially at pharmacologic doses. For example, in the current studies body weight gains of females at 14 weeks would suggest that the animals were not responding in the same way to different doses of oxymetholone. Therefore, responses that were not dose-related may be the result of higher doses of this synthetic steroid having an inhibitory or toxic effect on the normal hormone physiology.

Administration of oxymetholone produced a number of neoplastic and nonneoplastic effects in the 2-year study. Significant oxymetholone-related increased incidences of hepatocellular adenoma and adenoma or carcinoma (combined) occurred in 100 mg/kg female rats in the current 2-year study. The spontaneous occurrence of these neoplasms in female rats is quite rare, and only low incidences of hepatocellular adenoma have occurred in female historical controls for methylcellulose gavage, drinking water, and dosed feed studies. Clear evidence for the liver neoplasms in female rats was based on the 16% incidence of hepatocellular adenomas being much higher than the NTP's historical control incidences in feed (0.4%) and drinking water (1.4%) controls and also on the fact that there were two carcinomas. Carcinomas have not

been observed in feed or drinking water historical control female rats. These results support the human data indicating an association of hepatocellular carcinoma with anabolic steroids in patients receiving long-term therapy (*PDR,* 1998). The incidences of basophilic and clear cell foci were significantly greater than those in the vehicle controls. Although foci are commonly found as a spontaneous lesion in aging male and female F344/N rats, induction of some types of foci is considered to be an indicator of hepatocarcinogenic potential. A 39-week dietary administration of oxymetholone increased the number and size of liver foci in F344/N rats pretreated with N-diethylnitrosamine, a finding suggesting the potential for promotion of rat liver carcinogenesis (Shimoji *et al.*, 1990). The increases in incidences of liver neoplasms in the current study could be related to the effect of synthetic androgens in lowering circulating estrogen and progesterone levels. In a cohort study of 22,597 Swedish women who were prescribed replacement hormones, the risk for liver and biliary tract neoplasms was reduced by about 40% in those women taking estrogen-progestins combinations (Persson *et al.*, 1996). The association between oxymetholone and liver toxicity is well known and, as such, is indicated in the product description for Anadrol®-50 (*PDR*, 1998). Oxymetholone is listed by the International Agency for Research on Cancer (1982) as having limited evidence of carcinogenicity and by the NTP (1998) as reasonably anticipated to cause cancer.

There are known to be androgen, estrogen, and progesterone receptors in the lung and enzymes that metabolize these steroids (Milewich *et al.*, 1986; Nielsen *et al.*, 1987; Sonderfan *et al.*, 1989; Kaufmann *et al.*, 1995; Kuiper *et al.*, 1997). In humans, lung neoplasms (small-cell neoplasms, squamous cell carcinomas, and adenocarcinomas) were found to have binding sites for testosterone but not estrogen, and testosterone had a proliferative effect (Chaudhuri *et al.*, 1982; Kobayashi *et al.*, 1982; Beattie *et al.*, 1985; Maasberg *et al.*, 1989). At 2 years, the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in 30 mg/kg females was significantly increased compared with that of concurrent vehicle controls and exceeded the historical control ranges. The highest incidence of these neoplasms previously observed in female historical control groups for feed studies was 3/50 (6%). While there is no increased incidence of lung neoplasms in 100 mg/kg females, the increased incidence in the 30 mg/kg group of females was considered to be related to treatment with oxymetholone.

The incidences of alveolar/bronchiolar neoplasms were significantly decreased in 30 mg/kg males at 2 years. However, the incidence in the concurrent vehicle control males exceeded the historical control ranges for methylcellulose gavage and drinking water studies. Moreover, as is commonly observed in historical control groups, the incidence in 30 mg/kg males was zero. Therefore, the significant decrease seen in this group was not considered to be chemical related.

One of the known sites affected by large doses of anabolic steroids in men and women is the skin (e.g., sebaceous gland hypertrophy and acne) (Scott and Scott, 1992). The skin was shown to be a site of accumulation of radioactivity in rats after administration of radiolabeled oxymetholone (Sanders and Matthews, 1991). The combined incidence of neoplasms of the skin was significantly increased in 100 mg/kg females at 2 years and exceeded the historical control ranges. In addition, the incidence of keratoacanthoma was increased in 30 mg/kg females. Spontaneous skin neoplasms of epithelial origin (epidermal and adnexal tumors) are considerably more common in male F344/N rats than in females. This gender difference implies that sex steroids may play a role in the development of these neoplasms; therefore, masculinization of females by oxymetholone may provide a biologic basis for the skin neoplasm effect in females. In male rats in this study, the incidences of subcutaneous tissue neoplasms were significantly increased in 3 mg/kg males at 2 years. Although the incidence of such neoplasms of the concurrent vehicle control group (0%) was less than the average historical control incidences (e.g., for feed studies, 6.5%), the combined incidence of 14% in 3 mg/kg males exceeded historical control ranges (e.g., for feed studies, 0%-12%) and may have been related to administration of oxymetholone.

Polderman *et al.* (1995) reported that high doses of exogenous testosterone esters increase the production of adrenal androgens in women, indicating that adrenal gland function is in part moderated by anabolic androgens. The adrenal gland was shown to be a site of radioactivity accumulation in F344 rats after radiolabelled oxymetholone administration

(Sanders and Matthew, 1991). Treatment with 17α-methyl-5-androstene-3β, 17β-diol, a chemical structurally similar to the oxymetholone metabolite 17α-methyl-5α-androstane-3β, 17β-diol, caused an increased secretion of 11-deoxycorticosterone in rats (Brownie *et al.*, 1988). During development, adrenal glucocorticoids influence the differentiation of neurogenic progenitor cells to chromaffin cells (Michelsohn and Anderson, 1992). Chromaffin cells have been shown to have glucocorticoid receptor sites and glucocorticoids are known to increase the activity of the enzyme phenylethanolamine-N-methyltransferase, the terminal enzyme of the epinephrine biosynthetic pathway in the adrenal medulla of the rat (Kelner and Pollard, 1985; Wurtman and Axelrod, 1965, 1966). At 2 years in the current studies, the incidences of pheochromocytoma in 150 mg/kg males were significantly increased. The incidence exceeded the historical control ranges and, of the 29 males in the 150 mg/kg group that had pheochromocytomas, 19 had bilateral neoplasms as compared to only three bilateral neoplasms in the 19 controls with pheochromocytoma. However, there was no increase in the incidence of medullary hyperplasia, generally considered a precursor lesion to pheochromocytoma, in treated males. In addition, adrenal medullary proliferative lesions occur at a high and variable rate in male F344/N rats. Therefore, it is uncertain if the increase in pheochromocytoma incidence in 150 mg/kg males is related to administration of oxymetholone.

The incidence of pheochromocytoma in 100 mg/kg female rats also exceeded the historical control ranges. However, the incidence did not significantly exceed that of the concurrent vehicle control group, and only four of the females with pheochromocytomas had bilateral neoplasms. Although the incidence of medullary hyperplasia was increased in 100 mg/kg females at 2 years, there was no dose response. Therefore, this marginal increase in the incidence of this lesion was not considered to be related to administration of oxymetholone.

The incidences and severities of nephropathy were significantly increased in 30 and 150 mg/kg males at 2 years and in 100 mg/kg females at all time points. In addition, the incidences of renal tubule adenoma in 3 and 150 mg/kg male rats were greater than the historical control ranges for drinking water and feed studies and were suggestive of a neoplastic effect on the renal tubule. Therefore, an extended evaluation of the kidney was conducted. When the standard and extended evaluations were combined, the incidence of renal tubule adenoma in the 3 mg/kg male rats was significantly increased relative to that in the vehicle controls and exceeded the historical incidences of renal tubule adenoma from previous NTP extended kidney evaluations of control male F344/N rats. Therefore, although the incidences of renal tubule adenoma were not increased in the 30 and 150 mg/kg males, the increase in the incidence in 3 mg/kg males may have been related to administration of oxymetholone. In contrast to males, only a single additional proliferative lesion (hyperplasia in a vehicle control) was found in the extended evaluation of kidneys from female rats.

Nonneoplastic effects, apparently related to the feminizing/masculinizing actions of oxymetholone, were observed in the mammary gland of both male and female rats. The most remarkable treatment-related change in the mammary gland of males was an overall increase in the amount of tubulo-alveolar glandular tissue present as compared to that observed for the vehicle controls. In treated females, the increased alveolar component cytologically resembled the mammary gland tissue of vehicle control males. Gynecomastia is a response observed following anabolic steroid administration. Androgen treatment to ovariectomized rats stimulated tubulo-alveolar and ductal growth of the mammary gland as well as the secretory activity of acinar cells (Sourla *et al.*, 1998). It has also been reported that exogenous androgens have an inhibitory effect on the growth of mammary gland tumors (Gatto *et al.*, 1998).

Oxymetholone administration also induced decreased incidences of neoplasms in some organs in the F344/N rats that may have been the result of the effects of this synthetic androgen on the hypothalamus-pituitary-gonadal axis. In females, there were decreased incidences of uterine, mammary gland, and pituitary gland neoplasms. In males and females, the incidences of mononuclear cell leukemia were significantly decreased, and in males, the incidences of interstitial cell hyperplasia and adenoma of the testis were significantly decreased.

The major effects in the current studies are generally consistent with expectations, given the high doses of

exogenous anabolic androgen used. It is apparent from the atrophied testes and ovaries that the production of gonadal androgens and estrogens has been abolished or greatly reduced. Thus, it would be expected that the anabolic androgenic effects of circulating levels of oxymetholone and its metabolites would predominate. The actual effect of administration of oxymetholone on endogenous hormone production, across the dose ranges used in these studies, is difficult to predict, but it is possible that complex hormonal effects may account for the lack of a dose response seen with some of the neoplasms observed in these studies.

CONCLUSIONS

Under the conditions of this 2-year gavage study, there was *equivocal evidence of carcinogenic activity** of oxymetholone in male F344/N rats based on increased incidences of subcutaneous tissue fibromas and fibromas or fibrosarcomas (combined) of the skin, variably increased incidences of benign and benign or malignant pheochromocytomas (combined) of the adrenal gland, and increased incidences of renal tubule adenomas. There was *clear evidence of carcinogenic activity* of oxymetholone in female F344/N rats based on increased incidences of hepatocellular neoplasms. Increased incidences of alveolar/bronchiolar neoplasms and skin neoplasms in female rats were also related to oxymetholone administration.

Decreased incidences of alveolar/bronchiolar neoplasms and testicular interstitial cell adenomas in males; uterine stromal polyps or stromal sarcomas (combined), mammary gland neoplasms, and pituitary gland pars distalis adenomas in females; and mononuclear cell leukemia in males and females were related to oxymetholone administration.

In addition, gavage administration of oxymetholone to male and female F344/N rats resulted in a spectrum of nonneoplastic effects frequently reported with administration of synthetic anabolic androgens.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF OXYMETHOLONE

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone[a]

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Disposition Summary				
Animals initially in study	90	90	90	90
3-Month interim evaluation	10	10	10	9
6-Month interim evaluation	10	10	10	10
12-Month interim evaluation	9	10	10	10
18-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths		1		3
Moribund	24	22	25	15
Natural deaths	12	12	11	12
Survivors				
Terminal sacrifice	15	15	14	20
Missexed				1
Animals examined microscopically	90	90	90	89

Systems Examined at 3 Months with No Neoplasms Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Integumentary System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

6-Month Interim Evaluation

Endocrine System				
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma			1 (10%)	

Systems Examined with No Neoplasms Observed
Alimentary System
Cardiovascular System
General Body System
Genital System
Hematopoietic System
Integumentary System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
12-Month Interim Evaluation				
Endocrine System				
Adrenal medulla	(9)	(10)	(10)	(10)
Pheochromocytoma benign	1 (11%)			
Pituitary gland	(9)	(10)	(10)	(10)
Pars distalis, adenoma	2 (22%)	2 (20%)	3 (30%)	
Thyroid gland	(9)	(10)	(10)	(10)
C-cell, adenoma	1 (11%)			
Genital System				
Preputial gland	(9)	(10)	(10)	(10)
Adenoma	1 (11%)			
Testes	(9)	(10)	(10)	(10)
Interstitial cell, adenoma	4 (44%)			
Systems Examined with No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
18-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Liver	(10)	(10)	(10)	(10)
Pancreas	(10)	(10)	(10)	(10)
Acinus, adenoma		1 (10%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adrenal medulla	(10)	(10)	(10)	(10)
Pheochromocytoma malignant	1 (10%)			
Pheochromocytoma benign	1 (10%)		1 (10%)	1 (10%)
Islets, pancreatic	(10)	(10)	(10)	(10)
Adenoma		1 (10%)		
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, adenoma	2 (20%)	6 (60%)	9 (90%)	5 (56%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, adenoma				1 (10%)
C-cell, carcinoma				1 (10%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
18-Month Interim Evaluation (continued)				
Genital System				
Preputial gland	(10)	(10)	(10)	(10)
Adenoma			1 (10%)	
Carcinoma		1 (10%)		
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	7 (70%)	2 (20%)		
Interstitial cell, adenoma	2 (20%)	3 (30%)		
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Keratoacanthoma			1 (10%)	
Respiratory System				
Lung	(10)	(10)	(9)	(10)
Chordoma, metastatic, uncertain primary site		1 (10%)		
Squamous cell carcinoma			1 (11%)	
Nose	(10)	(10)	(10)	(10)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear	2 (20%)		1 (10%)	
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(48)	(49)	(46)	(47)
Intestine large, rectum	(49)	(47)	(47)	(46)
Histiocytic sarcoma	1 (2%)			
Intestine large, cecum	(43)	(40)	(41)	(44)
Intestine small, duodenum	(48)	(49)	(49)	(47)
Liver	(51)	(50)	(50)	(49)
Hepatocellular carcinoma		1 (2%)		
Hepatocellular adenoma		1 (2%)	1 (2%)	
Hepatocellular adenoma, multiple	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Mesentery	(14)	(6)	(5)	(3)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Oral mucosa	(3)	(1)		
Squamous cell papilloma	1 (33%)	1 (100%)		
Pharyngeal, squamous cell papilloma	1 (33%)			
Pancreas	(49)	(48)	(50)	(48)
Acinus, adenoma			1 (2%)	
Stomach, forestomach	(51)	(50)	(49)	(48)
Squamous cell papilloma		1 (2%)	1 (2%)	
Tongue	(1)		(1)	(1)
Squamous cell papilloma	1 (100%)			1 (100%)
Cardiovascular System				
Blood vessel	(51)	(50)	(50)	(48)
Heart	(51)	(49)	(50)	(47)
Myocardium, schwannoma benign		1 (2%)		
Endocrine System				
Adrenal cortex	(51)	(50)	(50)	(49)
Adrenal medulla	(51)	(50)	(50)	(49)
Ganglioneuroma		1 (2%)		
Pheochromocytoma malignant			1 (2%)	1 (2%)
Pheochromocytoma benign	16 (31%)	14 (28%)	12 (24%)	10 (20%)
Bilateral, pheochromocytoma benign	3 (6%)	11 (22%)	9 (18%)	19 (39%)
Islets, pancreatic	(49)	(48)	(50)	(48)
Adenoma	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Carcinoma			2 (4%)	
Parathyroid gland	(46)	(44)	(48)	(43)
Pituitary gland	(51)	(50)	(50)	(49)
Pars distalis, adenoma	30 (59%)	32 (64%)	30 (60%)	19 (39%)
Thyroid gland	(51)	(48)	(50)	(49)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	5 (10%)	3 (6%)	5 (10%)	4 (8%)
C-cell, carcinoma			1 (2%)	
Follicular cell, adenoma		1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(51)	(50)	(50)	(49)
Preputial gland	(51)	(49)	(50)	(49)
Adenoma		2 (4%)	2 (4%)	
Carcinoma	3 (6%)	2 (4%)		1 (2%)
Prostate	(51)	(50)	(50)	(49)
Seminal vesicle	(51)	(49)	(50)	(48)
Testes	(51)	(50)	(50)	(49)
Bilateral, interstitial cell, adenoma	31 (61%)	9 (18%)		
Interstitial cell, adenoma	2 (4%)	11 (22%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(48)	(49)	(50)	(49)
Lymph node	(4)	(4)		(2)
Lymph node, mandibular	(51)	(47)	(50)	(49)
Rhabdomyosarcoma, metastatic, skeletal muscle		1 (2%)		
Lymph node, mesenteric	(50)	(49)	(49)	(48)
Spleen	(51)	(50)	(50)	(48)
Lipoma			1 (2%)	
Thymus	(42)	(42)	(38)	(39)
Integumentary System				
Mammary gland	(51)	(48)	(49)	(50)
Carcinoma			1 (2%)	
Fibroadenoma	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Fibroadenoma, multiple				1 (2%)
Histiocytic sarcoma	1 (2%)			
Skin	(51)	(50)	(49)	(50)
Basal cell carcinoma		1 (2%)		
Keratoacanthoma	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma				1 (2%)
Sebaceous gland, adenoma	1 (2%)			
Subcutaneous tissue, fibroma		5 (10%)	2 (4%)	2 (4%)
Subcutaneous tissue, fibrosarcoma		2 (4%)		
Subcutaneous tissue, lipoma			1 (2%)	
Subcutaneous tissue, schwannoma malignant	1 (2%)			
Musculoskeletal System				
Bone	(51)	(49)	(50)	(50)
Osteoma				1 (2%)
Skeletal muscle	(2)	(1)		
Histiocytic sarcoma	1 (50%)			
Rhabdomyosarcoma		1 (100%)		
Nervous System				
Brain	(51)	(50)	(50)	(50)
Astrocytoma malignant			2 (4%)	
Spinal cord	(5)	(1)	(4)	
Schwannoma malignant			1 (25%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
2-Year Study (continued)				
Respiratory System				
Lung	(51)	(50)	(50)	(47)
Alveolar/bronchiolar adenoma	4 (8%)	1 (2%)		3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)			
Chordoma, metastatic, uncertain primary site			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Nose	(50)	(49)	(50)	(50)
Squamous cell carcinoma			1 (2%)	
Glands, carcinoma	1 (2%)			
Olfactory epithelium, neoplasm NOS			1 (2%)	
Special Senses System				
Eye	(1)	(2)	(2)	(3)
Lids, squamous cell carcinoma			1 (50%)	
Urinary System				
Kidney	(51)	(50)	(50)	(49)
Renal tubule, adenoma		1 (2%)		2 (4%)
Renal tubule, oncocytoma benign		1 (2%)		1 (2%)
Transitional epithelium, carcinoma	1 (2%)			
Urinary bladder	(51)	(50)	(50)	(49)
Transitional epithelium, papilloma			1 (2%)	
Systemic Lesions				
Multiple organs	(51)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	21 (41%)	15 (30%)	7 (14%)	4 (8%)
Mesothelioma benign		1 (2%)		
Mesothelioma malignant	2 (4%)	1 (2%)		1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]				
6-Month interim evaluation			1	
12-Month interim evaluation	5	2	3	
18-Month interim evaluation	10	10	9	6
2-Year study	51	48	44	40
Total primary neoplasms				
6-Month interim evaluation			1	
12-Month interim evaluation	9	2	3	
18-Month interim evaluation	15	14	14	8
2-Year study	139	125	89	74
Total animals with benign neoplasms				
6-Month interim evaluation			1	
12-Month interim evaluation	5	2	3	
18-Month interim evaluation	10	10	9	6
2-Year study	50	45	40	39
Total benign neoplasms				
6-Month interim evaluation			1	
12-Month interim evaluation	9	2	3	
18-Month interim evaluation	12	13	12	7
2-Year study	108	102	70	67
Total animals with malignant neoplasms				
18-Month interim evaluation	3	1	2	1
2-Year study	28	22	16	7
Total malignant neoplasms				
18-Month interim evaluation	3	1	2	1
2-Year study	31	23	18	7
Total animals with metastatic neoplasms				
18-Month interim evaluation		1		
2-Year study		1	2	
Total metastatic neoplasms				
18-Month interim evaluation		1		
2-Year study		1	2	
Total animals with malignant neoplasms of uncertain primary site				
18-Month interim evaluation		1		
2-Year study			1	
Total animals with uncertain neoplasms-benign or malignant				
2-Year study			1	
Total uncertain neoplasms				
2-Year study			1	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: Vehicle Control

Number of Days on Study	316	366	384	429	464	471	479	486	486	519	524	549	549	553	589	591	596	600	605	611	611	633	646	646	654
Carcass ID Number	062	061	066	087	074	086	030	056	057	047	059	019	022	069	073	016	004	034	053	005	044	037	001	054	032
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Intestine large, cecum	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	A
Intestine small, ileum	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																							X		
Mesentery							+		+				+					+	+					+	+
Oral mucosa																+									
Squamous cell papilloma																									
Pharyngeal, squamous cell papilloma																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X	X						X	X							
Bilateral, pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenoma																X									
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X	X	X	X			X	X	X	X	X	X		X			X		X		X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X								X								X	
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X																		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X								X	X	X	X		X	X	X	X		
Interstitial cell, adenoma																								X	

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: Vehicle Control

Number of Days on Study	654	657	660	666	692	702	706	707	714	716	720	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	072	052	028	002	039	023	051	010	082	050	042	014	020	021	029	036	048	060	063	064	067	077	080	083	084	088	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Intestine large, cecum	+	+	+	+	A	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma, multiple																	X										1
Histiocytic sarcoma																											1
Mesentery			+		+			+		+			+					+			+						14
Oral mucosa				+													+										3
Squamous cell papilloma				X																							1
Pharyngeal, squamous cell papilloma																											1
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tongue	+																										1
Squamous cell papilloma	X																										1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign		X	X		X						X		X			X	X	X		X		X			X	X	16
Bilateral, pheochromocytoma benign							X								X												3
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X								X				X													4
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma		X	X	X	X			X					X	X	X		X	X		X	X	X					30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma				X																		X					5
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma															X			X									3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X		X		X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	31
Interstitial cell, adenoma																	X										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: Vehicle Control

Number of Days on Study	316	366	384	429	464	471	479	486	486	519	524	549	549	553	589	591	596	600	605	611	611	633	646	646	654
Carcass ID Number	062	061	066	087	074	086	030	056	057	047	059	019	022	069	073	016	004	034	053	005	044	037	001	054	032
Hematopoietic System																									
Bone marrow	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+
Lymph node								+										+		+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	M	+	M	M	M	+	+	+	+	+	+	M	+	+	M	+	+	M	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma						X														X					
Histiocytic sarcoma																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																				X					
Sebaceous gland, adenoma															X										
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+										+		
Histiocytic sarcoma																							X		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve															+	M					+				
Spinal cord															+	+					+				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X										X			
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Glands, carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Leukemia mononuclear								X			X				X		X			X		X		X	X
Mesothelioma malignant																		X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: Vehicle Control

Number of Days on Study	654	657	660	666	692	702	706	707	714	716	720	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	072	052	028	002	039	023	051	010	082	050	042	014	020	021	029	036	048	060	063	064	067	077	080	083	084	088	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																										+	4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibroadenoma								X																		X	4
Histiocytic sarcoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Keratoacanthoma													X									X	X				4
Sebaceous gland, adenoma																											1
Subcutaneous tissue, schwannoma malignant																								X			1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																											2
Histiocytic sarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Peripheral nerve			+							+																	4
Spinal cord			+							+																	5
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma																					X		X				4
Alveolar/bronchiolar carcinoma					X																						1
Histiocytic sarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glands, carcinoma									X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Transitional epithelium, carcinoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Leukemia mononuclear		X	X				X		X		X		X	X	X	X	X						X		X	X	21
Mesothelioma malignant													X														2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 3 mg/kg

Number of Days on Study	146	202	321	408	424	479	485	485	499	561	563	588	597	598	600	618	622	629	659	675	675	679	692	692	693
Carcass ID Number	155	136	109	164	096	124	098	102	139	165	143	153	131	152	093	154	147	115	112	144	173	128	094	130	125
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	A	+	+	+	A	+	+	A	+	+	A	+	+	A	A	+	+	A	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	A	+	A	+	A	+	+	A	+	+	A	+	+	A	+	+	+	A	+	+	+
Intestine small, ileum	A	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma					X																				
Mesentery						+				+											+	+			
Oral mucosa																									
Squamous cell papilloma																									
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Myocardium, schwannoma benign																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma											X														
Pheochromocytoma benign								X	X											X	X			X	X
Bilateral, pheochromocytoma benign																						X	X		
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenoma													X												
Parathyroid gland	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X				X	X	X	X	X		X	X	X	X		X	X			X	
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma												X								X					
Follicular cell, adenoma	X																								
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma			X																						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																			X				X		
Interstitial cell, adenoma								X					X												X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 3 mg/kg

Number of Days on Study	703	703	706	706	707	709	709	714	718	720	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	159	176	123	148	092	121	151	119	150	091	111	113	117	118	126	129	133	135	145	168	169	177	178	179	180	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X																					1
Hepatocellular adenoma																										1
Mesentery													+					+								6
Oral mucosa																					+					1
Squamous cell papilloma																					X					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																								X		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Myocardium, schwannoma benign											X															1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma																										1
Pheochromocytoma benign	X		X				X	X	X				X	X		X										14
Bilateral, pheochromocytoma benign		X		X	X					X		X						X	X		X				X	11
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma											X															2
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X		X	X	X	X	X		X	X			X	X	X		X	X		X		X	32
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, C-cell, adenoma													X													1
C-cell, adenoma																			X							3
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma														X												2
Carcinoma						X																				2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma					X				X	X		X		X					X		X					9
Interstitial cell, adenoma		X	X			X	X						X		X					X				X		11

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 3 mg/kg

Number of Days on Study	146	202	321	408	424	479	485	485	499	561	563	588	597	598	600	618	622	629	659	675	675	679	692	692	693
Carcass ID Number	155	136	109	164	096	124	098	102	139	165	143	153	131	152	093	154	147	115	112	144	173	128	094	130	125
Hematopoietic System																									
Bone marrow	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+										+											
Lymph node, mandibular	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Rhabdomyosarcoma, metastatic, skeletal muscle														X											
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	M	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma															X										
Keratoacanthoma																									
Subcutaneous tissue, fibroma						X																			
Subcutaneous tissue, fibrosarcoma								X													X				
Musculoskeletal System																									
Bone	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+											
Rhabdomyosarcoma														X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve													+												
Spinal cord													+												
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma										X															
Renal tubule, oncocytoma benign																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X				X							X	X	X	X	X		X	
Mesothelioma benign																									
Mesothelioma malignant																	X								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 3 mg/kg

Number of Days on Study	703	703	706	706	707	709	709	714	718	720	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	159	176	123	148	092	121	151	119	150	091	111	113	117	118	126	129	133	135	145	168	169	177	178	179	180	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node															+								+			4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma						X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Keratoacanthoma						X																				1
Subcutaneous tissue, fibroma		X					X														X			X		5
Subcutaneous tissue, fibrosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye						+															+					2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Renal tubule, oncocytoma benign													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X										X	X								X	X	X	15
Mesothelioma benign								X																		1
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 30 mg/kg

Number of Days on Study	281	353	437	517	527	538	564	577	597	601	605	609	622	629	640	644	644	653	666	666	669	680	681	692	693
Carcass ID Number	2267	2268	2338	1188	2445	2331	1192	2337	1185	2262	2222	2253	2247	1196	1194	2208	2211	1190	2210	2225	2227	2206	1181	1184	1198
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	A	+	+	+	A	A	A	+	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	+	A	+	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery						+						+									+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant									X																
Pheochromocytoma benign								X	X					X											
Bilateral, pheochromocytoma benign							X																	X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Carcinoma																					X				X
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X				X						X	X	X	X	X	X	X	X	X	X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X																	X		
C-cell, carcinoma												X													
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 30 mg/kg

Number of Days on Study	696	700	703	703	705	706	707	716	719	720	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	220	186	240	258	193	182	234	230	243	215	213	183	197	204	205	209	212	229	232	244	246	250	257	261	264	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, duodenum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																			X							1
Mesentery																		+				+				5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma														X												1
Stomach, glandular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue								+																		1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign	X		X	X						X					X		X	X		X					X	12
Bilateral, pheochromocytoma benign					X		X				X	X							X			X	X			9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									2
Carcinoma																										2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X		X	X				X	X	X	X	X	X	X	X	X	X		X		X		X	30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X									X		X			5
C-cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X											X	2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 30 mg/kg

Number of Days on Study	281	353	437	517	527	538	564	577	597	601	605	609	622	629	640	644	644	653	666	666	669	680	681	692	693
Carcass ID Number	267	268	238	188	445	231	192	237	185	262	222	253	247	196	194	208	211	190	210	225	227	206	181	184	198
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Thymus	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	M	+	M	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																							
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell carcinoma																						X			
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Peripheral nerve	+				+							+										+			
Spinal cord	+				+							+										+			
Schwannoma malignant	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma, metastatic, uncertain primary site												X													
Pheochromocytoma malignant, metastatic, adrenal medulla									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																		X							
Olfactory epithelium, neoplasm NOS						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+															+			
Lids, squamous cell carcinoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X				X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 30 mg/kg

Number of Days on Study	696	700	703	703	705	706	707	716	719	720	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	220	186	240	258	193	182	234	230	243	215	211	183	197	204	205	209	212	229	232	244	246	250	257	261	264	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma												X														1
Thymus	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	38
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Fibroadenoma						X																				1
Skin	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma			X																							1
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma							X						X													2
Subcutaneous tissue, lipoma				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																			X				X			2
Peripheral nerve																										4
Spinal cord																										4
Schwannoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma, metastatic, uncertain primary site																										1
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Olfactory epithelium, neoplasm NOS																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Lids, squamous cell carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																					X					1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X									X	X												7

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 150 mg/kg

Number of Days on Study	034	080	114	115	116	145	434	551	561	663	663	677	611	629	636	639	641	644	646	659	660	666	675	675
Carcass ID Number	310	313	292	328	335	317	327	276	295	297	326	315	302	343	300	294	274	316	352	304	284	287	281	290
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	A	+	+	+	M	+	A	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	M	+	A	+	+	A	+	+	+	A
Intestine small, duodenum	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	A	+	+	A	M	A	A	+	+	A	+	+	+	A
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	A	+	+	A	M	+	A	+	+	A	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Mesentery											+		+											
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach, glandular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Tongue																								
Squamous cell papilloma																								
Cardiovascular System																								
Blood vessel	+	+	+		+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Heart	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								
Pheochromocytoma benign														X					X			X		
Bilateral, pheochromocytoma benign												X	X							X			X	
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	M	+	+	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X			X	X						X				X		X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
C-cell, adenoma																							X	X
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Carcinoma														X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 150 mg/kg

Number of Days on Study	688	703	708	712	715	724	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	329	272	313	356	350	348	379	382	386	388	389	391	398	399	305	308	309	319	321	325	336	340	355	358	359	360	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, ileum	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery			+																								3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue								+																			1
Squamous cell papilloma								X																			1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant							X																				1
Pheochromocytoma benign		X				X	X	X	X															X	X		10
Bilateral, pheochromocytoma benign			X	X							X	X	X	X	X	X	X	X		X	X	X	X			X	19
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma							X																				1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X		X	X					X	X		X		X				X	X	X					19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma												X			X												4
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 150 mg/kg

Number of Days on Study	034	080	114	115	116	145	434	551	561	663	663	577	611	629	636	639	641	644	646	659	660	666	675	675
Carcass ID Number	310	313	292	328	335	317	327	276	295	277	326	315	302	343	300	294	274	316	352	304	284	287	281	290
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Lymph node												+												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	M	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma									X															
Fibroadenoma, multiple										X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								
Squamous cell papilloma																								
Subcutaneous tissue, fibroma							X																	
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																X								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Alveolar/bronchiolar adenoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye						+																		
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								
Renal tubule, oncocytoma benign																				X				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X					X				X							
Mesothelioma malignant																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Oxymetholone: 150 mg/kg

Number of Days on Study	688	703	708	712	715	724	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	329	272	313	356	350	348	379	382	386	388	389	391	398	399	305	308	309	319	321	325	336	340	355	358	359	360	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node			+																								2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	M	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	39
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																											1
Fibroadenoma, multiple																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma															X												1
Squamous cell papilloma																X											1
Subcutaneous tissue, fibroma	X																										2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar adenoma								X										X						X			3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																											
Eye									+													+					3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma									X												X						2
Renal tubule, oncocytoma benign																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X																								4
Mesothelioma malignant																	X										1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	19/51 (37%)	25/50 (50%)	21/50 (42%)	29/49 (59%)
Adjusted rate[b]	49.4%	62.9%	51.0%	75.5%
Terminal rate[c]	9/15 (60%)	8/15 (53%)	9/14 (64%)	18/20 (90%)
First incidence (days)	519	485	564	577
Poly-3 test[d]	P=0.015	P=0.147	P=0.534	P=0.009
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	19/51 (37%)	25/50 (50%)	21/50 (42%)	29/49 (59%)
Adjusted rate	49.4%	62.9%	51.0%	75.5%
Terminal rate	9/15 (60%)	8/15 (53%)	9/14 (64%)	18/20 (90%)
First incidence (days)	519	485	564	577
Poly-3 test	P=0.015	P=0.147	P=0.534	P=0.009
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/51 (8%)	1/50 (2%)	0/50 (0%)	3/47 (6%)
Adjusted rate	11.1%	2.7%	0.0%	8.5%
Terminal rate	2/15 (13%)	0/15 (0%)	0/14 (0%)	3/20 (15%)
First incidence (days)	549	720	—[e]	728 (T)
Poly-3 test	P=0.401	P=0.170N	P=0.050N	P=0.514N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/51 (10%)	1/50 (2%)	0/50 (0%)	3/47 (6%)
Adjusted rate	13.8%	2.7%	0.0%	8.5%
Terminal rate	2/15 (13%)	0/15 (0%)	0/14 (0%)	3/20 (15%)
First incidence (days)	549	720	—	728 (T)
Poly-3 test	P=0.505	P=0.095N	P=0.024N	P=0.370N
Mammary Gland: Fibroadenoma				
Overall rate	4/51 (8%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	11.0%	2.7%	2.6%	5.3%
Terminal rate	1/15 (7%)	0/15 (0%)	0/14 (0%)	0/20 (0%)
First incidence (days)	471	709	706	561
Poly-3 test	P=0.566N	P=0.173N	P=0.157N	P=0.319N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	4/51 (8%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rate	11.0%	2.7%	5.0%	5.3%
Terminal rate	1/15 (7%)	0/15 (0%)	0/14 (0%)	0/20 (0%)
First incidence (days)	471	709	353	561
Poly-3 test	P=0.525N	P=0.173N	P=0.296N	P=0.319N
Oral Cavity (Oral Mucosa, Tongue, or Pharynx): Squamous Cell Papilloma				
Overall rate	3/51 (6%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	8.3%	2.7%	0.0%	2.7%
Terminal rate	0/15 (0%)	1/15 (7%)	0/14 (0%)	1/20 (5%)
First incidence (days)	591	728 (T)	—	728 (T)
Poly-3 test	P=0.467N	P=0.298N	P=0.106N	P=0.299N
Pancreatic Islets: Adenoma				
Overall rate	4/49 (8%)	2/48 (4%)	2/50 (4%)	1/48 (2%)
Adjusted rate	11.6%	5.5%	5.1%	2.8%
Terminal rate	1/15 (7%)	1/15 (7%)	0/14 (0%)	1/20 (5%)
First incidence (days)	591	597	564	728 (T)
Poly-3 test	P=0.232N	P=0.309N	P=0.276N	P=0.163N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	4/49 (8%)	2/48 (4%)	4/50 (8%)	1/48 (2%)
Adjusted rate	11.6%	5.5%	10.1%	2.8%
Terminal rate	1/15 (7%)	1/15 (7%)	0/14 (0%)	1/20 (5%)
First incidence (days)	591	597	564	728 (T)
Poly-3 test	P=0.200N	P=0.309N	P=0.565N	P=0.163N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	30/51 (59%)	32/50 (64%)	30/50 (60%)	19/49 (39%)
Adjusted rate	65.2%	73.2%	69.2%	48.5%
Terminal rate	8/15 (53%)	9/15 (60%)	11/14 (79%)	7/20 (35%)
First incidence (days)	316	408	437	434
Poly-3 test	P=0.014N	P=0.271	P=0.429	P=0.083N
Preputial Gland: Carcinoma				
Overall rate	3/51 (6%)	2/49 (4%)	0/50 (0%)	1/49 (2%)
Adjusted rate	8.4%	5.4%	0.0%	2.8%
Terminal rate	2/15 (13%)	0/15 (0%)	0/14 (0%)	0/20 (0%)
First incidence (days)	479	321	—	629
Poly-3 test	P=0.361N	P=0.484N	P=0.104N	P=0.299N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/51 (6%)	4/49 (8%)	2/50 (4%)	1/49 (2%)
Adjusted rate	8.4%	10.6%	5.2%	2.8%
Terminal rate	2/15 (13%)	1/15 (7%)	2/14 (14%)	0/20 (0%)
First incidence (days)	479	321	728 (T)	629
Poly-3 test	P=0.179N	P=0.526	P=0.465N	P=0.299N
Skin: Keratoacanthoma				
Overall rate	4/51 (8%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rate	11.3%	2.7%	2.6%	2.7%
Terminal rate	3/15 (20%)	0/15 (0%)	0/14 (0%)	1/20 (5%)
First incidence (days)	611	709	703	728 (T)
Poly-3 test	P=0.325N	P=0.166N	P=0.151N	P=0.167N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	4/51 (8%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	11.3%	2.7%	2.6%	5.5%
Terminal rate	3/15 (20%)	0/15 (0%)	0/14 (0%)	2/20 (10%)
First incidence (days)	611	709	703	728 (T)
Poly-3 test	P=0.578N	P=0.166N	P=0.151N	P=0.321N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	4/51 (8%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rate	11.3%	2.7%	5.1%	5.5%
Terminal rate	3/15 (20%)	0/15 (0%)	0/14 (0%)	2/20 (10%)
First incidence (days)	611	709	680	728 (T)
Poly-3 test	P=0.536N	P=0.166N	P=0.294N	P=0.321N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	4/51 (8%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	11.3%	5.4%	5.1%	5.5%
Terminal rate	3/15 (20%)	0/15 (0%)	0/14 (0%)	2/20 (10%)
First incidence (days)	611	600	680	728 (T)
Poly-3 test	P=0.446N	P=0.314N	P=0.294N	P=0.321N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	0/51 (0%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rate	0.0%	13.3%	5.2%	5.3%
Terminal rate	0/15 (0%)	2/15 (13%)	1/14 (7%)	0/20 (0%)
First incidence (days)	—	479	707	434
Poly-3 test	P=0.523N	P=0.035	P=0.259	P=0.251
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	0/51 (0%)	7/50 (14%)	2/50 (4%)	2/50 (4%)
Adjusted rate	0.0%	18.2%	5.2%	5.3%
Terminal rate	0/15 (0%)	2/15 (13%)	1/14 (7%)	0/20 (0%)
First incidence (days)	—	479	707	434
Poly-3 test	P=0.338N	P=0.010	P=0.259	P=0.251
Testes: Adenoma				
Overall rate	33/51 (65%)	20/50 (40%)	0/50 (0%)	0/49 (0%)
Adjusted rate	81.4%	51.5%	0.0%	0.0%
Terminal rate	14/15 (93%)	8/15 (53%)	0/14 (0%)	0/20 (0%)
First incidence (days)	479	485	—	—
Poly-3 test	P<0.001N	P<0.001N	P<0.001N	P<0.001N
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/51 (10%)	4/48 (8%)	5/50 (10%)	4/49 (8%)
Adjusted rate	13.6%	10.9%	12.7%	11.0%
Terminal rate	1/15 (7%)	2/15 (13%)	3/14 (21%)	2/20 (10%)
First incidence (days)	486	588	538	675
Poly-3 test	P=0.517N	P=0.503N	P=0.588N	P=0.509N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/51 (10%)	4/48 (8%)	6/50 (12%)	4/49 (8%)
Adjusted rate	13.6%	10.9%	15.1%	11.0%
Terminal rate	1/15 (7%)	2/15 (13%)	3/14 (21%)	2/20 (10%)
First incidence (days)	486	588	538	675
Poly-3 test	P=0.493N	P=0.503N	P=0.556	P=0.509N
All Organs: Mononuclear Cell Leukemia				
Overall rate	21/51 (41%)	15/50 (30%)	7/50 (14%)	4/50 (8%)
Adjusted rate	53.3%	37.3%	17.3%	10.5%
Terminal rate	8/15 (53%)	5/15 (33%)	2/14 (14%)	0/20 (0%)
First incidence (days)	486	408	577	551
Poly-3 test	P<0.001N	P=0.105N	P<0.001N	P<0.001N
All Organs: Benign Neoplasms				
Overall rate	50/51 (98%)	45/50 (90%)	40/50 (80%)	39/50 (78%)
Adjusted rate	99.7%	95.8%	87.2%	91.1%
Terminal rate	15/15 (100%)	14/15 (93%)	13/14 (93%)	18/20 (90%)
First incidence (days)	316	146	437	434
Poly-3 test	P=0.126N	P=0.224N	P=0.007N	P=0.040N
All Organs: Malignant Neoplasms				
Overall rate	28/51 (55%)	22/50 (44%)	16/50 (32%)	7/50 (14%)
Adjusted rate	66.9%	50.9%	36.7%	18.3%
Terminal rate	10/15 (67%)	5/15 (33%)	4/14 (29%)	2/20 (10%)
First incidence (days)	366	321	281	551
Poly-3 test	P<0.001N	P=0.090N	P=0.003N	P<0.001N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	51/51 (100%)	48/50 (96%)	44/50 (88%)	40/50 (80%)
Adjusted rate	100.0%	97.9%	90.6%	92.2%
Terminal rate	15/15 (100%)	14/15 (93%)	13/14 (93%)	18/20 (90%)
First incidence (days)	316	146	281	434
Poly-3 test	P=0.095N	P=0.483N	P=0.027N	P=0.055N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle 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 the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE A4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Male F344/N Rats[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study			
Methyleugenol	5/50	2/50	7/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	6/330 (1.8%)	0/330	6/330 (1.8%)
Mean ± standard deviation	1.9% ± 1.3%		1.9% ± 1.3%
Range	0%-4%		0%-4%
Overall Historical Incidence: Feed Studies			
Total (%)	21/902 (2.3%)	7/902 (0.8%)	26/902 (2.9%)
Mean ± standard deviation	2.3% ± 3.2%	0.8% ± 1.6%	2.9% ± 3.5%
Range	0%-10%	0%-6%	0%-10%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE A4b
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Male F344/N Rats[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study			
Methyleugenol	0/50	0/50	0/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	3/331 (0.9%)	0/331	3/331 (0.9%)
Mean ± standard deviation	1.0% ± 1.1%		1.0% ± 1.1%
Range	0%-2%		0%-2%
Overall Historical Incidence: Feed Studies			
Total (%)	22/902 (2.4%)	7/902 (0.8%)	29/902 (3.2%)
Mean ± standard deviation	2.5% ± 3.3%	0.8% ± 1.2%	3.2% ± 3.6%
Range	0%-14%	0%-4%	0%-16%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE A4c
Historical Incidence of Skin (Subcutaneous Tissue) Neoplasms in Untreated Male F344/N Rats[a]

	Incidence in Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study			
Methyleugenol	1/50	0/50	1/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	8/331 (2.4%)	5/331 (1.5%)	13/331 (3.9%)
Mean ± standard deviation	2.7% ± 3.5%	1.5% ± 1.5%	4.2% ± 2.8%
Range	0%-8%	0%-4%	1%-8%
Overall Historical Incidence: Feed Studies			
Total (%)	50/904 (5.5%)	9/904 (1.0%)	59/904 (6.5%)
Mean ± standard deviation	5.6% ± 3.1%	1.0% ± 1.4%	6.5% ± 3.0%
Range	0%-10%	0%-4%	2%-10%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE A4d
Historical Incidence of Adrenal Medulla Pheochromocytoma in Untreated Male F344/N Rats[a]

	Incidence in Controls		
	Benign	Malignant	Benign or Malignant[b]
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study			
Methyleugenol	24/50	1/50	25/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	97/329 (29.5%)	11/329 (3.3%)	106/329 (32.2%)
Mean ± standard deviation	29.3% ± 9.6%	3.4% ± 2.7%	32.2% ± 9.0%
Range	18%-45%	0%-8%	24%-49%
Overall Historical Incidence: Feed Studies			
Total (%)	228/896 (25.5%)	28/896 (3.1%)	252/896 (28.1%)
Mean ± standard deviation	25.5% ± 9.7%	3.1% ± 3.1%	28.2% ± 8.4%
Range	10%-46%	0%-12%	14%-46%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database
[b] Drinking water and feed study incidences include benign, malignant, or complex pheochromocytoma.

TABLE A4e
Historical Incidence of Renal Tubule Adenoma in Untreated Male F344/N Rats[a]

	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study	
Methyleugenol	3/50
Overall Historical Incidence: Drinking Water Studies	
Total (%)	2/327 (0.6%)
Mean ± standard deviation	0.7% ± 1.0%
Range	0%-2%
Overall Historical Incidence: Feed Studies	
Total (%)	7/902 (0.8%)
Mean ± standard deviation	0.8% ± 1.2%
Range	0%-4%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE A4f
Historical Incidence of Testicular Adenoma in Untreated Male F344/N Rats[a]

	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study	
Methyleugenol	46/50
Overall Historical Incidence: Drinking Water Studies	
Total (%)	264/329 (80.2%)
Mean ± standard deviation	79.6% ± 11.0%
Range	65%-92%
Overall Historical Incidence: Feed Studies	
Total (%)	802/903 (88.8%)
Mean ± standard deviation	88.8% ± 6.0%
Range	74%-96%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone[a]

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
Disposition Summary				
Animals initially in study	90	90	90	90
3-Month interim evaluation	10	10	10	9
6-Month interim evaluation	10	10	10	10
12-Month interim evaluation	9	10	10	10
18-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths		1		3
Moribund	24	22	25	15
Natural deaths	12	12	11	12
Survivors				
Terminal sacrifice	15	15	14	20
Missexed				1
Animals examined microscopically	90	90	90	89
3-Month Interim Evaluation				
Alimentary System				
Esophagus	(10)	(10)	(10)	(9)
Muscularis, inflammation, chronic active			1 (10%)	
Intestine small, jejunum	(10)	(10)	(10)	(9)
Inflammation, chronic active	1 (10%)			
Peyer's patch, mineralization		1 (10%)		
Liver	(10)	(10)	(10)	(9)
Hepatodiaphragmatic nodule	2 (20%)	2 (20%)	1 (10%)	1 (11%)
Inflammation, chronic active	3 (30%)		1 (10%)	
Centrilobular, congestion	1 (10%)			
Centrilobular, vacuolization cytoplasmic	1 (10%)	5 (50%)	5 (50%)	
Cardiovascular System				
Heart	(10)	(10)	(10)	(9)
Hemorrhage		1 (10%)		
Myocardium, degeneration, chronic	10 (100%)	9 (90%)	7 (70%)	4 (44%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(9)
Accessory adrenal cortical nodule			2 (20%)	
Vacuolization cytoplasmic	8 (80%)	6 (60%)		8 (89%)
Thyroid gland	(10)	(10)	(10)	(9)
Ultimobranchial cyst	1 (10%)			
Genital System				
Preputial gland	(10)	(10)	(10)	(9)
Inflammation, chronic active	8 (80%)	7 (70%)	10 (100%)	6 (67%)
Prostate	(10)	(10)	(10)	(9)
Inflammation, chronic active		1 (10%)	1 (10%)	
Testes	(10)	(10)	(10)	(9)
Mineralization				1 (11%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
3-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mesenteric	(10)	(10)	(9)	(9)
Hemorrhage				1 (11%)
Integumentary System				
Mammary gland	(10)	(10)	(9)	(9)
Dilatation				8 (89%)
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Inflammation, chronic active	1 (10%)	4 (40%)	3 (30%)	4 (44%)
Mineralization			2 (20%)	1 (11%)
Vacuolization cytoplasmic			1 (10%)	
Urinary System				
Kidney	(10)	(10)	(10)	(9)
Mineralization		2 (20%)	2 (20%)	8 (89%)
Nephropathy	8 (80%)	7 (70%)	9 (90%)	8 (89%)
Renal tubule, hyperplasia				1 (11%)
Systems Examined with No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
6-Month Interim Evaluation				
Alimentary System				
Intestine small, duodenum	(10)	(10)	(10)	(10)
Inflammation, chronic active				1 (10%)
Intestine small, jejunum	(10)	(10)	(10)	(10)
Inflammation, granulomatous	1 (10%)			
Peyer's patch, mineralization			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule	1 (10%)	1 (10%)	1 (10%)	1 (10%)
Inflammation, chronic active	3 (30%)	1 (10%)	3 (30%)	1 (10%)
Bile duct, hyperplasia	3 (30%)			
Centrilobular, vacuolization cytoplasmic		1 (10%)		
Mesentery		(1)		
Fat, inflammation, chronic active		1 (100%)		
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy		2 (20%)		
Vein, inflammation, granulomatous	1 (10%)			
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration, chronic	10 (100%)	10 (100%)	9 (90%)	10 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
6-Month Interim Evaluation (continued)				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)	1 (10%)	1 (10%)
Vacuolization cytoplasmic	10 (100%)	8 (80%)		8 (80%)
Thyroid gland	(10)	(10)	(10)	(10)
Ultimobranchial cyst	1 (10%)			
Follicle, cyst	2 (20%)			
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Inflammation, chronic active			1 (10%)	
Preputial gland	(10)	(10)	(10)	(10)
Cyst			1 (10%)	
Inflammation, chronic active	7 (70%)	10 (100%)	9 (90%)	8 (80%)
Testes	(10)	(10)	(10)	(10)
Mineralization	1 (10%)			1 (10%)
Hematopoietic System				
Spleen	(10)	(10)	(10)	(10)
Capsule, hyperplasia			1 (10%)	
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Dilatation				9 (90%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active	2 (20%)	3 (30%)	8 (80%)	3 (30%)
Inflammation, granulomatous	1 (10%)	2 (20%)		
Mineralization		4 (40%)	4 (40%)	1 (10%)
Vacuolization cytoplasmic	1 (10%)	1 (10%)	1 (10%)	
Nose	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)		2 (20%)	
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	2 (20%)		1 (10%)	9 (90%)
Nephropathy	8 (80%)	7 (70%)	9 (90%)	10 (100%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)		
Systems Examined with No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
12-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(9)	(10)	(10)	(10)
Parasite metazoan			4 (40%)	1 (10%)
Intestine large, cecum	(9)	(10)	(10)	(10)
Parasite metazoan				1 (10%)
Intestine small, ileum	(9)	(10)	(10)	(10)
Peyer's patch, mineralization				1 (10%)
Liver	(9)	(10)	(9)	(10)
Basophilic focus		2 (20%)	2 (22%)	
Clear cell focus				1 (10%)
Cyst	1 (11%)			
Hepatodiaphragmatic nodule	2 (22%)	1 (10%)	1 (11%)	1 (10%)
Inflammation, chronic active	6 (67%)	7 (70%)	6 (67%)	
Necrosis		4 (40%)	2 (22%)	
Bile duct, hyperplasia	3 (33%)	5 (50%)	3 (33%)	
Centrilobular, vacuolization cytoplasmic	2 (22%)	3 (30%)	1 (11%)	
Mesentery		(1)		
Fat, inflammation, chronic active		1 (100%)		
Pancreas	(9)	(10)	(10)	(10)
Acinus, atrophy	1 (11%)	3 (30%)	4 (40%)	3 (30%)
Cardiovascular System				
Heart	(9)	(10)	(10)	(10)
Myocardium, degeneration, chronic	8 (89%)	9 (90%)	10 (100%)	10 (100%)
Endocrine System				
Adrenal cortex	(9)	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (11%)	1 (10%)		
Hypertrophy	1 (11%)			
Vacuolization cytoplasmic	9 (100%)	7 (70%)	9 (90%)	8 (80%)
Pituitary gland	(9)	(10)	(10)	(10)
Cyst	1 (11%)			
Hyperplasia	1 (11%)	4 (40%)	3 (30%)	1 (10%)
Pars nervosa, developmental malformation	1 (11%)			
Thyroid gland	(9)	(10)	(10)	(10)
Ultimobranchial cyst		1 (10%)	1 (10%)	1 (10%)
Genital System				
Preputial gland	(9)	(10)	(10)	(10)
Inflammation, chronic active	6 (67%)	6 (60%)	9 (90%)	7 (70%)
Testes	(9)	(10)	(10)	(10)
Degeneration				1 (10%)
Mineralization		2 (20%)	3 (30%)	6 (60%)
Interstitial cell, hyperplasia	8 (89%)	7 (70%)		
Hematopoietic System				
Lymph node, mandibular	(9)	(10)	(10)	(10)
Congestion	1 (11%)	1 (10%)		1 (10%)
Ectasia	1 (11%)			
Lymph node, mesenteric	(9)	(10)	(10)	(10)
Atrophy				1 (10%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
12-Month Interim Evaluation (continued)				
Hematopoietic System (continued)				
Spleen	(9)	(10)	(10)	(10)
Red pulp, depletion cellular	1 (11%)			
Thymus	(9)	(10)	(10)	(10)
Atrophy				7 (70%)
Integumentary System				
Mammary gland	(8)	(9)	(10)	(10)
Dilatation	4 (50%)	1 (11%)	5 (50%)	10 (100%)
Respiratory System				
Lung	(9)	(10)	(10)	(10)
Hemorrhage	1 (11%)	1 (10%)	1 (10%)	
Inflammation, chronic active	1 (11%)	3 (30%)	1 (10%)	2 (20%)
Mineralization	2 (22%)	1 (10%)	4 (40%)	4 (40%)
Vacuolization cytoplasmic		1 (10%)	2 (20%)	
Nose	(9)	(10)	(10)	(10)
Inflammation, chronic active	2 (22%)	1 (10%)		
Inflammation, suppurative	1 (11%)			
Urinary System				
Kidney	(9)	(10)	(10)	(10)
Mineralization	1 (11%)			9 (90%)
Necrosis			1 (10%)	
Nephropathy	9 (100%)	10 (100%)	10 (100%)	10 (100%)
Systems Examined with No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
18-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan		1 (10%)	1 (10%)	
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	2 (20%)	4 (40%)	1 (10%)	1 (10%)
Intestine small, ileum	(10)	(10)	(10)	(10)
Fibrosis			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus	4 (40%)	8 (80%)	9 (90%)	8 (80%)
Clear cell focus	2 (20%)		2 (20%)	2 (20%)
Degeneration, cystic		1 (10%)		
Eosinophilic focus	1 (10%)	1 (10%)	1 (10%)	
Hepatodiaphragmatic nodule		2 (20%)	1 (10%)	1 (10%)
Inflammation, chronic active	8 (80%)	5 (50%)	1 (10%)	
Mixed cell focus		1 (10%)		3 (30%)
Necrosis		1 (10%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
18-Month Interim Evaluation (continued)				
Alimentary System (continued)				
Liver (continued)				
Bile duct, hyperplasia	10 (100%)	6 (60%)	6 (60%)	
Centrilobular, vacuolization cytoplasmic	3 (30%)	5 (50%)	2 (20%)	1 (10%)
Mesentery	(3)	(1)	(3)	
Fat, congestion	1 (33%)			
Fat, inflammation, chronic active	2 (67%)	1 (100%)	3 (100%)	
Fat, mineralization			1 (33%)	
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy	1 (10%)	2 (20%)	2 (20%)	
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration, chronic	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Vacuolization cytoplasmic	4 (40%)	8 (80%)	10 (100%)	10 (100%)
Adrenal medulla	(10)	(10)	(10)	(10)
Hyperplasia	3 (30%)	1 (10%)	2 (20%)	
Islets, pancreatic	(10)	(10)	(10)	(10)
Pigmentation, hemosiderin				1 (10%)
Pituitary gland	(10)	(10)	(10)	(9)
Atrophy	1 (10%)			
Cyst	2 (20%)			
Hyperplasia	2 (20%)	3 (30%)	2 (20%)	1 (11%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia				1 (10%)
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Degeneration	1 (10%)			
Preputial gland	(10)	(10)	(10)	(10)
Inflammation, chronic active	10 (100%)	8 (80%)	9 (90%)	8 (80%)
Prostate	(10)	(10)	(10)	(10)
Inflammation, chronic active	2 (20%)	2 (20%)		
Seminal vesicle	(10)	(10)	(10)	(10)
Cyst				1 (10%)
Testes	(10)	(10)	(10)	(10)
Degeneration	2 (20%)	1 (10%)	2 (20%)	3 (30%)
Mineralization	3 (30%)	1 (10%)	7 (70%)	4 (40%)
Interstitial cell, hyperplasia	3 (30%)	4 (40%)		
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Myelofibrosis		1 (10%)		1 (10%)
Lymph node, mandibular	(10)	(10)	(10)	(10)
Ectasia			1 (10%)	
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation			1 (10%)	
Thymus	(10)	(10)	(9)	(10)
Atrophy	2 (20%)			1 (10%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
18-Month Interim Evaluation (continued)				
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Dilatation	2 (20%)	3 (30%)	1 (10%)	7 (70%)
Galactocele	2 (20%)	1 (10%)		
Lobular, hyperplasia				6 (60%)
Skin	(10)	(10)	(10)	(10)
Parakeratosis		1 (10%)		
Ulcer		1 (10%)		
Epidermis, cyst			1 (10%)	
Respiratory System				
Lung	(10)	(10)	(9)	(10)
Inflammation, chronic active		4 (40%)	3 (33%)	
Mineralization	1 (10%)	4 (40%)	6 (67%)	3 (30%)
Vacuolization cytoplasmic	1 (10%)	3 (30%)	1 (11%)	2 (20%)
Alveolar epithelium, hyperplasia	1 (10%)			
Nose	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)			
Inflammation, suppurative	1 (10%)	2 (20%)	1 (10%)	
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization				4 (40%)
Nephropathy	10 (100%)	10 (100%)	9 (90%)	10 (100%)
Pigmentation, hemosiderin				1 (10%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic active				1 (10%)
Systems Examined with No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(49)	(50)	(49)
Periesophageal tissue, hemorrhage				1 (2%)
Intestine large, colon	(48)	(49)	(46)	(47)
Inflammation, chronic active		1 (2%)		
Mineralization	1 (2%)	2 (4%)		
Parasite metazoan	3 (6%)		2 (4%)	3 (6%)
Intestine large, rectum	(49)	(47)	(47)	(46)
Parasite metazoan	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Intestine large, cecum	(43)	(40)	(41)	(44)
Inflammation, granulomatous	1 (2%)			
Intestine small, duodenum	(48)	(49)	(49)	(47)
Inflammation, chronic active		1 (2%)		
Mineralization	2 (4%)	1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(51)	(50)	(50)	(49)
Angiectasis	1 (2%)	2 (4%)		
Basophilic focus	23 (45%)	29 (58%)	41 (82%)	38 (78%)
Clear cell focus	2 (4%)	2 (4%)	6 (12%)	12 (24%)
Degeneration, cystic		4 (8%)		
Eosinophilic focus	6 (12%)	4 (8%)	4 (8%)	2 (4%)
Fatty change			1 (2%)	
Hematopoietic cell proliferation		2 (4%)	2 (4%)	
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule	7 (14%)	3 (6%)	2 (4%)	6 (12%)
Inflammation, chronic active	9 (18%)	4 (8%)	3 (6%)	1 (2%)
Mixed cell focus	2 (4%)	1 (2%)	4 (8%)	4 (8%)
Necrosis	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Bile duct, fibrosis				1 (2%)
Bile duct, hyperplasia	29 (57%)	27 (54%)	24 (48%)	
Centrilobular, congestion	1 (2%)			1 (2%)
Centrilobular, degeneration			1 (2%)	
Centrilobular, necrosis	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Centrilobular, vacuolization cytoplasmic	9 (18%)	6 (12%)	10 (20%)	2 (4%)
Mesentery	(14)	(6)	(5)	(3)
Fat, inflammation, chronic active	10 (71%)	4 (67%)	5 (100%)	3 (100%)
Fat, mineralization	5 (36%)	2 (33%)	3 (60%)	
Fat, necrosis	2 (14%)	2 (33%)	1 (20%)	
Oral mucosa	(3)	(1)		
Hyperplasia	1 (33%)			
Pancreas	(49)	(48)	(50)	(48)
Inflammation, chronic active	2 (4%)			
Acinus, atrophy	11 (22%)	7 (15%)	11 (22%)	4 (8%)
Salivary glands	(51)	(49)	(50)	(49)
Atrophy		2 (4%)		
Stomach, forestomach	(51)	(50)	(49)	(48)
Edema	2 (4%)			
Erosion		1 (2%)	1 (2%)	
Hyperkeratosis	1 (2%)			2 (4%)
Inflammation, chronic active	3 (6%)	3 (6%)	9 (18%)	4 (8%)
Mineralization	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Perforation			2 (4%)	
Ulcer	6 (12%)	2 (4%)	4 (8%)	5 (10%)
Epithelium, hyperplasia			2 (4%)	2 (4%)
Stomach, glandular	(51)	(50)	(49)	(48)
Erosion	2 (4%)		1 (2%)	
Hemorrhage		1 (2%)		
Mineralization	6 (12%)	6 (12%)	7 (14%)	7 (15%)
Ulcer				1 (2%)
Tongue	(1)		(1)	(1)
Vacuolization cytoplasmic			1 (100%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
2-Year Study (continued)				
Cardiovascular System				
Blood vessel	(51)	(50)	(50)	(48)
Mineralization	3 (6%)	5 (10%)	6 (12%)	7 (15%)
Thrombosis		1 (2%)		
Heart	(51)	(49)	(50)	(47)
Mineralization	3 (6%)	5 (10%)	8 (16%)	5 (11%)
Thrombosis		1 (2%)		2 (4%)
Myocardium, degeneration, chronic	43 (84%)	43 (88%)	48 (96%)	42 (89%)
Pericardium, inflammation, chronic active	1 (2%)			
Endocrine System				
Adrenal cortex	(51)	(50)	(50)	(49)
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage		2 (4%)		
Vacuolization cytoplasmic	22 (43%)	23 (46%)	40 (80%)	33 (67%)
Adrenal medulla	(51)	(50)	(50)	(49)
Hyperplasia	15 (29%)	17 (34%)	20 (40%)	15 (31%)
Inflammation, chronic active			1 (2%)	
Mineralization				1 (2%)
Necrosis	1 (2%)			
Islets, pancreatic	(49)	(48)	(50)	(48)
Hyperplasia	1 (2%)			1 (2%)
Pigmentation, hemosiderin			1 (2%)	
Parathyroid gland	(46)	(44)	(48)	(43)
Hyperplasia	10 (22%)	14 (32%)	17 (35%)	15 (35%)
Pituitary gland	(51)	(50)	(50)	(49)
Angiectasis				1 (2%)
Cyst	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Hyperplasia	2 (4%)	2 (4%)		1 (2%)
Mineralization	2 (4%)	1 (2%)		
Necrosis	2 (4%)			
Vacuolization cytoplasmic				1 (2%)
Pars distalis, fibrosis	1 (2%)			
Pars distalis, hyperplasia				1 (2%)
Pars nervosa, developmental malformation	1 (2%)			1 (2%)
Thyroid gland	(51)	(48)	(50)	(49)
Mineralization		1 (2%)		
Ultimobranchial cyst	1 (2%)	6 (13%)	3 (6%)	
C-cell, hyperplasia	1 (2%)			
Follicle, cyst	1 (2%)	1 (2%)		
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
2-Year Study (continued)				
Genital System				
Epididymis	(51)	(50)	(50)	(49)
Atypia cellular		2 (4%)	1 (2%)	
Degeneration	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic active		1 (2%)		
Inflammation, granulomatous	1 (2%)			
Preputial gland	(51)	(49)	(50)	(49)
Cyst	3 (6%)	2 (4%)		
Hyperplasia	1 (2%)	1 (2%)		
Inflammation, chronic active	45 (88%)	37 (76%)	42 (84%)	36 (73%)
Mineralization		2 (4%)		
Prostate	(51)	(50)	(50)	(49)
Atrophy		1 (2%)		
Inflammation, chronic active	10 (20%)	5 (10%)		
Inflammation, granulomatous	1 (2%)			
Mineralization		1 (2%)		2 (4%)
Seminal vesicle	(51)	(49)	(50)	(48)
Inflammation, chronic active	1 (2%)			
Inflammation, granulomatous	1 (2%)			
Mineralization	1 (2%)	1 (2%)		1 (2%)
Epithelium, hyperplasia	1 (2%)			
Testes	(51)	(50)	(50)	(49)
Cyst	1 (2%)			
Degeneration	9 (18%)	9 (18%)	37 (74%)	28 (57%)
Mineralization	17 (33%)	10 (20%)	33 (66%)	19 (39%)
Necrosis	1 (2%)			
Interstitial cell, hyperplasia	16 (31%)	22 (44%)		
Hematopoietic System				
Bone marrow	(48)	(49)	(50)	(49)
Myelofibrosis	1 (2%)	2 (4%)		
Necrosis	1 (2%)			
Lymph node	(4)	(4)		(2)
Ectasia	1 (25%)	2 (50%)		
Hemorrhage		1 (25%)		
Pigmentation, hemosiderin	1 (25%)			
Lymph node, mandibular	(51)	(47)	(50)	(49)
Amyloid deposition	1 (2%)			
Ectasia	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Inflammation, chronic active			1 (2%)	
Lymph node, mesenteric	(50)	(49)	(49)	(48)
Atrophy		1 (2%)	1 (2%)	1 (2%)
Congestion	1 (2%)			
Ectasia	3 (6%)	5 (10%)	3 (6%)	5 (10%)
Necrosis			1 (2%)	
Spleen	(51)	(50)	(50)	(48)
Accessory spleen				1 (2%)
Angiectasis		1 (2%)		
Congestion		2 (4%)		
Fibrosis	7 (14%)	3 (6%)	2 (4%)	
Hematopoietic cell proliferation	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Necrosis	1 (2%)			
Pigmentation, hemosiderin		1 (2%)		
Thrombosis			1 (2%)	
Lymphoid follicle, depletion cellular	1 (2%)	1 (2%)	1 (2%)	2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Thymus	(42)	(42)	(38)	(39)
Atrophy	6 (14%)	3 (7%)	7 (18%)	7 (18%)
Integumentary System				
Mammary gland	(51)	(48)	(49)	(50)
Angiectasis	1 (2%)			
Dilatation	31 (61%)	24 (50%)	23 (47%)	23 (46%)
Galactocele	1 (2%)	4 (8%)	1 (2%)	7 (14%)
Hyperplasia		1 (2%)		
Hyperplasia, focal			1 (2%)	1 (2%)
Mineralization	2 (4%)	4 (8%)	3 (6%)	2 (4%)
Pigmentation, hemosiderin	1 (2%)			
Lobular, hyperplasia			4 (8%)	35 (70%)
Skin	(51)	(50)	(49)	(50)
Inflammation, chronic active				1 (2%)
Parakeratosis	1 (2%)	1 (2%)		1 (2%)
Ulcer		1 (2%)		
Epidermis, cyst	2 (4%)	1 (2%)		
Hair follicle, cyst				1 (2%)
Musculoskeletal System				
Bone	(51)	(49)	(50)	(50)
Fibrous osteodystrophy	2 (4%)	8 (16%)	13 (26%)	15 (30%)
Osteosclerosis	1 (2%)			
Nervous System				
Brain	(51)	(50)	(50)	(50)
Hemorrhage			2 (4%)	
Necrosis	2 (4%)			
Meninges, infiltration cellular, histiocyte			1 (2%)	
Spinal cord	(5)	(1)	(4)	
Demyelination			1 (25%)	
Respiratory System				
Lung	(51)	(50)	(50)	(47)
Congestion			1 (2%)	1 (2%)
Edema		1 (2%)		1 (2%)
Hemorrhage	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic active	12 (24%)	13 (26%)	11 (22%)	14 (30%)
Mineralization	19 (37%)	25 (50%)	27 (54%)	28 (60%)
Necrosis	1 (2%)		1 (2%)	
Proteinosis		1 (2%)		
Vacuolization cytoplasmic	6 (12%)	7 (14%)	7 (14%)	4 (9%)
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Interstitium, fibrosis	1 (2%)	2 (4%)		
Nose	(50)	(49)	(50)	(50)
Inflammation, chronic active	3 (6%)		2 (4%)	1 (2%)
Inflammation, suppurative	4 (8%)	6 (12%)	3 (6%)	2 (4%)
Trachea	(50)	(49)	(50)	(49)
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)	1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	150 mg/kg
2-Year Study (continued)				
Special Senses System				
Eye	(1)	(2)	(2)	(3)
Degeneration		1 (50%)		
Cornea, inflammation, suppurative			1 (50%)	
Cornea, mineralization			1 (50%)	
Cornea, necrosis			1 (50%)	
Lens, mineralization		1 (50%)		2 (67%)
Retina, degeneration	1 (100%)	1 (50%)		2 (67%)
Urinary System				
Kidney	(51)	(50)	(50)	(49)
Cyst	1 (2%)	7 (14%)	4 (8%)	6 (12%)
Degeneration	1 (2%)			
Hyperplasia, oncocytic		1 (2%)		
Inflammation, chronic active		1 (2%)		
Mineralization	6 (12%)	6 (12%)	9 (18%)	25 (51%)
Nephropathy	43 (84%)	47 (94%)	50 (100%)	48 (98%)
Pigmentation, hemosiderin	4 (8%)	4 (8%)	2 (4%)	4 (8%)
Renal tubule, accumulation, hyaline droplet	2 (4%)			
Renal tubule, hyperplasia	3 (6%)	2 (4%)	3 (6%)	1 (2%)
Urinary bladder	(51)	(50)	(50)	(49)
Hemorrhage		1 (2%)		
Inflammation, chronic active	1 (2%)	1 (2%)		2 (4%)
Mineralization	1 (2%)			
Muscularis, inflammation, suppurative	1 (2%)			
Transitional epithelium, hyperplasia				1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF OXYMETHOLONE

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TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone[a]

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Disposition Summary				
Animals initially in study	90	90	90	90
3-Month interim evaluation	10	10	10	10
6-Month interim evaluation	10	10	10	10
12-Month interim evaluation	10	10	10	10
18-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	1		1	1
Moribund	9	11	10	10
Natural deaths	15	10	9	8
Survivors				
Terminal sacrifice	25	29	30	31
Animals examined microscopically	90	90	90	90
Systems Examined at 3 and 6 Months with No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
12-Month Interim Evaluation				
Endocrine System				
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, adenoma		1 (10%)	1 (10%)	
Genital System				
Uterus	(10)	(10)	(10)	(10)
Polyp stromal		1 (10%)		
Systems Examined with No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
18-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular adenoma				1 (10%)
Endocrine System				
Adrenal medulla	(10)	(10)	(10)	(10)
Pheochromocytoma benign	1 (10%)			
Islets, pancreatic	(10)	(10)	(10)	(10)
Carcinoma				1 (10%)
Pituitary gland	(10)	(9)	(10)	(10)
Pars distalis, adenoma	3 (30%)	3 (33%)	1 (10%)	2 (20%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, adenoma			2 (20%)	2 (20%)
Follicular cell, carcinoma		1 (10%)		
Genital System				
Clitoral gland	(9)	(10)	(8)	(10)
Adenoma		2 (20%)		
Uterus	(10)	(10)	(10)	(10)
Carcinoma	1 (10%)			
Polyp stromal	1 (10%)	1 (10%)	1 (10%)	
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Carcinoma	1 (10%)			
Fibroadenoma	3 (30%)	1 (10%)	1 (10%)	1 (10%)
Skin	(10)	(10)	(10)	(10)
Hemangiopericytoma			1 (10%)	
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma			1 (10%)	1 (10%)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear	1 (10%)			
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Fibrosarcoma	1 (2%)			
Intestine large, colon	(46)	(46)	(49)	(48)
Leiomyoma		1 (2%)		
Intestine large, rectum	(44)	(47)	(46)	(50)
Intestine large, cecum	(38)	(44)	(42)	(45)
Intestine small, duodenum	(47)	(48)	(49)	(49)
Intestine small, jejunum	(43)	(45)	(43)	(44)
Intestine small, ileum	(40)	(44)	(44)	(46)
Liver	(50)	(50)	(50)	(49)
Fibrosarcoma	1 (2%)			
Hepatocellular carcinoma				2 (4%)
Hepatocellular adenoma		1 (2%)	1 (2%)	8 (16%)
Hepatocellular adenoma, multiple	1 (2%)			
Mesentery	(5)	(3)	(12)	(10)
Fibrosarcoma	1 (20%)			
Oral mucosa		(1)		
Squamous cell carcinoma		1 (100%)		
Pancreas	(50)	(49)	(49)	(49)
Salivary glands	(50)	(49)	(50)	(49)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Tongue		(1)		(1)
Squamous cell papilloma		1 (100%)		
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(49)
Heart	(50)	(50)	(50)	(49)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma benign	7 (14%)	4 (8%)	2 (4%)	6 (12%)
Bilateral, pheochromocytoma benign				4 (8%)
Islets, pancreatic	(49)	(49)	(49)	(49)
Adenoma		1 (2%)		1 (2%)
Pituitary gland	(50)	(50)	(49)	(50)
Pars distalis, adenoma	27 (54%)	26 (52%)	18 (37%)	14 (28%)
Thyroid gland	(50)	(49)	(50)	(49)
C-cell, adenoma	5 (10%)	8 (16%)	7 (14%)	4 (8%)
Follicular cell, adenoma	1 (2%)			
General Body System				
Peritoneum	(1)			
Fibrosarcoma, metastatic, uncertain primary site	1 (100%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
2-Year Study (continued)				
Genital System				
Clitoral gland	(50)	(48)	(50)	(50)
Adenoma	4 (8%)	4 (8%)	2 (4%)	2 (4%)
Carcinoma	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Squamous cell papilloma	2 (4%)		1 (2%)	
Ovary	(50)	(49)	(50)	(49)
Uterus	(50)	(50)	(50)	(50)
Fibrosarcoma	1 (2%)			
Hemangiosarcoma				1 (2%)
Polyp stromal	4 (8%)	8 (16%)	2 (4%)	
Sarcoma stromal		1 (2%)		
Cervix, sarcoma stromal	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(49)
Lymph node	(4)	(1)	(1)	(1)
Lymph node, mandibular	(49)	(48)	(48)	(48)
Lymph node, mesenteric	(50)	(48)	(49)	(49)
Spleen	(50)	(49)	(50)	(49)
Thymus	(45)	(47)	(44)	(42)
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Carcinoma	3 (6%)			
Fibroadenoma	15 (30%)	11 (22%)	1 (2%)	4 (8%)
Fibroadenoma, multiple	6 (12%)			
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma				1 (2%)
Keratoacanthoma			4 (8%)	
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma				2 (4%)
Pinna, melanoma malignant	1 (2%)			
Subcutaneous tissue, fibroma			1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, lipoma				1 (2%)
Sweat gland, carcinoma				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(49)	(50)
Sarcoma		1 (2%)		
Skeletal muscle	(1)			
Fibrosarcoma, metastatic, uncertain primary site	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma			6 (12%)	1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)	
Sarcoma, metastatic, bone		1 (2%)		
Nose	(49)	(50)	(49)	(50)
Trachea	(50)	(50)	(50)	(49)
Special Senses System				
None				
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Mesenchymal tumor benign		1 (2%)		
Renal tubule, adenoma				1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Leiomyoma				1 (2%)
Transitional epithelium, carcinoma				1 (2%)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Leukemia mononuclear	12 (24%)	11 (22%)	11 (22%)	5 (10%)
Lymphoma malignant			2 (4%)	
Mesothelioma malignant			1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]				
12-Month interim evaluation		2	1	
18-Month interim evaluation	8	4	5	5
2-Year study	45	45	37	37
Total primary neoplasms				
12-Month interim evaluation		2	1	
18-Month interim evaluation	11	8	7	8
2-Year study	94	85	61	66
Total animals with benign neoplasms				
12-Month interim evaluation		2	1	
18-Month interim evaluation	6	4	5	5
2-Year study	44	40	29	33
Total benign neoplasms				
12-Month interim evaluation		2	1	
18-Month interim evaluation	8	7	7	7
2-Year study	72	66	45	52
Total animals with malignant neoplasms				
18-Month interim evaluation	3	1		1
2-Year study	17	18	16	12
Total malignant neoplasms				
18-Month interim evaluation	3	1		1
2-Year study	22	19	16	14
Total animals with metastatic neoplasms				
2-Year study	1	1		
Total metastatic neoplasms				
2-Year study	2	1		
Total animals with malignant neoplasms of uncertain primary site				
2-Year study	1			

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: Vehicle Control

Number of Days on Study	478	478	506	533	540	543	548	549	561	562	566	573	573	574	589	621	625	678	684	693	705	706	707	707	708
Carcass ID Number	361	418	368	362	377	403	387	363	402	366	393	365	420	446	383	378	382	443	404	441	399	424	389	394	388
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma					X																				
Intestine large, colon	+	+	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	A	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	+	+	A	+	A	A	A	A	A	+	A	+	A	A	A	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	A	A	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	A	+	+	A	+	A	A	+	A	+	A	A	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma					X																				
Hepatocellular adenoma, multiple																									
Mesentery					+									+						+	+				
Fibrosarcoma					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign															X			X			X		X	X	
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X			X		X	X	X	X			X		X			X	X			X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X		X				X
Follicular cell, adenoma																									
General Body System																									
Peritoneum					+																				
Fibrosarcoma, metastatic, uncertain primary site					X																				
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Carcinoma																									
Squamous cell papilloma		X																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma					X																				
Polyp stromal				X																					X
Cervix, sarcoma stromal																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: Vehicle Control

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	371	390	391	392	400	407	408	415	421	425	434	438	445	367	376	379	381	395	398	406	409	411	417	422	444	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Hepatocellular adenoma, multiple												X														1
Mesentery																			+							5
Fibrosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X		X								7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X		X			X	X	X			X	X			X		X	X	X	X	X		27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X			X								5
Follicular cell, adenoma																	X									1
General Body System																										
Peritoneum																										1
Fibrosarcoma, metastatic, uncertain primary site																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X													X						X						4
Carcinoma																X										1
Squamous cell papilloma									X																	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Polyp stromal							X							X												4
Cervix, sarcoma stromal													X													1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: Vehicle Control

Number of Days on Study	478	478	506	533	540	543	548	549	561	562	566	573	573	574	589	621	625	678	684	693	705	706	707	707	708
Carcass ID Number	361	418	368	362	377	403	387	363	402	366	393	365	420	446	383	378	382	443	404	441	399	424	389	394	388
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+													+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma			X		X			X			X			X						X					
Fibroadenoma, multiple																						X	X	X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pinna, melanoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Fibrosarcoma, metastatic, uncertain primary site					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																			+						
Spinal cord																			+						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye												+													+
Lacrimal gland					+																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X											X	X	X	X			X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: Vehicle Control

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	371	390	391	392	400	407	408	415	421	425	434	438	445	367	376	379	381	395	398	406	409	411	417	422	424	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																			+							4
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma														X	X									X		3
Fibroadenoma		X	X		X		X						X	X				X	X						X	15
Fibroadenoma, multiple				X							X										X					6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pinna, melanoma malignant																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibrosarcoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X										X		X			X				X					12

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 3 mg/kg

Number of Days on Study	299	501	523	537	556	562	576	579	582	590	639	646	652	652	665	670	691	702	705	711	725	728	728	728	728
Carcass ID Number	468	513	470	539	485	535	555	534	452	482	465	494	457	459	501	521	490	466	463	481	462	467	472	476	496
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine large, rectum	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery	+																								
Oral mucosa																									
Squamous cell carcinoma																									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant								X																	
Pheochromocytoma benign															X				X						
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X			X	X				X	X		X	X	X			X	X	X		X
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X					X						
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																									
Carcinoma																			X						
Ovary	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X			X														X	X
Sarcoma stromal												X													

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 3 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	499	504	506	510	511	512	517	525	529	538	544	561	574	577	579	584	587	502	516	527	530	531	536	537	540	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyoma																					X					1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X																						1
Mesentery										+						+										3
Oral mucosa																					+					1
Squamous cell carcinoma																					X					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue									+																	1
Squamous cell papilloma									X																	1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign													X										X			4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X	X		X	X			X	X		X		X	X		X					X		26
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma					X	X			X										X	X		X				8
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma				X	X				X									X								4
Carcinoma														X		X										3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X	X								X		X										8
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 3 mg/kg

Number of Days on Study	299	501	523	537	556	562	576	579	582	590	639	646	652	652	665	670	691	702	705	711	725	728	728	728	728
Carcass ID Number	468	513	470	539	485	535	555	534	452	482	465	494	457	459	501	521	490	466	463	481	462	467	472	476	496
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+																						
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma														X					X		X				X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma											X														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, bone											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenchymal tumor benign																			X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X			X			X			X		X					X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 3 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	499	504	506	510	511	512	517	525	529	538	544	561	574	577	579	584	587	502	516	527	530	531	536	537	540	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma	X		X										X	X			X		X						X	11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																									+	1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesenchymal tumor benign																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X										X							X		X	11

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 30 mg/kg

Number of Days on Study	1	2	4	4	4	4	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
	1	2	4	7	7	9	6	6	3	5	5	6	7	7	7	9	9	9	0	1	2	2	2	2	2
	8	9	1	8	8	7	0	1	8	3	9	5	0	1	4	3	3	8	8	3	8	8	8	8	8
Carcass ID Number	5	5	5	5	5	5	5	5	6	5	5	5	5	6	5	5	6	5	5	5	5	5	5	5	5
	4	7	4	4	9	7	9	6	2	8	7	8	6	2	5	9	1	5	6	9	4	4	5	5	5
	5	0	9	2	7	8	2	8	3	1	9	6	0	5	7	3	5	1	5	6	6	8	0	3	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	A	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	A	A	+	M	A	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	A	+	A	A	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+
Intestine small, ileum	M	+	+	+	+	A	+	+	A	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery		+									+	+					+		+	+		+			
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign								X				X													
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X		X		X	X			X			X		X	X	X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X					X								
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma				X																					
Squamous cell papilloma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																	X								
Hematopoietic System																									
Bone marrow	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+																	
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 30 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	561	562	569	575	580	588	607	609	611	618	543	555	558	566	572	573	589	590	601	604	605	612	626	627	628	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X																					1
Mesentery			+					+					+									+			+	12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X			X	X				X		X	X			X	X								18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X						X			X							X	X							7
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X			X							2
Carcinoma																										1
Squamous cell papilloma														X												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X																									2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 30 mg/kg

Number of Days on Study	118	129	441	478	478	497	560	561	638	653	659	665	670	671	674	693	693	698	708	713	728	728	728	728	728
Carcass ID Number	545	570	549	542	597	578	592	568	623	581	579	586	560	625	557	593	615	551	565	596	546	548	550	553	554
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																			+						
Spinal cord																			+						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X																		X				
Alveolar/bronchiolar carcinoma																									
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X			X		X		X	X		X							
Lymphoma malignant									X			X													
Mesothelioma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 30 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	561	562	569	575	580	588	607	609	611	618	543	555	558	566	572	573	589	590	601	604	605	612	626	627	628	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma				X			X														X		X			4
Subcutaneous tissue, fibroma	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X				X		X																X			6
Alveolar/bronchiolar carcinoma									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X	X	X			X																11
Lymphoma malignant																										2
Mesothelioma malignant																X										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 100 mg/kg

Number of Days on Study	177	387	394	490	510	511	539	562	625	659	659	659	663	674	680	695	704	713	725	728	728	728	728	728	728
Carcass ID Number	660	718	647	704	736	703	732	693	672	641	664	713	642	639	675	644	695	700	654	633	635	643	648	657	663
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	A	+	+	+	M	+	A	M	+	+	A	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	A	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma										X												X			
Mesentery	+							+		+	+								+						+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																					X	X		X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	+	+	M	M	+	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X													X								
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma											X											X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+																		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 100 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	676	678	679	681	691	694	697	701	705	714	634	637	640	645	652	655	658	671	674	686	687	690	710	712	719	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma				X																	X					2
Hepatocellular adenoma		X	X							X		X				X								X		8
Mesentery						+						+									+		+			10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Tongue																				+						1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign	X										X				X			X	X		X					6
Bilateral, pheochromocytoma benign														X												4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X	X		X	X	X	X	X		X						X		X				X	14
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma							X																		X	4
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X														X					2
Carcinoma																								X		3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	M	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	42

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 100 mg/kg

Number of Days on Study	177	387	394	490	510	511	539	562	625	659	659	659	663	674	680	695	704	713	725	728	728	728	728	728	728
Carcass ID Number	660	718	647	704	636	703	632	693	672	641	664	713	642	639	675	644	695	700	654	633	635	643	648	657	663
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma		X						X						X	X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Squamous cell carcinoma																									
Squamous cell papilloma																			X						
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, lipoma																							X		
Sweat gland, carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+										+								
Spinal cord							+										+								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma				X																					
Transitional epithelium, carcinoma													X												
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X						X							X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Oxymetholone: 100 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	676	678	679	681	691	694	697	701	705	714	634	637	640	645	652	655	658	671	674	686	687	690	710	712	719	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																										4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																		X								1
Squamous cell carcinoma																				X						1
Squamous cell papilloma													X													2
Subcutaneous tissue, fibroma				X																						1
Subcutaneous tissue, lipoma																										1
Sweat gland, carcinoma																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										2
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma								X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Transitional epithelium, carcinoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																X										5

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	7/50 (14%)	4/50 (8%)	2/50 (4%)	10/49 (20%)
Adjusted rate[b]	17.2%	9.4%	4.7%	24.2%
Terminal rate[c]	2/25 (8%)	2/29 (7%)	0/30 (0%)	10/31 (32%)
First incidence (days)	589	665	561	728 (T)
Poly-3 test[d]	P=0.057	P=0.234N	P=0.066N	P=0.307
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	7/50 (14%)	5/50 (10%)	2/50 (4%)	10/49 (20%)
Adjusted rate	17.2%	11.7%	4.7%	24.2%
Terminal rate	2/25 (8%)	2/29 (7%)	0/30 (0%)	10/31 (32%)
First incidence (days)	589	579	561	728 (T)
Poly-3 test	P=0.082	P=0.340N	P=0.066N	P=0.307
Clitoral Gland: Adenoma				
Overall rate	4/50 (8%)	4/48 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	10.0%	9.9%	4.8%	4.7%
Terminal rate	3/25 (12%)	4/29 (14%)	2/30 (7%)	2/31 (7%)
First incidence (days)	621	728 (T)	728 (T)	728 (T)
Poly-3 test	P=0.230N	P=0.637N	P=0.317N	P=0.313N
Clitoral Gland: Carcinoma				
Overall rate	1/50 (2%)	3/48 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.5%	7.4%	2.4%	7.1%
Terminal rate	1/25 (4%)	2/29 (7%)	0/30 (0%)	2/31 (7%)
First incidence (days)	728 (T)	705	478	659
Poly-3 test	P=0.396	P=0.314	P=0.746N	P=0.329
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	7/48 (15%)	3/50 (6%)	5/50 (10%)
Adjusted rate	12.5%	17.2%	7.1%	11.8%
Terminal rate	4/25 (16%)	6/29 (21%)	2/30 (7%)	4/31 (13%)
First incidence (days)	621	705	478	659
Poly-3 test	P=0.420N	P=0.388	P=0.323N	P=0.596N
Liver: Hepatocellular Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	8/49 (16%)
Adjusted rate	2.5%	2.4%	2.4%	19.2%
Terminal rate	1/25 (4%)	1/29 (3%)	1/30 (3%)	7/31 (23%)
First incidence (days)	728 (T)	728 (T)	728 (T)	659
Poly-3 test	P<0.001	P=0.748N	P=0.749N	P=0.018
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	10/49 (20%)
Adjusted rate	2.5%	2.4%	2.4%	24.0%
Terminal rate	1/25 (4%)	1/29 (3%)	1/30 (3%)	9/31 (29%)
First incidence (days)	728 (T)	728 (T)	728 (T)	659
Poly-3 test	P<0.001	P=0.748N	P=0.749N	P=0.005
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	0/50 (0%)	6/50 (12%)	1/49 (2%)
Adjusted rate	0.0%	0.0%	14.1%	2.4%
Terminal rate	0/25 (0%)	0/29 (0%)	5/30 (17%)	1/31 (3%)
First incidence (days)	—[e]	—	441	728 (T)
Poly-3 test	P=0.471	—[f]	P=0.019	P=0.508

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	7/50 (14%)	1/49 (2%)
Adjusted rate	0.0%	0.0%	16.5%	2.4%
Terminal rate	0/25 (0%)	0/29 (0%)	6/30 (20%)	1/31 (3%)
First incidence (days)	—	—	441	728 (T)
Poly-3 test	P=0.488	—	P=0.009	P=0.508
Mammary Gland: Fibroadenoma				
Overall rate	21/50 (42%)	11/50 (22%)	1/50 (2%)	4/50 (8%)
Adjusted rate	48.9%	25.9%	2.4%	9.1%
Terminal rate	12/25 (48%)	8/29 (28%)	0/30 (0%)	0/31 (0%)
First incidence (days)	506	652	693	387
Poly-3 test	P<0.001N	P=0.020N	P<0.001N	P<0.001N
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.6%	0.0%	0.0%	0.0%
Terminal rate	3/25 (12%)	0/29 (0%)	0/30 (0%)	0/31 (0%)
First incidence (days)	728 (T)	—	—	—
Poly-3 test	P=0.179N	P=0.108N	P=0.109N	P=0.108N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	23/50 (46%)	11/50 (22%)	1/50 (2%)	4/50 (8%)
Adjusted rate	53.6%	25.9%	2.4%	9.1%
Terminal rate	14/25 (56%)	8/29 (28%)	0/30 (0%)	0/31 (0%)
First incidence (days)	506	652	693	387
Poly-3 test	P<0.001N	P=0.006N	P<0.001N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	27/50 (54%)	26/50 (52%)	18/49 (37%)	14/50 (28%)
Adjusted rate	59.7%	57.5%	40.5%	33.1%
Terminal rate	14/25 (56%)	16/29 (55%)	9/30 (30%)	13/31 (42%)
First incidence (days)	478	537	478	695
Poly-3 test	P=0.004N	P=0.498N	P=0.048N	P=0.008N
Skin: Keratoacanthoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate	0.0%	0.0%	9.6%	0.0%
Terminal rate	0/25 (0%)	0/29 (0%)	4/30 (13%)	0/31 (0%)
First incidence (days)	—	—	728 (T)	—
Poly-3 test	P=0.593N	—	P=0.066	—
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	9.6%	4.7%
Terminal rate	0/25 (0%)	0/29 (0%)	4/30 (13%)	1/31 (3%)
First incidence (days)	—	—	728 (T)	725
Poly-3 test	P=0.201	—	P=0.066	P=0.250
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	9.6%	7.1%
Terminal rate	0/25 (0%)	0/29 (0%)	4/30 (13%)	2/31 (7%)
First incidence (days)	—	—	728 (T)	725
Poly-3 test	P=0.077	—	P=0.066	P=0.129

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, Squamous Cell Carcinoma, or Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	5/50 (10%)
Adjusted rate	0.0%	0.0%	9.6%	11.9%
Terminal rate	0/25 (0%)	0/29 (0%)	4/30 (13%)	4/31 (13%)
First incidence (days)	—	—	728 (T)	725
Poly-3 test	P=0.008	—	P=0.066	P=0.035
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/50 (10%)	8/49 (16%)	7/50 (14%)	4/49 (8%)
Adjusted rate	12.5%	18.9%	16.6%	9.5%
Terminal rate	2/25 (8%)	6/29 (21%)	5/30 (17%)	2/31 (7%)
First incidence (days)	684	652	665	490
Poly-3 test	P=0.217N	P=0.311	P=0.415	P=0.467N
Uterus: Stromal Polyp				
Overall rate	4/50 (8%)	8/50 (16%)	2/50 (4%)	0/50 (0%)
Adjusted rate	9.9%	18.6%	4.8%	0.0%
Terminal rate	2/25 (8%)	6/29 (21%)	1/30 (3%)	0/31 (0%)
First incidence (days)	533	576	693	—
Poly-3 test	P=0.006N	P=0.206	P=0.319N	P=0.054N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	5/50 (10%)	9/50 (18%)	2/50 (4%)	0/50 (0%)
Adjusted rate	12.4%	20.8%	4.8%	0.0%
Terminal rate	3/25 (12%)	6/29 (21%)	1/30 (3%)	0/31 (0%)
First incidence (days)	533	576	693	—
Poly-3 test	P=0.003N	P=0.231	P=0.199N	P=0.026N
All Organs: Mononuclear Cell Leukemia				
Overall rate	12/50 (24%)	11/50 (22%)	11/50 (22%)	5/50 (10%)
Adjusted rate	28.7%	24.5%	25.0%	11.6%
Terminal rate	6/25 (24%)	4/29 (14%)	4/30 (13%)	2/31 (7%)
First incidence (days)	533	523	441	539
Poly-3 test	P=0.036N	P=0.422N	P=0.442N	P=0.042N
All Organs: Benign Neoplasms				
Overall rate	44/50 (88%)	40/50 (80%)	29/50 (58%)	33/50 (66%)
Adjusted rate	93.0%	86.0%	63.4%	73.2%
Terminal rate	24/25 (96%)	26/29 (90%)	18/30 (60%)	24/31 (77%)
First incidence (days)	478	537	441	387
Poly-3 test	P=0.015N	P=0.191N	P<0.001N	P=0.005N
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	18/50 (36%)	16/50 (32%)	12/50 (24%)
Adjusted rate	40.1%	38.6%	35.3%	27.5%
Terminal rate	10/25 (40%)	6/29 (21%)	6/30 (20%)	7/31 (23%)
First incidence (days)	533	523	441	539
Poly-3 test	P=0.115N	P=0.530N	P=0.403N	P=0.154N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	45/50 (90%)	37/50 (74%)	37/50 (74%)
Adjusted rate	94.4%	93.0%	77.9%	80.1%
Terminal rate	24/25 (96%)	26/29 (90%)	20/30 (67%)	25/31 (81%)
First incidence (days)	478	523	441	387
Poly-3 test	P=0.019N	P=0.561N	P=0.015N	P=0.026N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, liver, lung, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle 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 the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Female F344/N Rats[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study			
Methyleugenol	1/50	0/50	1/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	5/330 (1.5%)	0/330	5/330 (1.5%)
Mean ± standard deviation	1.4% ± 1.1%		1.4% ± 1.1%
Range	0%-3%		0%-3%
Overall Historical Incidence: Feed Studies			
Total (%)	4/901 (0.4%)	0/901	4/901 (0.4%)
Mean ± standard deviation	0.4% ± 1.1%		0.4% ± 1.1%
Range	0%-4%		0%-4%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE B4b
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Female F344/N Rats[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study			
Methyleugenol	0/50	1/50	1/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	5/330 (1.5%)	0/330	5/330 (1.5%)
Mean ± standard deviation	1.4% ± 1.1%		1.4% ± 1.1%
Range	0%-3%		0%-3%
Overall Historical Incidence: Feed Studies			
Total (%)	13/900 (1.4%)	4/900 (0.4%)	17/900 (1.9%)
Mean ± standard deviation	1.4% ± 1.8%	0.4% ± 0.9%	1.9% ± 1.9%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE B4c
Historical Incidence of Skin Neoplasms in Untreated Female F344/N Rats[a]

	Incidence in Controls			
	Keratoacanthoma	Squamous Cell Papilloma or Keratoacanthoma	Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma	Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma or Carcinoma, Malignant Basosquamous Tumor, or Squamous Cell Carcinoma
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study				
Methyleugenol	0/50	0/50	0/50	0/50
Overall Historical Incidence: Drinking Water Studies				
Total (%)	0/330	2/330 (0.6%)	4/330 (1.2%)	5/330 (1.5%)
Mean ± standard deviation		0.7% ± 1.0%	1.3% ± 1.6%	1.5% ± 1.5%
Range		0%-2%	0%-4%	0%-4%
Overall Historical Incidence: Feed Studies				
Total (%)	1/901 (0.1%)	9/901 (1.0%)	10/901 (1.1%)	17/901 (1.9%)
Mean ± standard deviation	0.1% ± 0.5%	1.0% ± 1.6%	1.1% ± 1.6%	1.9% ± 2.0%
Range	0%-2%	0%-6%	0%-6%	0%-8%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE B4d
Historical Incidence of Adrenal Medulla Pheochromocytoma in Untreated Female F344/N Rats[a]

	Incidence in Controls		
	Benign	Malignant	Benign or Malignant[b]
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study			
Methyleugenol	1/50	0/50	1/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	23/329 (7.0%)	1/329 (0.3%)	25/329 (7.6%)
Mean ± standard deviation	6.9% ± 3.7%	0.3% ± 0.8%	7.6% ± 3.5%
Range	4%-14%	0%-2%	4%-14%
Overall Historical Incidence: Feed Studies			
Total (%)	26/896 (2.9%)	4/896 (0.5%)	34/896 (3.8%)
Mean ± standard deviation	2.9% ± 1.9%	0.4% ± 0.9%	3.8% ± 1.9%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database
[b] Drinking water and feed study incidences include benign, malignant, or complex pheochromocytoma.

TABLE B4e
Historical Incidence of Uterine Neoplasms in Untreated Female F344/N Rats[a]

	Incidence in Controls		
	Stromal Polyp	Stromal Sarcoma	Stromal Polyp or Stromal Sarcoma
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study			
Methyleugenol	4/50	0/50	4/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	57/330 (17.3%)	1/330 (0.3%)	58/330 (17.6%)
Mean ± standard deviation	17.5% ± 6.4%	0.3% ± 0.8%	17.8% ± 5.9%
Range	8%-26%	0%-2%	10%-26%
Overall Historical Incidence: Feed Studies			
Total (%)	111/901 (12.3%)	4/901 (0.4%)	115/901 (12.8%)
Mean ± standard deviation	12.3% ± 7.7%	0.4% ± 1.1%	12.8% ± 7.5%
Range	2%-26%	0%-4%	2%-26%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE B4f
Historical Incidence of Mammary Gland Neoplasms in Untreated Female F344/N Rats[a]

	Incidence in Controls			
	Fibroadenoma	Adenoma	Carcinoma	Fibroadenoma, Adenoma, or Carcinoma
Historical Incidence at Battelle Columbus Laboratories: Gavage (Methylcellulose) Study				
Methyleugenol	36/50	0/50	2/50	37/50
Overall Historical Incidence: Drinking Water Studies				
Total (%)	121/330 (36.7%)	6/330 (1.8%)	11/330 (3.3%)	132/330 (40.0%)
Mean ± standard deviation	37.6% ± 14.6%	2.0% ± 1.8%	3.7% ± 4.3%	41.3% ± 12.8%
Range	24%-58%	0%-4%	0%-12%	28%-60%
Overall Historical Incidence: Feed Studies				
Total (%)	383/901 (42.5%)	21/901 (2.3%)	31/901 (3.4%)	418/901 (46.4%)
Mean ± standard deviation	42.5% ± 11.1%	2.3% ± 2.4%	3.4% ± 2.6%	46.4% ± 12.1%
Range	24%-60%	0%-8%	0%-8%	24%-64%

[a] Data as of 12 November 1997; methylcellulose gavage study (NTP, 1999) not in historical database

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone[a]

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
Disposition Summary				
Animals initially in study	90	90	90	90
3-Month interim evaluation	10	10	10	10
6-Month interim evaluation	10	10	10	10
12-Month interim evaluation	10	10	10	10
18-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	1		1	1
Moribund	9	11	10	10
Natural deaths	15	10	9	8
Survivors				
Terminal sacrifice	25	29	30	31
Animals examined microscopically	90	90	90	90
3-Month Interim Evaluation				
Alimentary System				
Intestine small, jejunum	(10)	(10)	(10)	(10)
Peyer's patch, mineralization			2 (20%)	
Liver	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule	2 (20%)	4 (40%)	1 (10%)	1 (10%)
Inflammation, chronic active		1 (10%)		1 (10%)
Mesentery	(1)			
Fat, inflammation, chronic active	1 (100%)			
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy		2 (20%)		
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration, chronic	1 (10%)	6 (60%)	3 (30%)	4 (40%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule			1 (10%)	
Thyroid gland	(10)	(10)	(10)	(10)
Ultimobranchial cyst	1 (10%)	2 (20%)		
Genital System				
Clitoral gland	(10)	(9)	(10)	(10)
Inflammation, chronic active	6 (60%)	5 (56%)	9 (90%)	9 (90%)
Ovary	(10)	(10)	(9)	(9)
Dysgenesis				9 (100%)
Periovarian tissue, cyst	1 (10%)	2 (20%)	2 (22%)	1 (11%)
Uterus	(10)	(10)	(10)	(10)
Hydrometra	3 (30%)	2 (20%)		7 (70%)
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Lobular, hyperplasia			2 (20%)	9 (90%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
3-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active	2 (20%)	6 (60%)	4 (40%)	4 (40%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	10 (100%)	9 (90%)	9 (90%)	10 (100%)
Nephropathy				8 (80%)
Systems Examined with No Lesions Observed				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Special Senses System				
6-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus		1 (10%)		
Hepatodiaphragmatic nodule	1 (10%)	5 (50%)	1 (10%)	2 (20%)
Inflammation, chronic active	2 (20%)	5 (50%)	4 (40%)	2 (20%)
Centrilobular, vacuolization cytoplasmic			1 (10%)	
Mesentery	(1)		(1)	
Fat, inflammation, chronic active	1 (100%)		1 (100%)	
Pancreas	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)			
Acinus, atrophy				1 (10%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration, chronic	5 (50%)	5 (50%)	7 (70%)	10 (100%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	3 (30%)	2 (20%)	1 (10%)	
Thyroid gland	(10)	(10)	(10)	(10)
Ultimobranchial cyst		1 (10%)	1 (10%)	2 (20%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
6-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Inflammation, chronic active	6 (60%)	7 (70%)	10 (100%)	8 (80%)
Ovary	(10)	(10)	(10)	(10)
Dysgenesis			10 (100%)	10 (100%)
Follicle, cyst	1 (10%)			
Periovarian tissue, cyst	1 (10%)			
Uterus	(10)	(10)	(10)	(10)
Hydrometra	2 (20%)	3 (30%)	4 (40%)	1 (10%)
Endometrium, cyst			1 (10%)	
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Dilatation				1 (10%)
Lobular, hyperplasia			10 (100%)	10 (100%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Hemorrhage		1 (10%)		
Inflammation, chronic active	2 (20%)	4 (40%)	7 (70%)	2 (20%)
Mineralization		2 (20%)	4 (40%)	1 (10%)
Special Senses System				
Eye			(1)	
Lens, mineralization			1 (100%)	
Retina, degeneration			1 (100%)	
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)		
Mineralization	10 (100%)	10 (100%)	10 (100%)	9 (90%)
Nephropathy		1 (10%)	2 (20%)	7 (70%)
Systems Examined with No Lesions Observed				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
12-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)			
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	2 (20%)			3 (30%)
Intestine large, cecum	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
12-Month Interim Evaluation (continued)				
Alimentary System (continued)				
Liver	(10)	(10)	(10)	(10)
Basophilic focus	4 (40%)	8 (80%)	2 (20%)	7 (70%)
Clear cell focus			1 (10%)	1 (10%)
Eosinophilic focus		1 (10%)		
Hepatodiaphragmatic nodule	1 (10%)	2 (20%)	2 (20%)	1 (10%)
Inflammation, chronic active	7 (70%)	5 (50%)	6 (60%)	3 (30%)
Bile duct, hyperplasia			1 (10%)	
Centrilobular, vacuolization cytoplasmic			7 (70%)	
Mesentery	(1)	(3)	(3)	(1)
Fat, inflammation, chronic active	1 (100%)	3 (100%)	3 (100%)	1 (100%)
Pancreas	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)			
Acinus, atrophy	2 (20%)	1 (10%)	1 (10%)	
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration, chronic	7 (70%)	8 (80%)	9 (90%)	9 (90%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	3 (30%)	2 (20%)		1 (10%)
Hyperplasia	1 (10%)			
Inflammation, chronic active				1 (10%)
Vacuolization cytoplasmic				10 (100%)
Pituitary gland	(10)	(10)	(10)	(10)
Cyst		2 (20%)		1 (10%)
Pars distalis, angiectasis		1 (10%)		
Thyroid gland	(10)	(10)	(10)	(10)
Ultimobranchial cyst			1 (10%)	
Follicle, cyst				1 (10%)
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Cyst			1 (10%)	
Inflammation, chronic active	4 (40%)	6 (60%)	6 (60%)	3 (30%)
Ovary	(10)	(10)	(10)	(10)
Dysgenesis			10 (100%)	10 (100%)
Follicle, cyst			1 (10%)	
Periovarian tissue, cyst	1 (10%)			
Uterus	(10)	(10)	(10)	(10)
Hydrometra		1 (10%)		1 (10%)
Endometrium, cyst	1 (10%)			
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Myelofibrosis	1 (10%)			
Spleen	(10)	(10)	(10)	(10)
Lymphoid follicle, depletion cellular			1 (10%)	
Thymus	(10)	(10)	(9)	(10)
Atrophy				2 (20%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
12-Month Interim Evaluation (continued)				
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Dilatation			1 (10%)	8 (80%)
Lobular, hyperplasia			10 (100%)	8 (80%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Hemorrhage		1 (10%)	1 (10%)	
Inflammation, chronic active	1 (10%)	4 (40%)	3 (30%)	
Mineralization	2 (20%)		2 (20%)	2 (20%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	9 (90%)	10 (100%)	10 (100%)	10 (100%)
Nephropathy	5 (50%)	6 (60%)	9 (90%)	10 (100%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)		
Systems Examined with No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
18-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan				1 (10%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	4 (40%)	4 (40%)	4 (40%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus	7 (70%)	10 (100%)	10 (100%)	9 (90%)
Clear cell focus		1 (10%)		3 (30%)
Hepatodiaphragmatic nodule	2 (20%)	1 (10%)	2 (20%)	1 (10%)
Inflammation, chronic active	7 (70%)	6 (60%)	7 (70%)	1 (10%)
Mixed cell focus			2 (20%)	
Bile duct, hyperplasia				1 (10%)
Centrilobular, vacuolization cytoplasmic			9 (90%)	1 (10%)
Mesentery	(4)	(3)	(2)	(1)
Fat, inflammation, chronic active	4 (100%)	3 (100%)	2 (100%)	1 (100%)
Fat, mineralization	1 (25%)			
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy	1 (10%)			
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration, chronic	6 (60%)	7 (70%)	8 (80%)	9 (90%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
18-Month Interim Evaluation (continued)				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Angiectasis		3 (30%)		
Vacuolization cytoplasmic			1 (10%)	9 (90%)
Adrenal medulla	(10)	(10)	(10)	(10)
Hyperplasia			1 (10%)	
Pituitary gland	(10)	(9)	(10)	(10)
Cyst	2 (20%)	1 (11%)	2 (20%)	1 (10%)
Hyperplasia	1 (10%)	1 (11%)		2 (20%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia				1 (10%)
Genital System				
Clitoral gland	(9)	(10)	(8)	(10)
Cyst				3 (30%)
Inflammation, chronic active	5 (56%)	3 (30%)	2 (25%)	4 (40%)
Ovary	(10)	(10)	(10)	(10)
Dysgenesis			8 (80%)	10 (100%)
Periovarian tissue, cyst	3 (30%)	1 (10%)	1 (10%)	1 (10%)
Uterus	(10)	(10)	(10)	(10)
Hydrometra	3 (30%)			2 (20%)
Endometrium, cyst		1 (10%)		
Endometrium, hyperplasia				1 (10%)
Hematopoietic System				
Lymph node, mandibular	(10)	(10)	(10)	(10)
Ectasia			1 (10%)	
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Ectasia		1 (10%)		
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	1 (10%)			
Pigmentation, hemosiderin	1 (10%)			
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Dilatation	4 (40%)	1 (10%)		1 (10%)
Galactocele	1 (10%)	1 (10%)		
Lobular, hyperplasia	1 (10%)		9 (90%)	9 (90%)
Skin	(10)	(10)	(10)	(10)
Epidermis, cyst	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)	4 (40%)	4 (40%)	3 (30%)
Mineralization	2 (20%)	1 (10%)	5 (50%)	3 (30%)
Nose	(10)	(10)	(10)	(10)
Inflammation, suppurative			1 (10%)	
Glands, hyperplasia			1 (10%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
18-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	8 (80%)	9 (90%)	10 (100%)	9 (90%)
Nephropathy	8 (80%)	4 (40%)	9 (90%)	10 (100%)
Renal tubule, hyperplasia				1 (10%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)		2 (20%)	
Systems Examined with No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Hemorrhage			1 (2%)	
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)
Ulcer				1 (2%)
Intestine large, colon	(46)	(46)	(49)	(48)
Parasite metazoan	1 (2%)		3 (6%)	
Intestine large, rectum	(44)	(47)	(46)	(50)
Parasite metazoan	2 (5%)	5 (11%)	5 (11%)	10 (20%)
Intestine small, duodenum	(47)	(48)	(49)	(49)
Inflammation, chronic active			1 (2%)	
Intestine small, jejunum	(43)	(45)	(43)	(44)
Inflammation, chronic active				1 (2%)
Intestine small, ileum	(40)	(44)	(44)	(46)
Inflammation, chronic active				1 (2%)
Liver	(50)	(50)	(50)	(49)
Basophilic focus	37 (74%)	40 (80%)	37 (74%)	41 (84%)
Clear cell focus	5 (10%)	11 (22%)	6 (12%)	14 (29%)
Cyst		1 (2%)		
Degeneration, cystic			1 (2%)	3 (6%)
Eosinophilic focus	8 (16%)	6 (12%)	3 (6%)	3 (6%)
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	2 (4%)	1 (2%)		
Hepatodiaphragmatic nodule	12 (24%)	6 (12%)	4 (8%)	9 (18%)
Inflammation, chronic active	17 (34%)	13 (26%)	10 (20%)	5 (10%)
Mixed cell focus	2 (4%)	7 (14%)	9 (18%)	7 (14%)
Necrosis	1 (2%)	2 (4%)		1 (2%)
Regeneration		1 (2%)		2 (4%)
Vacuolization cytoplasmic, focal	1 (2%)		1 (2%)	
Bile duct, hyperplasia	1 (2%)	3 (6%)	6 (12%)	
Centrilobular, necrosis				1 (2%)
Centrilobular, vacuolization cytoplasmic	7 (14%)	8 (16%)	6 (12%)	3 (6%)
Mesentery	(5)	(3)	(12)	(10)
Mineralization			1 (8%)	
Fat, inflammation, chronic active	2 (40%)	3 (100%)	10 (83%)	10 (100%)
Fat, mineralization	1 (20%)		3 (25%)	5 (50%)
Fat, necrosis	2 (40%)		2 (17%)	1 (10%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(49)	(49)	(49)
Atrophy		1 (2%)		
Inflammation, chronic active			2 (4%)	
Acinus, atrophy	8 (16%)	7 (14%)	5 (10%)	3 (6%)
Salivary glands	(50)	(49)	(50)	(49)
Inflammation, chronic active			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperkeratosis	1 (2%)			1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)		
Perforation	1 (2%)			
Ulcer	2 (4%)	2 (4%)	1 (2%)	
Epithelium, hyperplasia				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion		1 (2%)		
Mineralization		1 (2%)	1 (2%)	
Ulcer			3 (6%)	
Tongue		(1)		(1)
Angiectasis				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(49)
Thrombosis			1 (2%)	
Epicardium, inflammation, chronic active				2 (4%)
Myocardium, degeneration, chronic	29 (58%)	34 (68%)	40 (80%)	45 (92%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Accessory adrenal cortical nodule	1 (2%)			
Angiectasis	21 (42%)	26 (52%)	15 (30%)	3 (6%)
Hematopoietic cell proliferation		1 (2%)		
Hypertrophy		5 (10%)		
Metaplasia, osseous		1 (2%)		
Mineralization	1 (2%)			
Necrosis	1 (2%)			1 (2%)
Pigmentation			2 (4%)	
Vacuolization cytoplasmic	4 (8%)	5 (10%)	21 (42%)	36 (73%)
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia	5 (10%)	1 (2%)	3 (6%)	13 (27%)
Vacuolization cytoplasmic				1 (2%)
Islets, pancreatic	(49)	(49)	(49)	(49)
Hyperplasia	1 (2%)			
Parathyroid gland	(47)	(46)	(42)	(38)
Hyperplasia			2 (5%)	
Pituitary gland	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)			
Cyst	10 (20%)	9 (18%)	4 (8%)	1 (2%)
Hemorrhage	1 (2%)		2 (4%)	
Hyperplasia	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Mineralization			1 (2%)	1 (2%)
Pars distalis, angiectasis	1 (2%)	1 (2%)	1 (2%)	
Pars distalis, hyperplasia	1 (2%)	2 (4%)	2 (4%)	
Pars nervosa, developmental malformation			1 (2%)	1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(49)	(50)	(49)
Cyst		1 (2%)		1 (2%)
Hyperplasia		1 (2%)		
Ultimobranchial cyst	2 (4%)	1 (2%)		2 (4%)
C-cell, hyperplasia			2 (4%)	
General Body System				
None				
Genital System				
Clitoral gland	(50)	(48)	(50)	(50)
Cyst	6 (12%)	6 (13%)	5 (10%)	2 (4%)
Inflammation			1 (2%)	
Inflammation, chronic active	7 (14%)	8 (17%)	11 (22%)	18 (36%)
Ovary	(50)	(49)	(50)	(49)
Dysgenesis		1 (2%)	43 (86%)	49 (100%)
Corpus luteum, cyst		1 (2%)		
Follicle, cyst		2 (4%)	1 (2%)	1 (2%)
Periovarian tissue, cyst	4 (8%)		4 (8%)	2 (4%)
Uterus	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	2 (4%)	
Hydrometra	3 (6%)	4 (8%)	5 (10%)	6 (12%)
Inflammation, chronic active	1 (2%)			
Cervix, angiectasis				1 (2%)
Cervix, cyst	1 (2%)			1 (2%)
Endometrium, cyst	1 (2%)	1 (2%)	9 (18%)	3 (6%)
Endometrium, hyperplasia, cystic	1 (2%)		4 (8%)	3 (6%)
Endometrium, inflammation, chronic active		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(49)
Hyperplasia		1 (2%)		
Infiltration cellular			1 (2%)	
Myelofibrosis		2 (4%)	2 (4%)	
Lymph node	(4)	(1)	(1)	(1)
Ectasia	1 (25%)			
Lymph node, mandibular	(49)	(48)	(48)	(48)
Congestion	2 (4%)			
Ectasia		1 (2%)	1 (2%)	2 (4%)
Lymph node, mesenteric	(50)	(48)	(49)	(49)
Atrophy	1 (2%)		1 (2%)	
Ectasia		1 (2%)	3 (6%)	4 (8%)
Hemorrhage		1 (2%)		
Inflammation, granulomatous				1 (2%)
Inflammation, suppurative		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(49)	(50)	(49)
Accessory spleen		1 (2%)		1 (2%)
Angiectasis				1 (2%)
Congestion		1 (2%)		
Fibrosis	1 (2%)	1 (2%)	3 (6%)	
Hematopoietic cell proliferation	2 (4%)	6 (12%)		3 (6%)
Hyperplasia, focal	1 (2%)		1 (2%)	
Necrosis			1 (2%)	1 (2%)
Pigmentation, hemosiderin		1 (2%)		
Capsule, fibrosis			1 (2%)	
Lymphoid follicle, depletion cellular	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Thymus	(45)	(47)	(44)	(42)
Atrophy	3 (7%)	2 (4%)	7 (16%)	6 (14%)
Inflammation				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Dilatation	27 (54%)	34 (68%)	13 (27%)	17 (34%)
Galactocele	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Hyperplasia, focal	3 (6%)		1 (2%)	1 (2%)
Lobular, hyperplasia		1 (2%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Parakeratosis				1 (2%)
Ulcer				1 (2%)
Epidermis, cyst			1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(49)	(50)
Osteosclerosis	2 (4%)	2 (4%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Thrombosis		1 (2%)		
Vacuolization cytoplasmic		1 (2%)		
Spinal cord	(1)	(1)	(1)	(2)
Hemorrhage				1 (50%)
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Congestion			1 (2%)	
Cyst, squamous			1 (2%)	
Inflammation, chronic active	8 (16%)	12 (24%)	7 (14%)	17 (35%)
Mineralization	15 (30%)	23 (46%)	33 (66%)	33 (67%)
Necrosis		1 (2%)		
Pigmentation	2 (4%)	1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia	4 (8%)	10 (20%)	4 (8%)	9 (18%)
Alveolar epithelium, metaplasia, squamous		1 (2%)		
Interstitium, fibrosis	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Oxymetholone

	Vehicle Control	3 mg/kg	30 mg/kg	100 mg/kg
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(49)	(50)	(49)	(50)
Inflammation, suppurative	1 (2%)	3 (6%)		
Trachea	(50)	(50)	(50)	(49)
Inflammation, chronic active	1 (2%)			1 (2%)
Special Senses System				
Eye	(2)	(1)		
Lens, mineralization	1 (50%)	1 (100%)		
Retina, degeneration	1 (50%)	1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Congestion			1 (2%)	
Cyst				1 (2%)
Developmental malformation				1 (2%)
Hydronephrosis		1 (2%)		
Inflammation, chronic active	1 (2%)			1 (2%)
Metaplasia, osseous			1 (2%)	
Mineralization	27 (54%)	31 (62%)	35 (70%)	36 (73%)
Necrosis		1 (2%)		
Nephropathy	32 (64%)	26 (52%)	38 (76%)	41 (84%)
Pigmentation, hemosiderin	5 (10%)	7 (14%)	4 (8%)	3 (6%)
Urinary bladder	(50)	(50)	(49)	(50)
Hemorrhage		1 (2%)		
Inflammation, chronic active		3 (6%)	1 (2%)	
Transitional epithelium, hyperplasia			2 (4%)	1 (2%)

APPENDIX C
GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL 182
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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). Oxymetholone was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA1535 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of oxymetholone. In the absence of toxicity, 10,000 μg/plate was selected as the high dose.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOL

Testing was performed as reported by Galloway *et al.* (1987). Oxymetholone was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and three doses of oxymetholone; the high dose was limited by toxicity. A single flask per dose was used.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with oxymetholone for 10 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with oxymetholone and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 14-week toxicity study, peripheral blood samples were obtained from male and female $B6C3F_1$ mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each of five animals per dose group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

EVALUATION PROTOCOL

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and differing results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

RESULTS

In tests conducted by the NTP with oxymetholone, no indication of mutagenicity was observed. Oxymetholone was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535 when tested in a preincubation protocol with and without Aroclor 1254-induced rat or hamster liver S9 (Table C1; Zeiger *et al.*, 1992). Toxicity was not a limiting factor in concentration of oxymetholone tested, but formation of a precipitate was noted at concentrations of 3,333 μg/plate and greater. In tests with cultured CHO cells, no induction of chromosomal aberrations was observed, with or without S9 activation (Table C2). No cell cycle delay was noted in treated cultures, but lethality occurred at concentrations above 22 μg/mL. *In vivo*, no significant increases in the frequency of micronucleated normochromatic erythrocytes were observed in blood obtained from male and female mice at the termination of the 14-week study (Table C3).

TABLE C1
Mutagenicity of Oxymetholone in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/Plate[b] S9 Trial 1	S9 Trial 2	+ hamster S9 10%	+ hamster S9 30%	+ rat S9 10%	+ rat S9 30%
TA100	0	135 ± 16.3	156 ± 1.9	160 ± 2.4	147 ± 9.6	170 ± 9.1	181 ± 2.0
	100	131 ± 15.6	128 ± 7.6	135 ± 13.5	131 ± 2.7	173 ± 13.1	188 ± 1.2
	333	141 ± 12.3	127 ± 9.0	131 ± 10.7	139 ± 9.2	137 ± 7.0	181 ± 2.2
	1,000	121 ± 9.2	137 ± 11.7	130 ± 15.7	95 ± 3.1	140 ± 9.0	164 ± 14.9
	3,333[c]	83 ± 1.2	89 ± 8.7	126 ± 8.1	106 ± 12.2	117 ± 7.3	132 ± 9.2
	10,000[c]	90 ± 7.8	94 ± 5.7	81 ± 6.2	107 ± 11.7	103 ± 1.5	101 ± 8.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,082 ± 40.9	922 ± 82.6	955 ± 39.0	900 ± 12.7	516 ± 10.3	620 ± 25.2
TA1535	0	11 ± 2.4	7 ± 1.7	10 ± 2.4	14 ± 0.0	9 ± 1.9	20 ± 0.3
	100	10 ± 2.6	11 ± 1.2	11 ± 1.7	12 ± 1.9	9 ± 0.3	16 ± 0.3
	333	12 ± 2.5	12 ± 1.7	9 ± 1.0	10 ± 0.9	8 ± 1.9	16 ± 0.9
	1,000	10 ± 2.5	8 ± 2.3	6 ± 2.4	11 ± 1.8	11 ± 1.8	15 ± 2.9
	3,333[c]	9 ± 1.2	7 ± 3.2	6 ± 1.3	10 ± 0.9	7 ± 1.5	11 ± 1.0
	10,000[c]	5 ± 0.3	8 ± 1.5	7 ± 1.0	9 ± 0.3	6 ± 1.2	8 ± 0.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		601 ± 67.2	854 ± 57.4	114 ± 8.4	299 ± 49.9	95 ± 16.5	83 ± 11.1
TA97	0	206 ± 6.6	160 ± 10.7	202 ± 3.8	192 ± 10.8	179 ± 10.3	204 ± 9.5
	100	203 ± 3.2	192 ± 7.2	199 ± 6.8	181 ± 7.2	205 ± 5.5	221 ± 8.9
	333	184 ± 17.9	170 ± 15.0	217 ± 1.9	189 ± 20.8	194 ± 5.2	168 ± 6.8
	1,000	201 ± 6.8	123 ± 6.1	212 ± 13.9	184 ± 13.3	200 ± 3.2	174 ± 5.3
	3,333[c]	185 ± 14.6	102 ± 25.0	193 ± 14.2	202 ± 5.8	202 ± 6.7	131 ± 11.0
	10,000[c]	137 ± 13.0	58 ± 7.8	165 ± 12.8	153 ± 5.0	134 ± 11.5	37 ± 3.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		335 ± 25.2	740 ± 15.2	573 ± 24.4	549 ± 47.2	393 ± 20.6	410 ± 18.9
TA98	0	22 ± 3.8	36 ± 2.4	35 ± 1.7	42 ± 2.2	39 ± 0.3	34 ± 3.3
	100	21 ± 2.7	33 ± 3.8	40 ± 5.2	39 ± 0.6	32 ± 3.0	24 ± 3.8
	333	18 ± 3.7	23 ± 1.2	32 ± 2.9	31 ± 1.2	32 ± 2.3	24 ± 6.7
	1,000	15 ± 1.9	26 ± 3.2	32 ± 4.8	35 ± 1.7	31 ± 1.2	21 ± 2.0
	3,333[c]	12 ± 0.9	31 ± 3.5	27 ± 1.7	32 ± 1.2	30 ± 1.2	19 ± 1.9
	10,000[c]	13 ± 2.3	30 ± 0.9	27 ± 2.7	27 ± 5.9	16 ± 1.9	21 ± 4.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		316 ± 14.3	654 ± 57.2	934 ± 35.5	525 ± 45.2	408 ± 21.2	102 ± 7.6

[a] Study was performed at SRI International. The detailed protocol and these data are presented by Zeiger *et al.* (1992). 0 μg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Precipitate on plate
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE C2
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Oxymetholone[a]

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
S9					
Harvest time: 12.0 hours					
Summary: Negative					
Dimethylsulfoxide[b]		200	2	0.01	0.5
Mitomycin-C[c]	0.4	25	16	0.64	32.0
Oxymetholone	4.7	200	2	0.01	1.0
	10	200	1	0.01	0.5
	22	200	2	0.01	1.0
					P=0.355[d]
+S9					
Harvest time: 12.0 hours					
Summary: Negative					
Dimethylsulfoxide		200	0	0.00	0.0
Cyclophosphamide[c]	20	25	25	1.00	56.0
Oxymetholone	4.7	200	7	0.04	0.5
	10	200	2	0.01	1.0
	22	200	4	0.02	2.0
					P=0.014

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by Galloway *et al*. (1987).
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE C3
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with Oxymetholone by Gavage for 14 Weeks[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/1,000 NCEs[b]	NCEs[b] (%)
Male				
Control		5	1.20 ± 0.34	95.90 ± 0.32
Oxymetholone	160	5	1.00 ± 0.16	95.80 ± 0.48
	320	5	1.80 ± 0.34	96.40 ± 0.22
	630	5	1.00 ± 0.16	96.00 ± 0.23
	1,250	5	1.60 ± 0.48	96.50 ± 0.26
	2,500	5	1.90 ± 0.37	96.56 ± 0.33
			P=0.059[c]	
Female				
Control		5	1.10 ± 0.48	96.66 ± 0.55
Oxymetholone	160	5	1.50 ± 0.22	97.16 ± 0.29
	320	5	1.40 ± 0.24	96.82 ± 0.49
	630	5	1.70 ± 0.44	97.40 ± 0.32
	1,250	5	1.20 ± 0.46	96.76 ± 0.33
	2,500	5	1.90 ± 0.37	97.26 ± 0.33
			P=0.136	

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by MacGregor *et al*. (1990). NCE=normochromatic erythrocyte.
[b] Mean ± standard error
[c] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)

APPENDIX D
HEMATOLOGY
AND CLINICAL CHEMISTRY RESULTS

TABLE D1 **Hematology and Clinical Chemistry Data for Rats in the 14-Week Gavage Study of Oxymetholone** **188**

TABLE D1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Gavage Study of Oxymetholone[a]

	Vehicle Control	80 mg/kg	160 mg/kg	315 mg/kg	625 mg/kg	1,250 mg/kg
Male						
n						
Day 5	10	10	10	10	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	9
Hematology						
Hematocrit (%)						
Day 5	42.4 ± 0.5	41.9 ± 0.6	43.2 ± 0.5	43.6 ± 0.4	44.2 ± 0.5*	44.2 ± 0.6*
Day 19	44.2 ± 0.5	43.3 ± 0.4	45.3 ± 0.5	46.8 ± 0.5**	46.5 ± 0.7**	46.0 ± 0.5**
Week 14	47.9 ± 0.3	47.4 ± 0.5	48.2 ± 0.4	48.5 ± 0.4	50.1 ± 0.6**	48.3 ± 0.5
Hemoglobin (g/dL)						
Day 5	14.3 ± 0.1	14.2 ± 0.2	14.6 ± 0.1	14.6 ± 0.1	14.9 ± 0.2*	14.9 ± 0.2*
Day 19	15.3 ± 0.2	15.0 ± 0.1	15.5 ± 0.2	15.8 ± 0.2*	15.7 ± 0.2	15.5 ± 0.2
Week 14	15.8 ± 0.2	15.8 ± 0.1	16.1 ± 0.1	16.1 ± 0.1	16.3 ± 0.2	15.7 ± 0.2
Erythrocytes ($10^6/\mu L$)						
Day 5	6.59 ± 0.11	6.53 ± 0.12	6.73 ± 0.12	6.71 ± 0.09	6.96 ± 0.12	6.93 ± 0.13
Day 19	7.28 ± 0.12	7.23 ± 0.11	7.54 ± 0.13	7.74 ± 0.10*	7.84 ± 0.17*	7.67 ± 0.12*
Week 14	8.76 ± 0.09	9.23 ± 0.08**	9.36 ± 0.08**	9.32 ± 0.07**	9.50 ± 0.10**	9.02 ± 0.10**
Reticulocytes ($10^6/\mu L$)						
Day 5	0.29 ± 0.02	0.26 ± 0.01	0.24 ± 0.01	0.29 ± 0.02	0.24 ± 0.02	0.23 ± 0.02
Day 19	0.16 ± 0.02	0.15 ± 0.01	0.10 ± 0.01**	0.10 ± 0.01**	0.09 ± 0.01**	0.12 ± 0.01**
Week 14	0.20 ± 0.02	0.16 ± 0.02	0.19 ± 0.02	0.16 ± 0.01	0.21 ± 0.01	0.20 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)						
Day 5	0.02 ± 0.01	0.03 ± 0.01	0.07 ± 0.02	0.01 ± 0.01	0.03 ± 0.02	0.05 ± 0.02
Day 19	0.01 ± 0.01	0.04 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)						
Day 5	64.4 ± 0.4	64.3 ± 0.4	64.2 ± 0.7	65.0 ± 0.5	63.6 ± 0.5	63.8 ± 0.6
Day 19	60.8 ± 0.5	60.0 ± 0.5	60.1 ± 0.4	60.5 ± 0.4	59.3 ± 0.5	59.9 ± 0.4
Week 14	54.7 ± 0.3	51.3 ± 0.3**	51.5 ± 0.2**	52.0 ± 0.1**	52.8 ± 0.3	53.6 ± 0.2
Mean cell hemoglobin (pg)						
Day 5	21.7 ± 0.2	21.8 ± 0.2	21.7 ± 0.2	21.8 ± 0.1	21.4 ± 0.3	21.5 ± 0.2
Day 19	21.0 ± 0.2	20.7 ± 0.2	20.5 ± 0.2	20.5 ± 0.1	20.1 ± 0.2**	20.2 ± 0.2**
Week 14	18.0 ± 0.1	17.1 ± 0.1**	17.2 ± 0.1**	17.3 ± 0.1*	17.2 ± 0.1**	17.4 ± 0.2
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.6 ± 0.2	33.9 ± 0.2	33.8 ± 0.3	33.6 ± 0.1	33.6 ± 0.3	33.7 ± 0.2
Day 19	34.6 ± 0.2	34.6 ± 0.1	34.2 ± 0.1	33.8 ± 0.2**	33.9 ± 0.2*	33.8 ± 0.3*
Week 14	32.9 ± 0.3	33.3 ± 0.2	33.4 ± 0.2	33.3 ± 0.2	32.5 ± 0.1	32.4 ± 0.2
Platelets ($10^3/\mu L$)						
Day 5	932.2 ± 19.7	884.2 ± 50.7	924.5 ± 26.1	976.3 ± 14.0	962.1 ± 33.2	985.2 ± 16.7
Day 19	854.5 ± 15.3	842.9 ± 23.1	826.5 ± 14.9	801.9 ± 9.0*	797.4 ± 16.4*	759.3 ± 18.7**
Week 14	730.8 ± 11.6	781.6 ± 14.9*	799.9 ± 13.3**	803.5 ± 10.6**	764.9 ± 24.4	744.6 ± 12.9
Leukocytes ($10^3/\mu L$)						
Day 5	6.28 ± 0.24	6.17 ± 0.22	7.47 ± 0.45	7.29 ± 0.29*	7.68 ± 0.38**	8.82 ± 0.34**
Day 19	7.36 ± 0.20	7.53 ± 0.27	7.00 ± 0.40	6.87 ± 0.41	7.87 ± 0.47	6.67 ± 0.37
Week 14	7.99 ± 0.22	7.33 ± 0.23	6.47 ± 0.18**	7.23 ± 0.24**	6.57 ± 0.27**	6.69 ± 0.33**
Segmented neutrophils ($10^3/\mu L$)						
Day 5	0.63 ± 0.07	0.72 ± 0.08	0.83 ± 0.07	0.94 ± 0.09**	1.13 ± 0.15**	1.37 ± 0.17**
Day 19	0.91 ± 0.08	0.77 ± 0.06	0.91 ± 0.11	1.11 ± 0.14	1.38 ± 0.16*	1.23 ± 0.11*
Week 14	1.47 ± 0.24	1.14 ± 0.09	1.36 ± 0.07	2.01 ± 0.17*	1.88 ± 0.15*	2.12 ± 0.18**

TABLE D1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Gavage Study of Oxymetholone

	Vehicle Control	80 mg/kg	160 mg/kg	315 mg/kg	625 mg/kg	1,250 mg/kg
Male (continued)						
n						
Day 5	10	10	10	10	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	9
Hematology (continued)						
Lymphocytes ($10^3/\mu L$)						
Day 5	5.55 ± 0.22	5.38 ± 0.19	6.57 ± 0.40	6.21 ± 0.25	6.47 ± 0.29*	7.35 ± 0.28**
Day 19	6.30 ± 0.21	6.60 ± 0.23	6.00 ± 0.31	5.61 ± 0.32	6.36 ± 0.34	5.34 ± 0.30
Week 14	6.37 ± 0.31	6.03 ± 0.15	5.01 ± 0.20**	5.10 ± 0.28**	4.65 ± 0.20**	4.40 ± 0.19**
Monocytes ($10^3/\mu L$)						
Day 5	0.05 ± 0.02	0.04 ± 0.02	0.05 ± 0.02	0.09 ± 0.03	0.07 ± 0.01	0.08 ± 0.02
Day 19	0.09 ± 0.01	0.11 ± 0.03	0.06 ± 0.02	0.09 ± 0.02	0.08 ± 0.03	0.06 ± 0.02
Week 14	0.08 ± 0.02	0.05 ± 0.02	0.03 ± 0.01	0.07 ± 0.02	0.03 ± 0.02	0.05 ± 0.02
Eosinophils ($10^3/\mu L$)						
Day 5	0.06 ± 0.02	0.02 ± 0.02	0.02 ± 0.01	0.05 ± 0.02	0.01 ± 0.01	0.03 ± 0.01
Day 19	0.07 ± 0.02	0.05 ± 0.02	0.03 ± 0.02	0.07 ± 0.03	0.04 ± 0.02	0.05 ± 0.02
Week 14	0.08 ± 0.02	0.11 ± 0.03	0.06 ± 0.02	0.04 ± 0.02	0.02 ± 0.01	0.12 ± 0.04
Fibrinogen (mg/dL)						
Week 14	217.1 ± 2.0	241.7 ± 5.6*	220.9 ± 4.2	222.7 ± 5.3	209.2 ± 5.8	224.9 ± 8.0
Activated partial thromboplastin time (seconds)						
Week 14	21.8 ± 0.3	20.4 ± 0.3**	20.1 ± 0.3**	19.7 ± 0.3**	20.1 ± 0.8**[b]	19.9 ± 0.6**
Thromboplastin time (seconds)						
Week 14	15.2 ± 0.3	15.3 ± 0.3	15.5 ± 0.3	15.8 ± 0.3	14.8 ± 0.4[c]	16.2 ± 0.7
Clinical Chemistry						
Creatinine (mg/dL)						
Day 5	0.62 ± 0.01	0.61 ± 0.01	0.59 ± 0.01	0.59 ± 0.01	0.58 ± 0.02*	0.56 ± 0.02**
Day 19	0.62 ± 0.01	0.61 ± 0.01	0.57 ± 0.02*	0.56 ± 0.02**	0.54 ± 0.02**	0.54 ± 0.02**
Week 14	0.70 ± 0.00	0.66 ± 0.03	0.59 ± 0.01**	0.60 ± 0.02**	0.50 ± 0.00**	0.51 ± 0.01**
Total protein (g/dL)						
Day 5	6.2 ± 0.1	6.2 ± 0.1	6.1 ± 0.1	5.8 ± 0.0**	5.8 ± 0.1**	5.7 ± 0.1**
Day 19	6.5 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.5 ± 0.1	6.3 ± 0.1
Week 14	7.0 ± 0.1	6.9 ± 0.1	7.1 ± 0.1	6.9 ± 0.0	6.4 ± 0.1**	6.3 ± 0.1**
Albumin (g/dL)						
Day 5	4.4 ± 0.0	4.4 ± 0.1	4.4 ± 0.1	4.3 ± 0.0	4.2 ± 0.1*	4.1 ± 0.1**
Day 19	4.6 ± 0.0	4.5 ± 0.0	4.5 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.7 ± 0.1
Week 14	4.9 ± 0.1	5.0 ± 0.1	5.2 ± 0.0**	5.1 ± 0.0	4.9 ± 0.1	4.7 ± 0.1
Cholesterol (mg/dL)						
Day 5	82 ± 2	61 ± 2**	54 ± 3**	37 ± 2**	33 ± 3**	31 ± 3**
Day 19	73 ± 1	48 ± 1**	38 ± 1**	29 ± 2**	30 ± 2**	25 ± 2**
Week 14	85 ± 3	32 ± 1**	26 ± 1**	21 ± 2**	19 ± 2**	21 ± 3**
Triglycerides (mg/dL)						
Day 5	159 ± 14	183 ± 18	265 ± 35*	282 ± 26**	214 ± 41*	227 ± 34*
Day 19	242 ± 16	273 ± 36	325 ± 38	369 ± 41*	298 ± 47	295 ± 25
Week 14	298 ± 30	283 ± 15	215 ± 19	293 ± 40	446 ± 45*	405 ± 43*
Alanine aminotransferase (IU/L)						
Day 5	39 ± 2	42 ± 2	45 ± 2*	45 ± 2*	52 ± 4**	50 ± 4**
Day 19	39 ± 2	36 ± 1	39 ± 1	40 ± 1	45 ± 3	42 ± 3
Week 14	53 ± 2	49 ± 2	44 ± 2**	43 ± 1**	36 ± 3**	39 ± 2**

TABLE D1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Gavage Study of Oxymetholone

	Vehicle Control	80 mg/kg	160 mg/kg	315 mg/kg	625 mg/kg	1,250 mg/kg
Male (continued)						
n						
Day 5	10	10	10	10	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	9
Clinical Chemistry (continued)						
Creatine kinase (IU/L)						
Day 5	739 ± 59	788 ± 110	718 ± 84	726 ± 65	1,105 ± 231	804 ± 88
Day 19	524 ± 90[d]	384 ± 29	443 ± 51	470 ± 84	561 ± 96	594 ± 145
Week 14	243 ± 32	261 ± 54	285 ± 42	260 ± 20	264 ± 26	334 ± 41
Sorbitol dehydrogenase (IU/L)						
Day 5	21 ± 1	22 ± 1	21 ± 1	19 ± 1	21 ± 2	22 ± 2
Day 19	21 ± 1	19 ± 1	18 ± 1*	16 ± 1**	19 ± 1*	16 ± 1**
Week 14	20 ± 1	18 ± 1	17 ± 1*	17 ± 1*	21 ± 5**	22 ± 6*
5′-Nucleotidase (IU/L)						
Day 5	33 ± 1	31 ± 1	29 ± 1**	24 ± 1**	24 ± 2**	21 ± 1**
Day 19	31 ± 1	27 ± 1**	25 ± 0**	21 ± 1**	19 ± 1**	18 ± 1**
Week 14	36 ± 1	29 ± 1**	25 ± 1**	20 ± 1**	18 ± 1**	19 ± 1**
Bile salts (μmol/L)						
Day 5	46.7 ± 7.6	32.2 ± 3.4	38.6 ± 5.9	49.8 ± 4.5	40.6 ± 5.3	34.1 ± 4.1
Day 19	34.4 ± 4.4	36.1 ± 4.6	43.4 ± 3.6	52.3 ± 3.0**	46.0 ± 3.0	38.5 ± 2.5
Week 14	19.4 ± 2.4	25.8 ± 3.9	26.8 ± 3.6	33.8 ± 3.6**	30.7 ± 2.3*	31.9 ± 2.7**
Female						
n						
Day 5	10	10	10	10	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Hematology						
Hematocrit (%)						
Day 5	44.1 ± 0.7	44.3 ± 0.6	43.8 ± 0.4	43.8 ± 0.4	43.3 ± 0.4	43.7 ± 0.6
Day 19	46.8 ± 0.3	45.7 ± 0.5	44.8 ± 0.4*	45.1 ± 0.4	46.6 ± 0.5	46.8 ± 0.4
Week 14	45.0 ± 0.8	48.3 ± 0.4**	49.0 ± 0.4**	49.5 ± 0.5**	51.9 ± 0.5**	52.1 ± 0.9**
Hemoglobin (g/dL)						
Day 5	14.8 ± 0.2	14.8 ± 0.1	14.8 ± 0.1	14.8 ± 0.1	14.7 ± 0.1	14.9 ± 0.2
Day 19	15.8 ± 0.1	15.6 ± 0.1	15.5 ± 0.2	15.5 ± 0.1	16.0 ± 0.2	16.1 ± 0.1
Week 14	15.3 ± 0.3	16.5 ± 0.1**	16.4 ± 0.1**	16.3 ± 0.1**	16.8 ± 0.1**	16.9 ± 0.3**
Erythrocytes (10^6/μL)						
Day 5	6.83 ± 0.13	6.94 ± 0.11	6.82 ± 0.06	6.84 ± 0.09	6.81 ± 0.09	6.87 ± 0.10
Day 19	7.37 ± 0.07	7.33 ± 0.10	7.33 ± 0.06	7.49 ± 0.08	7.69 ± 0.08*	7.75 ± 0.08**
Week 14	7.69 ± 0.15	8.85 ± 0.07**	9.26 ± 0.06**	9.18 ± 0.06**	9.54 ± 0.09**	9.37 ± 0.18**
Reticulocytes (10^6/μL)						
Day 5	0.22 ± 0.02	0.25 ± 0.02	0.24 ± 0.01	0.26 ± 0.02	0.26 ± 0.02	0.24 ± 0.03
Day 19	0.11 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.06 ± 0.00**	0.08 ± 0.01**
Week 14	0.18 ± 0.01	0.19 ± 0.01	0.16 ± 0.02	0.18 ± 0.01	0.18 ± 0.02	0.15 ± 0.01
Nucleated erythrocytes (10^3/μL)						
Day 5	0.02 ± 0.01	0.05 ± 0.02	0.07 ± 0.03	0.06 ± 0.03	0.05 ± 0.01	0.08 ± 0.03*
Day 19	0.01 ± 0.01	0.03 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

TABLE D1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Gavage Study of Oxymetholone

	Vehicle Control	80 mg/kg	160 mg/kg	315 mg/kg	625 mg/kg	1,250 mg/kg
Female (continued)						
n						
Day 5	10	10	10	10	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Hematology (continued)						
Mean cell volume (fL)						
Day 5	64.6 ± 0.3	63.9 ± 0.4	64.3 ± 0.2	64.0 ± 0.4	63.6 ± 0.4	63.6 ± 0.3*
Day 19	63.5 ± 0.2	62.3 ± 0.3*	61.1 ± 0.2**	60.3 ± 0.2**	60.6 ± 0.3**	60.3 ± 0.2**
Week 14	58.5 ± 0.2	54.6 ± 0.2**	52.9 ± 0.1**	53.9 ± 0.3**	54.4 ± 0.2**	55.6 ± 0.3
Mean cell hemoglobin (pg)						
Day 5	21.7 ± 0.2	21.3 ± 0.2	21.6 ± 0.1	21.6 ± 0.2	21.6 ± 0.2	21.7 ± 0.2
Day 19	21.4 ± 0.1	21.2 ± 0.2	21.1 ± 0.1	20.8 ± 0.1**	20.8 ± 0.1**	20.7 ± 0.1**
Week 14	19.9 ± 0.1	18.6 ± 0.1**	17.7 ± 0.1**	17.8 ± 0.1**	17.6 ± 0.1**	18.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.6 ± 0.3	33.4 ± 0.2	33.7 ± 0.1	33.8 ± 0.2	33.9 ± 0.2	34.1 ± 0.3
Day 19	33.7 ± 0.1	34.1 ± 0.2	34.6 ± 0.2**	34.4 ± 0.2**	34.2 ± 0.1**	34.4 ± 0.2**
Week 14	34.0 ± 0.2	34.1 ± 0.1	33.4 ± 0.2*	33.0 ± 0.3**	32.3 ± 0.2**	32.4 ± 0.3**
Platelets ($10^3/\mu L$)						
Day 5	869.7 ± 12.4	905.4 ± 17.3	886.7 ± 19.2	879.1 ± 28.0	946.0 ± 21.5**	914.4 ± 6.8*
Day 19	826.3 ± 16.6	832.5 ± 13.2	886.2 ± 13.4*	861.7 ± 13.4	837.7 ± 12.1	824.4 ± 26.4
Week 14	641.7 ± 21.2	726.1 ± 12.1*	752.1 ± 10.7**	757.3 ± 9.8**	653.6 ± 14.4	690.0 ± 15.8
Leukocytes ($10^3/\mu L$)						
Day 5	6.08 ± 0.20	6.44 ± 0.33	7.14 ± 0.30*	7.35 ± 0.28**	7.95 ± 0.36**	7.89 ± 0.46**
Day 19	6.90 ± 0.33	7.52 ± 0.62	7.93 ± 0.39	7.66 ± 0.40	7.99 ± 0.52	8.67 ± 0.50*
Week 14	7.51 ± 0.46	9.69 ± 0.72	8.22 ± 0.44	7.86 ± 0.58	7.50 ± 0.69	8.32 ± 0.58
Segmented neutrophils ($10^3/\mu L$)						
Day 5	0.59 ± 0.08	0.70 ± 0.08	0.91 ± 0.06**	1.07 ± 0.12**	1.08 ± 0.12**	1.22 ± 0.15**
Day 19	0.57 ± 0.07	0.71 ± 0.10	0.78 ± 0.10	1.14 ± 0.10**	1.24 ± 0.13**	1.41 ± 0.19**
Week 14	1.55 ± 0.21	2.06 ± 0.47	2.05 ± 0.25	2.02 ± 0.22	2.21 ± 0.27	2.50 ± 0.22**
Lymphocytes ($10^3/\mu L$)						
Day 5	5.41 ± 0.18	5.63 ± 0.32	6.09 ± 0.22	6.11 ± 0.20	6.73 ± 0.32**	6.52 ± 0.41*
Day 19	6.19 ± 0.31	6.69 ± 0.56	7.08 ± 0.40	6.42 ± 0.37	6.65 ± 0.43	7.14 ± 0.39
Week 14	5.86 ± 0.47	7.47 ± 0.44	6.05 ± 0.42	5.72 ± 0.52	5.17 ± 0.51	5.77 ± 0.48
Monocytes ($10^3/\mu L$)						
Day 5	0.06 ± 0.02	0.07 ± 0.03	0.09 ± 0.02	0.11 ± 0.02	0.08 ± 0.03	0.12 ± 0.02
Day 19	0.08 ± 0.02	0.07 ± 0.02	0.03 ± 0.01	0.06 ± 0.02	0.08 ± 0.02	0.08 ± 0.03
Week 14	0.07 ± 0.02	0.04 ± 0.02	0.06 ± 0.02	0.03 ± 0.01	0.05 ± 0.02	0.03 ± 0.02
Eosinophils ($10^3/\mu L$)						
Day 5	0.02 ± 0.01	0.04 ± 0.01	0.05 ± 0.02	0.07 ± 0.02	0.06 ± 0.02	0.03 ± 0.01
Day 19	0.06 ± 0.02	0.05 ± 0.02	0.04 ± 0.01	0.04 ± 0.02	0.02 ± 0.01	0.04 ± 0.02
Week 14	0.04 ± 0.02	0.11 ± 0.02	0.06 ± 0.02	0.09 ± 0.02	0.06 ± 0.02	0.03 ± 0.01
Fibrinogen (mg/dL)						
Week 14	170.2 ± 3.5	200.3 ± 4.0**[d]	194.4 ± 4.8**	179.5 ± 5.6	177.6 ± 3.4	184.0 ± 4.9
Activated partial thromboplastin time (seconds)						
Week 14	20.8 ± 0.3	21.7 ± 0.4	20.9 ± 0.3	20.3 ± 0.7	22.0 ± 0.4*	21.9 ± 0.4*
Thromboplastin time (seconds)						
Week 14	14.3 ± 0.4	16.7 ± 0.4**	16.7 ± 0.5**	17.4 ± 0.7**	18.8 ± 0.6**	18.1 ± 0.4**

TABLE D1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Gavage Study of Oxymetholone

	Vehicle Control	80 mg/kg	160 mg/kg	315 mg/kg	625 mg/kg	1,250 mg/kg
Female (continued)						
n						
Day 5	10	10	10	10	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Clinical Chemistry						
Creatinine (mg/dL)						
Day 5	0.62 ± 0.01	0.63 ± 0.02	0.61 ± 0.01	0.59 ± 0.01	0.60 ± 0.00	0.57 ± 0.02*
Day 19	0.64 ± 0.02	0.62 ± 0.01	0.64 ± 0.03	0.59 ± 0.01*	0.57 ± 0.02**	0.56 ± 0.02**
Week 14	0.64 ± 0.02	0.57 ± 0.02*	0.52 ± 0.02**	0.49 ± 0.01**	0.46 ± 0.02**	0.46 ± 0.02**
Total protein (g/dL)						
Day 5	5.9 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	5.8 ± 0.0	5.7 ± 0.1*	5.5 ± 0.1**
Day 19	6.3 ± 0.1	6.1 ± 0.1*	6.2 ± 0.1	6.0 ± 0.1**	5.9 ± 0.1**	6.1 ± 0.0**
Week 14	6.7 ± 0.1	6.5 ± 0.1	6.6 ± 0.1	6.4 ± 0.1*	6.1 ± 0.1**	6.1 ± 0.1**
Albumin (g/dL)						
Day 5	4.3 ± 0.0	4.3 ± 0.0	4.3 ± 0.0	4.3 ± 0.0	4.3 ± 0.0	4.2 ± 0.1
Day 19	4.6 ± 0.0	4.4 ± 0.1	4.5 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	4.5 ± 0.1
Week 14	4.8 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	4.9 ± 0.1	4.7 ± 0.1	4.6 ± 0.1
Cholesterol (mg/dL)						
Day 5	94 ± 3	84 ± 2*	78 ± 2**	68 ± 2**	60 ± 2**	43 ± 1**
Day 19	90 ± 2[d]	72 ± 2**	53 ± 2**	42 ± 3**	28 ± 2**	29 ± 1**
Week 14	95 ± 2	44 ± 2**	25 ± 2**	23 ± 2**	19 ± 2**	22 ± 1**
Triglycerides (mg/dL)						
Day 5	146 ± 22	161 ± 10	156 ± 10	172 ± 15	179 ± 16	125 ± 19
Day 19	127 ± 10	170 ± 8	237 ± 25*	262 ± 41*	156 ± 39	156 ± 46
Week 14	152 ± 13	398 ± 66**	192 ± 45	216 ± 38	237 ± 42	268 ± 28*
Alanine aminotransferase (IU/L)						
Day 5	37 ± 1	40 ± 1	43 ± 1**	41 ± 1**	49 ± 2**	51 ± 3**
Day 19	31 ± 1	35 ± 1**	38 ± 1**	35 ± 1**	48 ± 2**	44 ± 3**
Week 14	48 ± 3	45 ± 2	45 ± 1	48 ± 2	48 ± 2	45 ± 2
Creatine kinase (IU/L)						
Day 5	580 ± 47	602 ± 75	575 ± 68	568 ± 77	595 ± 79	782 ± 164
Day 19	491 ± 42	444 ± 65	633 ± 130	476 ± 68	734 ± 158	841 ± 186
Week 14	233 ± 37	273 ± 70	276 ± 41	385 ± 97	275 ± 47	243 ± 37
Sorbitol dehydrogenase (IU/L)						
Day 5	20 ± 1	18 ± 1	20 ± 1	18 ± 1	19 ± 1	22 ± 2
Day 19	24 ± 2	22 ± 1	22 ± 1	20 ± 1	21 ± 1	20 ± 1
Week 14	19 ± 1	29 ± 6	21 ± 2	21 ± 1	20 ± 3	26 ± 5
5′-Nucleotidase (IU/L)						
Day 5	36 ± 1	38 ± 1	37 ± 1	33 ± 1	31 ± 1**	28 ± 1**
Day 19	37 ± 2	38 ± 1	31 ± 1**	24 ± 1**	19 ± 1**	19 ± 1**
Week 14	35 ± 1	27 ± 1**	23 ± 1**	20 ± 1**	19 ± 1**[d]	19 ± 1**
Bile salts (μmol/L)						
Day 5	45.7 ± 3.6	37.3 ± 4.1	38.3 ± 2.4	39.2 ± 3.4	34.2 ± 2.9*	26.4 ± 2.1**[d]
Day 19	31.2 ± 1.7	27.9 ± 2.4	41.2 ± 6.5	35.0 ± 2.8	48.5 ± 3.7**	45.2 ± 3.7**
Week 14	36.3 ± 5.7	31.5 ± 2.9	23.6 ± 2.6	25.6 ± 2.6	28.4 ± 3.7	29.9 ± 3.4

* Significantly different (P≤0.05) from the vehicle control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8
[c] n=7
[d] n=9

APPENDIX E
TISSUE WEIGHTS AND TISSUE-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE E1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Gavage Study of Oxymetholone 194

TABLE E2 Tissue Weights and Tissue-Weight-to-Body-Weight Ratios for Rats in the 14-Week Gavage Study of Oxymetholone 195

TABLE E3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Gavage Study of Oxymetholone 196

TABLE E1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Gavage Study of Oxymetholone[a]

	Vehicle Control	80 mg/kg	160 mg/kg	315 mg/kg	625 mg/kg	1,250 mg/kg
Male						
n	10	10	10	10	9	9
Necropsy body wt	381 ± 3	357 ± 7*	331 ± 9**	305 ± 5**	279 ± 9**	270 ± 2**
Heart						
Absolute	1.117 ± 0.018	1.043 ± 0.024	1.058 ± 0.034	1.042 ± 0.021	0.949 ± 0.029**	1.007 ± 0.022*
Relative	2.93 ± 0.04	2.92 ± 0.03	3.19 ± 0.06**	3.42 ± 0.05**	3.40 ± 0.03**	3.73 ± 0.08**
R. Kidney						
Absolute	1.358 ± 0.028	1.394 ± 0.029	1.477 ± 0.052	1.658 ± 0.052**	1.769 ± 0.056**	2.138 ± 0.042**
Relative	3.56 ± 0.07	3.91 ± 0.08	4.46 ± 0.12**	5.43 ± 0.15**	6.36 ± 0.20**	7.92 ± 0.16**
Liver						
Absolute	14.819 ± 0.386	14.681 ± 0.312	13.580 ± 0.575	12.866 ± 0.350**	12.388 ± 0.441**	12.431 ± 0.489**
Relative	38.84 ± 0.81	41.21 ± 0.86	40.98 ± 1.38	42.14 ± 0.87	44.41 ± 1.16**	46.01 ± 1.68**
Lung						
Absolute	2.105 ± 0.062	1.897 ± 0.074	1.735 ± 0.076**	1.628 ± 0.041**	1.436 ± 0.051**	1.513 ± 0.063**
Relative	5.52 ± 0.13	5.32 ± 0.21	5.24 ± 0.20	5.34 ± 0.15	5.15 ± 0.13	5.60 ± 0.22
R. Testis						
Absolute	1.529 ± 0.023	1.174 ± 0.025**	1.051 ± 0.034**	0.936 ± 0.027**	0.879 ± 0.021**	0.909 ± 0.024**
Relative	4.01 ± 0.06	3.29 ± 0.04**	3.17 ± 0.07**	3.07 ± 0.07**	3.16 ± 0.07**	3.37 ± 0.09**
Thymus						
Absolute	0.328 ± 0.018	0.286 ± 0.019[b]	0.244 ± 0.011**	0.197 ± 0.010**	0.156 ± 0.011**	0.137 ± 0.010**
Relative	0.86 ± 0.04	0.79 ± 0.05[b]	0.74 ± 0.04	0.65 ± 0.03**	0.56 ± 0.03**	0.51 ± 0.04**
Female						
n	10	10	10	10	10	9
Necropsy body wt	198 ± 4	258 ± 5**	256 ± 6**	230 ± 4**	222 ± 4**	219 ± 4*
Heart						
Absolute	0.679 ± 0.012	0.789 ± 0.011**	0.857 ± 0.026**	0.777 ± 0.014**	0.811 ± 0.027**	0.816 ± 0.029**
Relative	3.43 ± 0.06	3.07 ± 0.05**	3.35 ± 0.06	3.38 ± 0.07	3.65 ± 0.06	3.73 ± 0.09*
R. Kidney						
Absolute	0.701 ± 0.010	0.980 ± 0.014**	1.169 ± 0.043**	1.204 ± 0.033**	1.388 ± 0.035**	1.521 ± 0.037**
Relative	3.55 ± 0.06	3.82 ± 0.08	4.56 ± 0.10**	5.23 ± 0.12**	6.27 ± 0.12**	6.96 ± 0.10**
Liver						
Absolute	6.474 ± 0.192	9.731 ± 0.131**	9.602 ± 0.486**	9.047 ± 0.324**	9.114 ± 0.285**	9.668 ± 0.205**
Relative	32.66 ± 0.70	37.86 ± 0.63**	37.41 ± 1.42**	39.26 ± 1.13**	41.08 ± 0.77**	44.27 ± 0.76**
Lung						
Absolute	1.335 ± 0.028	1.388 ± 0.050	1.353 ± 0.071	1.284 ± 0.053	1.246 ± 0.056	1.201 ± 0.045
Relative	6.75 ± 0.14	5.42 ± 0.27**	5.28 ± 0.24**	5.60 ± 0.27**	5.65 ± 0.29*	5.50 ± 0.21**
Thymus						
Absolute	0.245 ± 0.008	0.251 ± 0.008	0.209 ± 0.009*	0.144 ± 0.006**	0.132 ± 0.008**	0.110 ± 0.010**
Relative	1.24 ± 0.03	0.98 ± 0.03**	0.82 ± 0.04**	0.63 ± 0.03**	0.59 ± 0.03**	0.50 ± 0.04**
Uterus						
Absolute	0.609 ± 0.074	0.530 ± 0.019	0.783 ± 0.043	1.742 ± 0.139**	1.448 ± 0.156**	1.607 ± 0.283**
Relative	3.10 ± 0.40	2.07 ± 0.09	3.08 ± 0.19	7.53 ± 0.54**	6.53 ± 0.71**	7.31 ± 1.22**

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE E2
Tissue Weights and Tissue-Weight-to-Body-Weight Ratios for Rats in the 14-Week Gavage Study of Oxymetholone[a]

	Vehicle Control	80 mg/kg	160 mg/kg	315 mg/kg	625 mg/kg	1,250 mg/kg
Male						
n	10	10	10	10	9	9
Necropsy body wt	381 ± 3	357 ± 7*	331 ± 9**	305 ± 5**	279 ± 9**	270 ± 2**
Gastrocnemius (wet)						
Absolute	1.688 ± 0.149	1.729 ± 0.040	1.458 ± 0.132	1.289 ± 0.126*	1.313 ± 0.048	1.364 ± 0.033
Relative	4.41 ± 0.37	4.87 ± 0.17	4.42 ± 0.41	4.24 ± 0.42	4.71 ± 0.17	5.05 ± 0.11
Gastrocnemius (dry)						
Absolute	0.482 ± 0.045	0.495 ± 0.011	0.414 ± 0.039	0.361 ± 0.036*	0.366 ± 0.015*	0.376 ± 0.011
Relative	1.26 ± 0.11	1.39 ± 0.05	1.26 ± 0.12	1.19 ± 0.12	1.31 ± 0.05	1.39 ± 0.04
Sartorius (wet)						
Absolute	0.467 ± 0.044	0.370 ± 0.021	0.393 ± 0.032	0.352 ± 0.051	0.314 ± 0.027*	0.308 ± 0.045*
Relative	1.22 ± 0.11	1.04 ± 0.07	1.19 ± 0.09	1.16 ± 0.18	1.12 ± 0.09	1.14 ± 0.17
Sartorius (dry)						
Absolute	0.138 ± 0.012	0.105 ± 0.007	0.114 ± 0.008	0.095 ± 0.014*	0.092 ± 0.009*	0.082 ± 0.011**
Relative	0.36 ± 0.03	0.30 ± 0.02	0.34 ± 0.02	0.31 ± 0.05	0.33 ± 0.03	0.30 ± 0.04
Female						
n	10	10	10	10	10	9
Necropsy body wt	198 ± 4	258 ± 5**	256 ± 6**	230 ± 4**	222 ± 4**	219 ± 4*
Gastrocnemius (wet)						
Absolute	1.142 ± 0.042	1.440 ± 0.024**	1.303 ± 0.069*	1.270 ± 0.034	1.227 ± 0.030	1.151 ± 0.051
Relative	5.78 ± 0.25	5.60 ± 0.12	5.08 ± 0.22*	5.52 ± 0.15	5.54 ± 0.11	5.28 ± 0.23
Gastrocnemius (dry)						
Absolute	0.316 ± 0.014	0.405 ± 0.007**	0.363 ± 0.021	0.353 ± 0.011	0.337 ± 0.009	0.313 ± 0.014
Relative	1.60 ± 0.08	1.58 ± 0.04	1.42 ± 0.07	1.53 ± 0.04	1.52 ± 0.03	1.43 ± 0.06
Sartorius (wet)						
Absolute	0.306 ± 0.033	0.357 ± 0.032	0.290 ± 0.029	0.291 ± 0.030	0.380 ± 0.026	0.306 ± 0.016
Relative	1.55 ± 0.17	1.39 ± 0.13	1.14 ± 0.11	1.27 ± 0.13	1.71 ± 0.10	1.41 ± 0.08
Sartorius (dry)						
Absolute	0.086 ± 0.009	0.102 ± 0.011	0.084 ± 0.010	0.082 ± 0.009	0.116 ± 0.009	0.084 ± 0.005
Relative	0.43 ± 0.04	0.40 ± 0.04	0.33 ± 0.04	0.36 ± 0.04	0.52 ± 0.04	0.39 ± 0.02

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Tissue weights (absolute weights) and body weights are given in grams; tissue-weight-to-body-weight ratios (relative weights) are given as mg tissue weight/g body weight (mean ± standard error).

TABLE E3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Gavage Study of Oxymetholone[a]

	Vehicle Control	160 mg/kg	320 mg/kg	630 mg/kg	1,250 mg/kg	2,500 mg/kg
n	10	10	10	10	10	10
Male						
Necropsy body wt	37.6 ± 1.2	40.7 ± 0.9	40.8 ± 1.3	40.3 ± 1.0	38.8 ± 1.5	38.7 ± 0.7
Heart						
Absolute	0.176 ± 0.006	0.183 ± 0.004	0.171 ± 0.004	0.179 ± 0.007	0.169 ± 0.007	0.180 ± 0.011
Relative	4.71 ± 0.19	4.51 ± 0.12	4.20 ± 0.13	4.44 ± 0.17	4.37 ± 0.14	4.65 ± 0.29
R. Kidney						
Absolute	0.315 ± 0.011	0.320 ± 0.007	0.340 ± 0.007	0.346 ± 0.007*	0.370 ± 0.011**	0.415 ± 0.005**
Relative	8.43 ± 0.31	7.89 ± 0.13	8.36 ± 0.17	8.59 ± 0.18	9.61 ± 0.29**	10.74 ± 0.18**
Liver						
Absolute	1.679 ± 0.090	1.757 ± 0.061	1.768 ± 0.072	1.883 ± 0.068	1.944 ± 0.095	2.081 ± 0.050**
Relative	44.54 ± 1.71	43.16 ± 0.92	43.28 ± 0.92	46.64 ± 1.14	50.10 ± 1.06*	53.89 ± 1.41**
Lung						
Absolute	0.232 ± 0.010	0.231 ± 0.006	0.231 ± 0.010	0.266 ± 0.013*	0.224 ± 0.006	0.234 ± 0.007
Relative	6.20 ± 0.25	5.72 ± 0.23	5.66 ± 0.20	6.61 ± 0.32	5.84 ± 0.19	6.07 ± 0.20
R. Testis						
Absolute	0.115 ± 0.002	0.116 ± 0.003	0.114 ± 0.002	0.115 ± 0.002	0.111 ± 0.002	0.110 ± 0.003
Relative	3.08 ± 0.10	2.88 ± 0.10	2.82 ± 0.09	2.86 ± 0.09	2.89 ± 0.09	2.84 ± 0.08
Thymus						
Absolute	0.045 ± 0.005	0.057 ± 0.006	0.047 ± 0.005	0.047 ± 0.003	0.052 ± 0.004	0.047 ± 0.003
Relative	1.18 ± 0.10	1.40 ± 0.14	1.15 ± 0.12	1.17 ± 0.09	1.33 ± 0.08	1.21 ± 0.09
Female						
Necropsy body wt	30.3 ± 1.0	33.7 ± 1.1*	33.2 ± 0.8	31.7 ± 0.9	32.1 ± 0.8	30.5 ± 0.7
Heart						
Absolute	0.139 ± 0.006	0.142 ± 0.004	0.152 ± 0.006	0.147 ± 0.004	0.154 ± 0.007	0.148 ± 0.002
Relative	4.67 ± 0.27	4.26 ± 0.20	4.58 ± 0.17	4.66 ± 0.17	4.83 ± 0.23	4.85 ± 0.08
R. Kidney						
Absolute	0.190 ± 0.004	0.243 ± 0.004**	0.271 ± 0.006**	0.272 ± 0.004**	0.309 ± 0.005**	0.326 ± 0.010**
Relative	6.30 ± 0.17	7.25 ± 0.22*	8.21 ± 0.24**	8.63 ± 0.21**	9.67 ± 0.24**	10.68 ± 0.19**
Liver						
Absolute	1.225 ± 0.029	1.411 ± 0.042*	1.516 ± 0.041**	1.437 ± 0.036**	1.663 ± 0.044**	1.703 ± 0.053**
Relative	40.76 ± 1.13	41.94 ± 0.87	45.79 ± 1.28**	45.54 ± 1.08**	51.87 ± 0.74**	55.82 ± 0.75**
Lung						
Absolute	0.204 ± 0.008	0.239 ± 0.010	0.229 ± 0.012	0.234 ± 0.011	0.224 ± 0.009	0.218 ± 0.008
Relative	6.81 ± 0.38	7.22 ± 0.50	6.93 ± 0.42	7.43 ± 0.36	7.02 ± 0.31	7.18 ± 0.31
Thymus						
Absolute	0.048 ± 0.003	0.048 ± 0.003	0.046 ± 0.003	0.046 ± 0.001	0.039 ± 0.002*	0.035 ± 0.002**
Relative	1.59 ± 0.09	1.42 ± 0.08	1.39 ± 0.07	1.47 ± 0.07	1.22 ± 0.06**	1.15 ± 0.04**
Uterus						
Absolute	0.166 ± 0.011	0.123 ± 0.005**	0.125 ± 0.003**	0.127 ± 0.003**	0.170 ± 0.005	0.176 ± 0.003
Relative	5.56 ± 0.40	3.66 ± 0.15**	3.76 ± 0.07**	4.03 ± 0.15**	5.32 ± 0.21	5.79 ± 0.13

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX F
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

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TABLE F2 Summary of Estrous Cycle Characterization for Female Rats in the 14-Week Gavage Study of Oxymetholone 198

TABLE F3 Summary of Reproductive Tissue Evaluations for Male Mice in the 14-Week Gavage Study of Oxymetholone 199

TABLE F4 Summary of Estrous Cycle Characterization for Female Mice in the 14-Week Gavage Study of Oxymetholone 199

TABLE F1
Summary of Reproductive Tissue Evaluations for Male Rats in the 14-Week Gavage Study of Oxymetholone[a]

	Vehicle Control	80 mg/kg	315 mg/kg	1,250 mg/kg
n	10	10	10	9
Weights (g)				
Necropsy body weight	381 ± 3	357 ± 7*	305 ± 5**	270 ± 2**
L. cauda epididymis	0.154 ± 0.005	0.133 ± 0.004**	0.120 ± 0.003**	0.121 ± 0.009**
L. epididymis	0.453 ± 0.008	0.379 ± 0.008**	0.337 ± 0.015**	0.362 ± 0.015**
L. testis	1.585 ± 0.019	1.243 ± 0.022**	0.988 ± 0.015**	0.982 ± 0.021**
Spermatid measurements				
Spermatid heads (10^7/g testis)	10.18 ± 0.19	12.01 ± 0.38**	13.44 ± 0.32**	12.20 ± 1.21**
Spermatid heads (10^7/testis)	16.12 ± 0.24	14.87 ± 0.37*	13.25 ± 0.23**	11.95 ± 1.19**
Spermatid count (mean/10^{-4} mL suspension)	80.58 ± 1.22	74.35 ± 1.86*	66.23 ± 1.14**	64.08 ± 2.16**
Epididymal spermatozoal measurements				
Motility (%)	64.81 ± 1.67	65.53 ± 2.05	63.44 ± 2.74	63.69 ± 3.09
Concentration (10^6/g cauda epididymal tissue)	829 ± 57	884 ± 63	672 ± 38	774 ± 87

* Significantly different (P≤0.05) from the vehicle control group by Dunnett's test (necropsy body weight) or Shirley's test (tissue weights and spermatid measurements)
** P≤0.01
[a] Data are presented as mean ± standard error. Differences from the vehicle control group for epididymal spermatozoal measurements are not significant by Dunn's test.

TABLE F2
Summary of Estrous Cycle Characterization for Female Rats in the 14-Week Gavage Study of Oxymetholone[a]

	Vehicle Control	80 mg/kg	315 mg/kg	1,250 mg/kg
n	10	10	10	9
Necropsy body weight (g)	198 ± 4	258 ± 5**	230 ± 4**	219 ± 4*
Estrous cycle length (days)	4.95 ± 0.09	5.10 ± 0.26	5.10 ± 0.12	5.00 ± 0.19
Estrous stages (% of cycle)[b]				
Diestrus	34.2	50.0	33.3	35.2
Proestrus	14.2	15.0	20.8	20.4
Estrus	32.5	17.5	25.0	24.1
Metestrus	19.2	17.5	19.2	16.7
Uncertain diagnoses	0.0	0.0	1.7	3.7

* Significantly different (P≤0.05) from the vehicle control group by Dunnett's test
** P≤0.01
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group for estrous cycle length are not significant by Dunn's test.
[b] Evidence shows that females in the 80 mg/kg group differ significantly (Wilk's Criterion, P≤0.05) from the vehicle control females in the relative length of time spent in the estrous stages. Dosed females spent more time in diestrus and less time in estrus than vehicle control females.

TABLE F3
Summary of Reproductive Tissue Evaluations for Male Mice in the 14-Week Gavage Study of Oxymetholone[a]

	Vehicle Control	630 mg/kg	1,250 mg/kg	2,500 mg/kg
n	9	10	10	10
Weights (g)				
Necropsy body weight	37.6 ± 1.2[b]	40.3 ± 1.0	38.8 ± 1.5	38.7 ± 0.7
L. cauda epididymis	0.013 ± 0.000	0.012 ± 0.001	0.012 ± 0.001	0.011 ± 0.000*
L. epididymis	0.038 ± 0.002	0.041 ± 0.003	0.041 ± 0.001	0.038 ± 0.001
L. testis	0.113 ± 0.002	0.112 ± 0.002	0.108 ± 0.002	0.105 ± 0.002**
Spermatid measurements				
Spermatid heads (10^7/g testis)	21.87 ± 0.62	20.90 ± 0.51	21.12 ± 0.71	22.67 ± 0.81
Spermatid heads (10^7/testis)	2.48 ± 0.08	2.33 ± 0.05	2.28 ± 0.07	2.37 ± 0.08
Spermatid count (mean/10^{-4} mL suspension)	77.47 ± 2.49	72.70 ± 1.47	71.23 ± 2.29	74.18 ± 2.61
Epididymal spermatozoal measurements				
Motility (%)	67.24 ± 1.92	62.51 ± 1.44	56.17 ± 1.91**	57.52 ± 3.08**
Concentration (10^6/g cauda epididymal tissue)	1,407 ± 119	1,356 ± 113	1,253 ± 111	1,539 ± 334

* Significantly different (P≤0.05) from the vehicle control group by Shirley's test
** P≤0.01
[a] Data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (necropsy body weight) or Dunn's test (left epididymal weight, spermatid measurements, and epididymal spermatozoal concentration).
[b] n=10

TABLE F4
Summary of Estrous Cycle Characterization for Female Mice in the 14-Week Gavage Study of Oxymetholone[a]

	Vehicle Control	630 mg/kg	1,250 mg/kg	2,500 mg/kg
n	10	10	10	10
Necropsy body weight (g)	30.3 ± 1.0	31.7 ± 0.9	32.1 ± 0.8	30.5 ± 0.7
Estrous cycle length (days)	4.50 ± 0.40	7.60 ± 0.50**	6.90 ± 0.10**	6.88 ± 0.13**[c]
Estrous stages (% of cycle)[b]				
Diestrus	31.7	43.3	62.5	62.5
Proestrus	10.8	15.0	16.7	13.3
Estrus	37.5	26.7	7.5	7.5
Metestrus	20.0	15.0	13.3	16.7

** Significantly different (P≤0.01) from the vehicle control group by Shirley's test
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group for necropsy body weight are not significant by Dunnett's test.
[b] Evidence shows that females in the 1,250 and 2,500 mg/kg groups differ significantly (Wilk's Criterion, P≤0.01) from the vehicle control females in the relative time spent in the estrous stages. Dosed females spent more time in diestrus and less time in estrus than vehicle control females.
[c] Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.

APPENDIX G
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Oxymetholone

Oxymetholone was obtained from Syntex Corporation (Republic of Panama) in one lot (S090189), which was used during the 16-day, 14-week, and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the oxymetholone studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white fluffy powder, was identified as oxymetholone by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*; Bond *et al.*, 1988; Weast, 1988) of oxymetholone; the ultraviolet/visible spectrum was also consistent with a concomitantly analyzed United States Pharmacopeia (USP) reference standard. The infrared and nuclear magnetic resonance spectra are presented in Figures G1 and G2. The melting point range of lot S090189 was 174.9° to 179.0° C and was consistent with a literature reference (*USP*, 1989). The optical rotation value for 2 g oxymetholone in 100 mL *p*-dioxane was determined to be $[\alpha]^{25}_{D} = +36.1°$, which was also consistent with a literature reference (Weast, 1988).

The purity of lot S090189 was determined with elemental analyses, weight loss on drying, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). TLC was performed on Whatman Silica Gel 60A F-254 plates with two solvent systems: 1) ethyl acetate:hexane:glacial acetic acid (85:13:2) and 2) toluene:acetone:glacial acetic acid (80:18:2). The plates were examined under ultraviolet light (254 nm) with a spray of 0.5 g vanillin in 100 mL of sulfuric acid:ethanol (4:1). After spraying, the plates were dried at 120° C for 2 to 3 minutes. Progesterone in chloroform was used as a reference standard. HPLC was performed with a Zorbax Rx column with ultraviolet detection (280 nm) and a solvent system of water with 1% glacial acetic acid:acetonitrile with 1% glacial acetic acid (50:50). The flow rate was 1 mL/minute.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for oxymetholone. Weight loss on drying indicated 0.09% water. TLC by each system indicated a major spot and no impurities. HPLC indicated one major peak and no impurities with areas of 0.1% or greater relative to the major peak area. Major peak comparisons of lot S090189 to a dried USP reference standard with the same HPLC system but with a solvent ratio of 40:60 and with valerophenone added as an internal standard indicated a purity of 102% ± 1% for lot S090189. The overall purity of lot S090189 was determined to be greater than 99%.

Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory. HPLC was performed using the system described for the major peak comparison. These studies indicated that oxymetholone is stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. Throughout the studies, the bulk chemical was stored at room temperature in amber glass jars. Stability was monitored during the 16-day, 14-week, and 2-year studies using HPLC. No degradation of the bulk chemical was detected.

Methylcellulose

Methylcellulose was obtained from Fisher Scientific Company (Pittsburgh, PA) in two lots (876672 and 946150) and from Sigma Chemical Corporation (St. Louis, MO) in one lot (48F0090). Lot 876672 was used in all studies and lots 946150 and 48F0090 were used in the 2-year study. Identity, purity, and stability analyses of lot 876672 were conducted by the analytical chemistry laboratory during the 16-day and 14-week studies. The identity of all lots was confirmed by the study laboratory during the 2-year study.

The chemical, a white powder, was identified as methylcellulose by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure of methylcellulose. The infrared spectrum was consistent with a literature reference (*Sadtler Pharmaceutical Grating Spectra*, 1974). The methoxy group content of 31.7%, assuming 1.8° of substitution, estimated from the nuclear magnetic resonance spectrum was consistent with the theoretical value for methylcellulose. No melting point was observed up to 300° C; the sample decomposed at 250° to 300° C. USP XXI analyses for the apparent viscosity, weight loss on drying, residue on ignition, arsenic content, heavy metal content, and percent methoxy content were also performed.

The purity of lot 876672 was determined by Karl Fischer water analysis, elemental analyses, functional group titration, and HPLC. For functional group titration, a methoxy group determination was performed by Galbraith Laboratories, Inc. (Knoxville, TN). HPLC was performed with a Toyo Soda TSK G4000 SW column with refractive index detection and a solvent system of 0.005 M sodium dodecyl sulfate in water. The flow rate was 1.0 mL/minute.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for methylcellulose based on 1.8° of substitution and corrected for 1.94% water. In addition, elemental analyses indicated 0.058% sodium. Karl Fischer water analysis indicated 1.94% ± 0.03% water. Functional group titration indicated 30.62% ± 0.08% methoxy group content; this value is consistent with the theoretical value, assuming 1.8° of substitution (30.4%), and with the estimate of the methoxy group content from the nuclear magnetic resonance spectrum. The complete battery of USP tests for methylcellulose indicated the following results: the apparent viscosity was 3,749 to 4,060 cP; the weight loss on drying was 1.9% ± 0.3%; the residue on ignition was less than 0.3%; the tests for arsenic and heavy metals were passed; and the methoxy group contents were 30.3% ± 0.2% for lot 876672 and 28.3% ± 0.0% for the USP reference material. The chemical met the USP specifications for methylcellulose for all analyses. HPLC indicated one major peak and no impurities with areas greater than or equal to 0.1% relative to the major peak area. Cumulative analytical data indicated that lot 876672 of methylcellulose was suitable for use as a dosing vehicle.

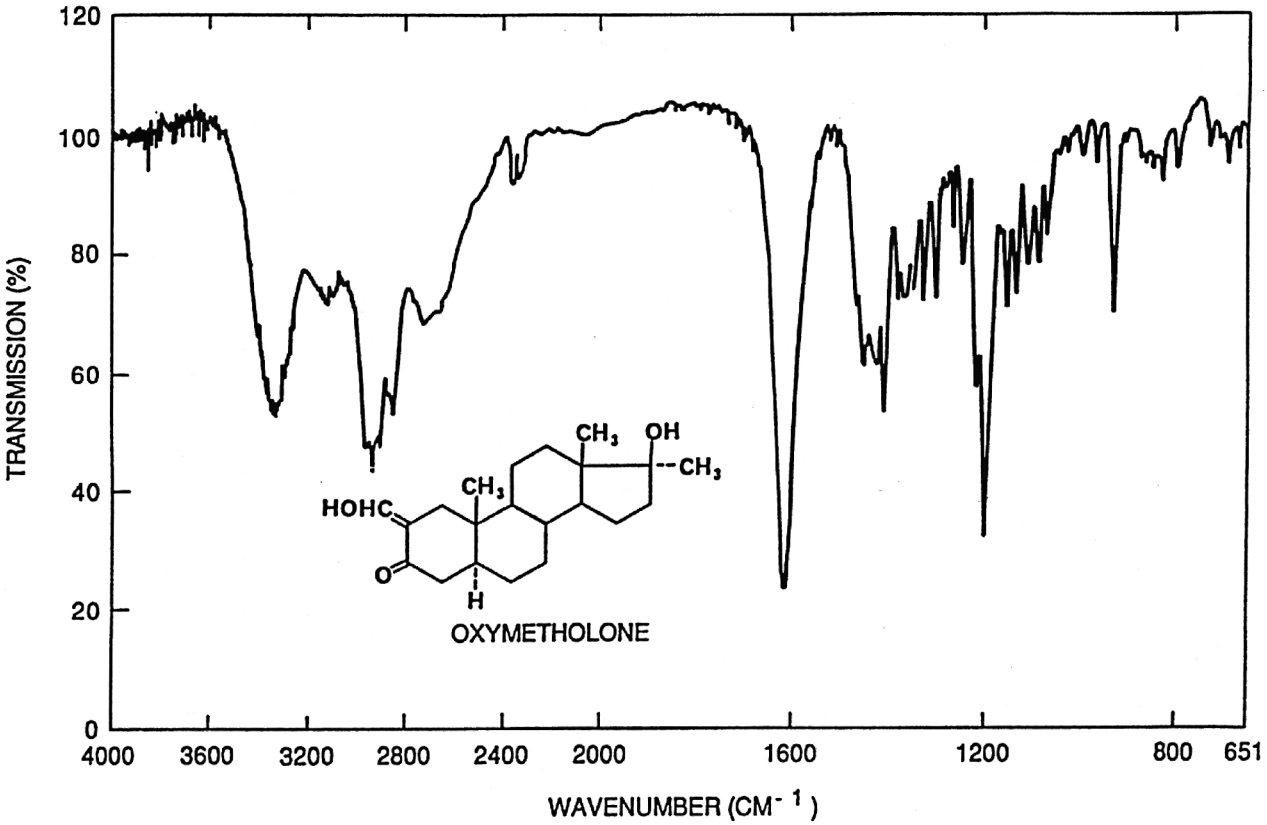
Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory. Gas chromatography (USP XXI method) was performed to determine the methoxy group content using thermal conductivity detection with a helium carrier gas at a flow rate of 20 mL/minute, a 10% SP-2100 on 100/120 Chromosorb WHP glass column, an isothermal oven temperature of 100° C, and toluene as an internal standard. These studies indicated that methylcellulose was stable as a bulk chemical for 3 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in the original containers in the dark at room temperature. Stability and purity were monitored during the 2-year study by comparing the methoxy group content to a frozen reference sample of lot 876672. These analyses were conducted at Galbraith Laboratories, Inc. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The vehicle was prepared by mixing methylcellulose with heated, deionized water and then diluting with water to form a 0.5% solution, which was allowed to cool. The solution was stored at room temperature. Oxymetholone was mixed with the dosing vehicle to form a paste, which was then added to the remaining vehicle and stirred until a homogeneous solution was obtained (Table G1). The dose formulations were stored at 5° C in amber glass jars in the 16-day studies and at room temperature in amber glass jars for up to 35 days in the 14-week and 2-year studies.

Homogeneity studies were performed by the study laboratory on the 31.25 and 500 mg/mL (16-day studies), 15.75 and 250 mg/mL (14-week studies), and 0.6 and 30 mg/mL (2-year study) dose formulations. Samples were analyzed with HPLC on a Zorbax C_8 or Zorbax Rx-C_8 (2-year study) column with ultraviolet detection (280 nm) and a solvent system of acetonitrile:water:acetic acid (85:15:0.5). The flow rate was 1.0 mL/min for the 16-day and 14-week studies; decanophenone was added as an internal standard. Stability studies of the 31.25 mg/mL (16-day studies), 250 mg/mL (14-week studies), and 0.6 mg/mL (2-year study) formulations were also performed using the same HPLC system used for the homogeneity analyses. Homogeneity was confirmed, and the stability of the dose formulations was confirmed for 28 days (16-day studies) or 35 days (14-week and 2-year studies) at up to room temperature when stored protected from light. Formulations were also stable for a minimum of 3 hours when stored open to air and light. Resuspendability of the 500 mg/mL formulation after storage for 28 days at 5° C or at room temperature was also confirmed with the same HPLC system used for the homogeneity analyses.

Periodic analyses of the dose formulations of oxymetholone were conducted at the study laboratory using HPLC. Dose formulations were analyzed once during the 16-day studies (Table G2), every 4 to 8 weeks during the 14-week studies (Table G3), and approximately every 8 weeks during the 2-year study (Table G4). Four of the five dose formulations analyzed and used during the 16-day studies were within 10% of the target concentration. The dose formulation in the 16-day studies that was 116% of the target concentration was considered to be acceptable and was used for dosing. Five of the 10 animal room samples were within 10% of the target concentration. Of the dose formulations analyzed during the 14-week studies, 80% (12/15) were within 10% of the target concentration, with no value greater than 116% of the target concentration. The three formulations that were out of specification were remixed, and the remixes were determined to be within 10% of the target concentrations. Of the animal room samples, 70% (21/30) were within 10% of the target concentration, with no value greater than 121% of the target concentration; the variability in the animal room sample concentrations was likely due to the high viscosity and small volume of the samples and the presence of a thin crust of oxymetholone on the lip of the dosing vials. All 56 of the dose formulations analyzed during the 2-year study were within 10% of the target concentration, with no value less than 90% or greater than 109% of the target concentration. Of the animal room samples, 70% (14/20) were within 10% of the target concentration, ranging from 72% to 168% of the target concentrations. Variations in postadministration values during all the studies were thought to be caused by difficulties in resuspension of the formulations.



Oxymetholone	MRI No.: 437N	Instrument: Analect RFX-75 FT-IR
Lot No.: S090189	Date: 12/8/89	Resolution= 4.0 Gain= 1.0
Batch No.: 01	Operator: K. Russo	Scans= 64
Task No.: BS/CV-2441	Remarks: Computer correction of baseline	Concentration= ~1.2% (w/w) in potassium bromide disc

FIGURE G1
Infrared Absorption Spectrum of Oxymetholone

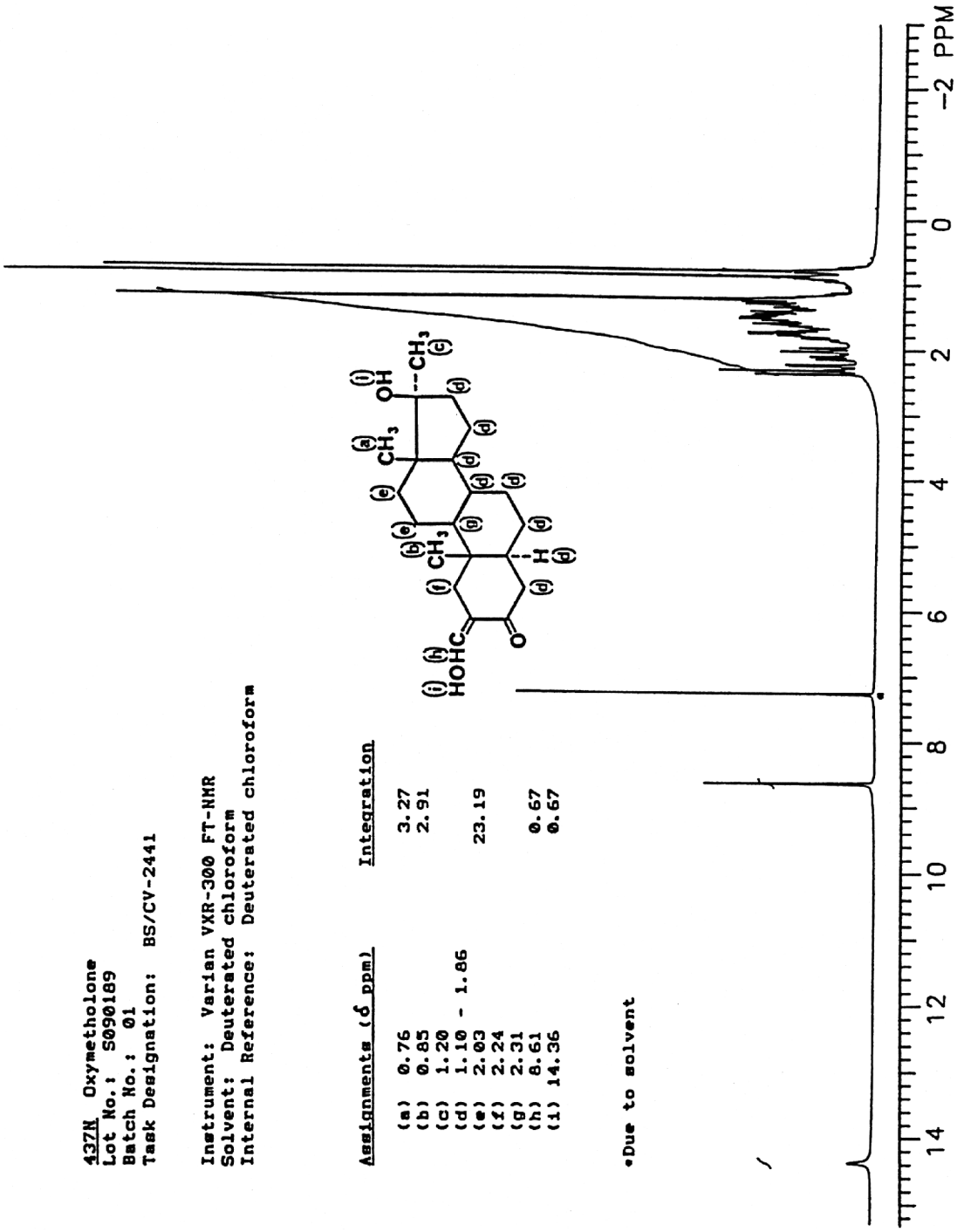


FIGURE G2
Nuclear Magnetic Resonance Spectrum of Oxymetholone

TABLE G1
Preparation and Storage of Dose Formulations in the Gavage Studies of Oxymetholone

16-Day Studies	14-Week Studies	2-Year Study
Preparation		
The dosing vehicle was prepared by mixing methylcellulose with heated deionized water while stirring and then diluting with water to form a 0.5% solution, which was allowed to cool. Oxymetholone was added to the required amount of the vehicle and stirred manually to form a paste; the remaining vehicle was added, and the mixture was stirred with a magnetic stirrer until a homogeneous preparation was obtained. The doses were prepared once during the studies.	Same as 16-day studies except the doses were prepared approximately every 4 weeks.	Same as 14-week studies. From month 7 through the end of the study, 100 mL portions of the dose formulations were removed from the bottom of the carboys and reintroduced at the top of the mixture while stirring continued.
Chemical Lot Number		
S090189	S090189	S090189
Maximum Storage Time		
28 days	35 days	35 days
Storage Conditions		
Stored in amber glass jars at 5° C	Stored in amber glass jars at room temperature	Stored in amber glass jars with Teflon-lined lids and magnetic stir bars at room temperature
Study Laboratory		
Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)

TABLE G2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 16-Day Gavage Studies of Oxymetholone

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
22 November 1991	26 November 1991	31.25	28.6	–8
		62.5	64.5	+3
		125	137.4	+10
		250	290.6	+16
		500	540.6	+8
	19 December 1991[b]	31.25	35.1	+12
		62.5	73.5	+18
		125	140.3	+12
		250	287.7	+15
		500	533.3	+7
Mice				
22 November 1991	26 November 1991	31.25	28.6	–8
		62.5	64.5	+3
		125	137.4	+10
		250	290.6	+16
		500	540.6	+8
	19 December 1991[b]	31.25	33.7	+8
		62.5	61.5	–2
		125	137.6	+10
		250	286.3	+15
		500	524.3	+5

[a] Results of duplicate analyses. Dosing volume=5 mL/kg for rats; 31.25 mg/mL=160 mg/kg, 62.5 mg/mL=315 mg/kg, 125 mg/mL=625 mg/kg, 250 mg/mL=1,250 mg/kg, 500 mg/mL=2,500 mg/kg. Dosing volume=10 mL/kg for mice; 31.25 mg/mL=320 mg/kg, 62.5 mg/mL=630 mg/kg, 125 mg/mL=1,250 mg/kg, 250 mg/mL=2,500 mg/kg, 500 mg/mL=5,000 mg/kg
[b] Animal room samples

TABLE G3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Gavage Studies of Oxymetholone

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
6 May 1992	7-8 May 1992	16	15.7	−2
		32	31.7	−1
		63	67.5	+7
		125	136	+9
		250	276	+10
	8-9 June 1992[b]	16	17.2	+8
		32	34.6	+8
		63	71.3	+13
		125	139	+11
		250	302	+21
1 June 1992	3 June 1992	16	14.9	–7
		32	32.0	0
		63	69.7	+11
		125	145	+16
		250	283	+13
5 June 1992	5 June 1992	63	63.2[c]	0
		125	132[c]	+6
		250	246[c]	–2
	10 and 13-14 July 1992[b]	16	16.2	+1
		32	36.4	+14
		63	62.9	0
		125	144	+15
		250	239	–4
27 July 1992	30 July 1992	16	15.6	−2
		32	32.1	0
		63	60.2	–4
		125	132	+6
		250	253	+1
	26-28 August 1992[b]	16	14.8	–7
		32	32.8	+3
		63	58.4[d]	–7
		125	118[d]	–6
		250	203	–19

TABLE G3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Gavage Studies of Oxymetholone

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice				
6 May 1992	7-8 May 1992	16	15.7	−2
		32	31.7	−1
		63	67.5	+7
		125	136	+9
		250	276	+10
	8-9 June 1992[b]	16	15.4[d]	−4
		32	31.7[d]	−1
		63	70.3	+12
		125	137	+10
		250	289	+16
1 June 1992	3 June 1992	16	14.9	−7
		32	32.0	0
		63	69.7	+11
		125	145	+16
		250	283	+13
5 June 1992	5 June 1992	63	63.2[c]	0
		125	132[c]	+6
		250	246[c]	−2
	10 and 13-14 July 1992[b]	16	14.9	−7
		32	31.7	−1
		63	62.4	−1
		125	138	+10
		250	236	−6
27 July 1992	30 July 1992	16	15.6	−2
		32	32.1	0
		63	60.2	−4
		125	132	+6
		250	253	+1
	26-28 August 1992[b]	16	14.7	−8
		32	28.7	−10
		63	57.8	−8
		125	110[e]	−12
		250	224	−10

[a] Results of duplicate analyses. Dosing volume for rats=5 mL/kg; 16 mg/mL=80 mg/kg, 32 mg/mL=160 mg/kg, 63 mg/mL=315 mg/kg, 125 mg/mL=625 mg/kg, 250 mg/mL=1,250 mg/kg. Dosing volume for mice=10 mL/kg; 16 mg/mL=160 mg/kg, 32 mg/mL=320 mg/kg, 63 mg/mL=630 mg/kg, 125 mg/mL=1,250 mg/kg, 250 mg/mL=2,500 mg/kg
[b] Animal room samples
[c] Results of remix
[d] Results of triplicate analyses
[e] Results of quadruplicate analyses

TABLE G4
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Gavage Study of Oxymetholone

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
12 April 1993	13-14 April 1993	0.6	0.606	+1
		6	5.93	-1
		20	18.5	-7
		30	28.9	-4
	27 May 1993[b]	0.6	0.600	0
		6	5.78	–4
		20	18.2	–9
		30	30.6	+2
7 June 1993	8 June 1993	0.6	0.558	–7
		6	5.74	-4
		20	19.8	–1
		30	32.7	+9
2 August 1993	3 August 1993	0.6	0.605	+1
		6	6.15	+3
		20	19.8	–1
		30	28.6	–5
20 September 1993	21 September 1993	0.6	0.588	–2
		6	6.10	+2
		20	20.3	+2
		30	29.1	-3
	26-29 October 1993[b]	0.6	0.642	+7
		6	10.1	+68
		20	21.6	+8
		30	30.6	+2
17 November 1993	17-18 November 1993	0.6	0.596	–1
		6	5.79	–3
		20	20.3	+2
		30	31.7	+6
10 January 1994	11-12 January 1994	0.6	0.563	-6
		6	5.55	–7
		20	19.6	–2
		30	26.9	–10
7 March 1994	8 March 1994	0.6	0.586	–2
		6	6.02	0
		20	20.3	+2
		30	28.2	–6
	14-15 April 1994[b]	0.6	0.551	–8
		6	5.31	–11
		20	14.3	–28
		30	22.2	–26
2 May 1994	3-4 May 1994	0.6	0.588	–2
		6	5.93	–1
		20	18.4	–8
		30	28.1	–6

TABLE G4
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Gavage Study of Oxymetholone

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
27 June 1994	29-29 June 1994	0.6	0.618	+3
		6	5.56	−7
		20	18.9	−5
		30	27.9	–7
22 August 1994	25 August 1994	0.6	0.607	+1
		6	5.95	−1
		20	19.8	−1
		30	27.9	–7
	27 September 1994[b]	0.6	0.595	−1
		6	5.72	−5
		20	19.1	−4
		30	27.5	–8
17 October 1994	18 October 1994	0.6	0.584	−3
		6	5.57	−7
		20	19.1	−4
		30	28.4	–5
12 December 1994	13-14 December 1994	0.6	0.550	−8
		6	5.71	−5
		20	19.1	−4
		30	28.2	–6
6 February 1995	9-13 February 1995	0.6	0.587	−2
		6	6.02	0
		20	19.2	−4
		30	29.9	0
	20-21 March 1995[b]	0.6	0.578	−4
		6	5.19	−13
		20	19.8	−1
		30	25.9	–14
10 April 1995	10 April 1995	0.6	0.590	−2
		6	6.10	+2
		20	20.7	+4
		30	31.0	+3

[a] Results of duplicate analyses. Dosing volume=5 mL/kg; 0.6 mg/mL=3 mg/kg, 6 mg/mL=30 mg/kg, 20 mg/mL=100 mg/kg, 30 mg/mL=150 mg/kg
[b] Animal room samples

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

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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] NCI, 1976; NIH, 1978
[b] Ingredients were 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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.94 ± 0.48	22.1 – 23.6	25
Crude fat (% by weight)	5.35 ± 0.18	5.00 – 5.80	25
Crude fiber (% by weight)	3.14 ± 0.29	2.60 – 4.00	25
Ash (% by weight)	6.27 ± 0.17	5.72 – 6.64	25
Amino Acids (% of total diet)			
Arginine	1.273 ± 0.083	1.100 – 1.390	12
Cystine	0.307 ± 0.068	0.181 – 0.400	12
Glycine	1.152 ± 0.051	1.060 – 1.220	12
Histidine	0.581 ± 0.029	0.531 – 0.630	12
Isoleucine	0.913 ± 0.034	0.867 – 0.965	12
Leucine	1.969 ± 0.053	1.850 – 2.040	12
Lysine	1.269 ± 0.050	1.200 – 1.370	12
Methionine	0.436 ± 0.104	0.306 – 0.699	12
Phenylalanine	0.999 ± 0.114	0.665 – 1.110	12
Threonine	0.899 ± 0.059	0.824 – 0.985	12
Tryptophan	0.216 ± 0.146	0.107 – 0.671	12
Tyrosine	0.690 ± 0.091	0.564 – 0.794	12
Valine	1.079 ± 0.057	0.962 – 1.170	12
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.223	1.830 – 2.570	11
Linolenic	0.273 ± 0.034	0.210 – 0.320	11
Vitamins			
Vitamin A (IU/kg)	6,750 ± 563	5,500 – 8,800	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	35.24 ± 8.58	22.5 – 48.9	12
Thiamine (ppm)	17.17 ± 3.53	14.0 – 26.0	24
Riboflavin (ppm)	7.78 ± 0.899	6.10 – 9.00	12
Niacin (ppm)	98.73 ± 23.21	65.0 – 150.0	12
Pantothenic acid (ppm)	32.94 ± 8.92	23.0 – 59.2	12
Pyridoxine (ppm)	9.28 ± 2.49	5.60 – 14.0	12
Folic acid (ppm)	2.56 ± 0.70	1.80 – 3.70	12
Biotin (ppm)	0.265 ± 0.046	0.190 – 0.354	12
Vitamin B_{12} (ppb)	41.6 ± 18.6	10.6 – 65.0	12
Choline (ppm)	2,955 ± 382	2,300 – 3,430	11
Minerals			
Calcium (%)	1.16 ± 0.07	1.03 – 1.33	25
Phosphorus (%)	0.89 ± 0.03	0.840 – 0.970	25
Potassium (%)	0.886 ± 0.059	0.772 – 0.971	10
Chloride (%)	0.531 ± 0.082	0.380 – 0.635	10
Sodium (%)	0.316 ± 0.031	0.258 – 0.370	12
Magnesium (%)	0.165 ± 0.010	0.148 – 0.180	12
Sulfur (%)	0.266 ± 0.060	0.208 – 0.420	11
Iron (ppm)	348.0 ± 83.7	255.0 – 523.0	12
Manganese (ppm)	93.27 ± 5.62	81.7 – 102.0	12
Zinc (ppm)	59.42 ± 9.73	46.1 – 81.6	12
Copper (ppm)	11.63 ± 2.46	8.09 – 15.4	12
Iodine (ppm)	3.49 ± 1.14	1.52 – 5.83	11
Chromium (ppm)	1.57 ± 0.53	0.60 – 2.09	12
Cobalt (ppm)	0.81 ± 0.27	0.49 – 1.23	8

TABLE H4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.53 ± 0.16	0.10 – 0.80	25
Cadmium (ppm)	0.04 ± 0.01	0.04 – 0.06	25
Lead (ppm)	0.24 ± 0.06	0.20 – 0.40	25
Mercury (ppm)[c]	<0.02		25
Selenium (ppm)	0.34 ± 0.10	0.10 – 0.50	25
Aflatoxins (ppm)	<5.0		25
Nitrate nitrogen (ppm)[d]	7.57 ± 2.71	2.90 – 14.0	25
Nitrite nitrogen (ppm)[d]	1.40 ± 0.88	0.30 – 3.50	25
BHA (ppm)[e]	1.32 ± 1.84	0.05 – 10.0	25
BHT (ppm)[e]	1.69 ± 1.12	0.18 – 5.0	25
Aerobic plate count (CFU/g)	134,480 ± 132,537	20,000 – 460,000	25
Coliform (MPN/g)	143 ± 558	3 – 2,800	25
Escherichia coli (MPN/g)	6 ± 3.6	3 – 10	25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[f]	12.30 ± 4.02	4.0 – 23.0	25
N-Nitrosodimethylamine (ppb)[f]	10.61 ± 3.78	3.0 – 21.0	25
N-Nitrosopyrrolidine (ppb)[f]	1.70 ± 0.78	1.0 – 4.0	25
Pesticides (ppm)			
α-BHC	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.10		25
Estimated PCBs	<0.20		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.10		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.13 ± 0.16	0.02 – 0.83	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] All values except for lots milled November and December 1991 were less than the detection limit. The detection limit is given as the mean.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

APPENDIX I
SENTINEL ANIMAL PROGRAM

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SENTINEL ANIMAL PROGRAM

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 serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are 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.

Serum samples were collected from randomly selected rats and mice during the 14-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
14-Week Study	
ELISA	
PVM (pheumonia virus of mice)	Study termination
RCV/SDA (rat corona/sialodacryodenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Hemagglutination Inhibition	
H-1	6, 12, and 18 months, study termination
KRV	6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE	
14-Week Study	
ELISA	
Ectromelia virus	Study termination
EDIM (epizootic diarrhea of infant mice)	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (Lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus-FL	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

RESULTS

Two rats had positive titers for *M. arthritidis* at the end of the 2-year study. Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positives.

APPENDIX J
SINGLE-DOSE TOXICOKINETIC STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

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SINGLE-DOSE TOXICOKINETIC STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

INTRODUCTION

Oxymetholone is a synthetic anabolic steroid that has been used clinically for the treatment of anemia. Single-dose toxicokinetic studies of oxymetholone following a single gavage dose or intravenous injection in male and female F344/N rats and male B6C3F$_1$ mice were conducted by the National Toxicology Program.

MATERIALS AND METHODS

Technical-grade oxymetholone was obtained from Syntex Corporation (Republic of Panama) in one lot (S090189), which was also used in the 16-day, 14-week, and 2-year studies conducted at Battelle Columbus Laboratories. Methylcellulose for the gavage vehicle was obtained from Research Triangle Institute (Research Triangle Park, NC) in one lot (914390). The intravenous injection vehicle, dimethylacetamide:water (5:1), was formulated with N,N-dimethylacetamide obtained from Aldrich (Milwaukee, WI) in one lot (08612MW). Gavage formulations were prepared as described in Appendix G.

F344/N rats were obtained from Charles River Laboratories, Inc. (Raleigh, NC), and male B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD) and acclimated for 2 weeks at the NIEHS, an AAALAC accredited facility, prior to being assigned to the study. Rats and mice were housed individually in filter-topped polycarbonate cages containing 1 inch of hardwood bedding (Beta Chip, Northern Products Corp., Warrensburg, NY). Room environmental conditions included a relative humidity of 50% $\pm$ 10%, 12:12 hour light/dark cycle, 10 to 15 fresh air changes per hour, and an ambient temperature of 22° $\pm$ 1° C. Animals received NIH-07 open formula diet and deionized water *ad libitum*. In-house quality assurance data and vender health surveillance data confirmed that the rats and mice were free of known pathogenic bacteria, viruses, mycoplasmal agents, endoparasites, and ectoparasites. All animal procedures received prior approval from the NIEHS Animal Care and Use Committee.

Groups of seven to nine male and three female rats were administered a single dose of 30 or 120 mg oxymetholone/kg body weight in 0.5% methylcellulose by gavage. Groups of six or seven male rats were administered a single intravenous injection of 20 mg/kg oxymetholone in dimethylacetamide:water. Groups of six male mice were administered a single dose of 120 mg/kg in 0.5% methylcellulose by gavage. Groups of seven male mice were administered a single intravenous injection of 20 mg/kg in dimethylacetamide:water. The dosing volume was 5 mL/kg body weight by gavage or 1 mL/kg by intravenous injection into the tail vein. The animals were anesthetized with a mixture of carbon dioxide and oxygen, and blood samples were collected by cardiac puncture. In the rat intravenous injection studies, blood was collected from two or three male rats per time point at 5, 10, 20, 30, 60, and 120 minutes after oxymetholone administration; in addition, blood was collected from two male rats at 240 minutes after oxymetholone administration. In the rat gavage studies, blood was collected from three male and three female rats in the 30 mg/kg group per time point at 40, 120, and 240 minutes (males) or 120 minutes (females); blood was collected from one to three male and three female rats in the 120 mg/kg group per time point at 10, 20, 40, 60, 90, 120, 180, 240, 300, 360, 480, 720, and 1,440 minutes (males) or 120 minutes (females) after oxymetholone administration. In the male mouse gavage study, blood was collected from three male mice per time point at 10, 40, 60, 120, 240, and 360 minutes. In the male mouse intravenous injection study, blood was collected from three male mice per time point at 5, 10, 20, 30, 60, 120, and 240 minutes. Blood samples were collected only once from each animal. The samples were collected into heparinized tubes, and the plasma was separated and decanted and stored at 20° C or lower until analysis.

All animals were observed twice daily for signs of morbidity and mortality. Individual body weights were recorded at randomization and on study day 1. Body weights from study day 1 were used for the calculation of dosing volumes.

Plasma samples were analyzed at Cedra Corporation (Austin, TX) using the methods described in the Materials and Methods section for the determination of oxymetholone in plasma.

The average plasma concentrations of oxymetholone were calculated. The logarithms of these values were plotted as a function of time. The areas under the plasma concentration versus time curves (AUC_t) were calculated using the trapezoidal rule of the form $AUC_t = \sum\{(C_n+C_{n-1})/2\}\times\{t_n\ t_{n-1}\}$, where AUC_t is the cumulative area under the curve to time t and C_{n-1} and C_n are successive concentrations at t_{n-1} and t_n, respectively. The areas under the curve to infinity (AUC_0^∞) for all groups were calculated from $AUC_0^\infty = AUC_t+C_t/\lambda$, where C_t is the last measured time point and λ is the elimination rate constant determined from the slope of the terminal phase of the log plasma concentration-time profiles. Linear regression of the natural logarithm of the concentrations forming the terminal phase of the kinetic profiles gave the slope (λ). The half-lives ($t_{½}$) were calculated as $\ln(2)/\lambda$. For intravenous doses, the total body clearance (Cl_{tot}) was calculated as dose/AUC_0^∞; the volume of distribution (V_d) was calculated as Cl_{tot}/λ. For gavage doses, total body clearance was calculated as Cl_{tot}/F, and the volume of distribution was calculated as V_d/F, where F was the oral bioavailability of oxymetholone and

$$F = \frac{Dose_{iv} \times AUC_{0\ oral}^{\infty}}{Dose_{oral} \times AUC_{0\ iv}^{\infty}} \ .$$

The maximum observed concentration (C_{max}) and corresponding time (T_{max}) were determined from the plasma concentration-time data as the maximum observed plasma concentration and corresponding time, respectively.

RESULTS

The greatest concentration of oxymetholone in plasma for male rats that received 20 mg/kg oxymetholone by intravenous injection was at the first time point measured, 5 minutes after administration (Table J1). The semilogarithmic plot of plasma concentration-time data for male rats administered 20 mg/kg oxymetholone by intravenous injection is shown in Figure J1. The concentration of oxymetholone in plasma was greatest 120 minutes after administration of 30 or 120 mg/kg oxymetholone to male rats by gavage (Table J2). The concentration of oxymetholone in plasma was measured only at 120 minutes after dosing for 30 and 120 mg/kg females (Table J2). The semilogarithmic plot of plasma concentration-time data for male rats administered 30 or 120 mg/kg oxymetholone by single gavage dose are shown in Figures J2 and J3. Bioavailability of the 120 mg/kg gavage dose was determined to be 17%.

The concentration of oxymetholone in plasma was greatest at the first time point measured, 5 minutes after administration of 20 mg/kg oxymetholone to male mice by intravenous injection (Table J3). The semilogarithmic plot of plasma concentration-time data for male mice administered 20 mg/kg oxymetholone by intravenous injection is shown in Figure J4. The concentration of oxymetholone in plasma was greatest 60 minutes after administration of 120 mg/kg oxymetholone to male mice by single gavage administration (Table J4). The semilogarithmic plot of plasma concentration-time data for male mice administered 120 mg/kg oxymetholone by single gavage administration is shown in Figure J5.

The time to maximum mean concentration was 2 hours for male rats that received 30 or 120 mg/kg oxymetholone by gavage, and the time to maximum mean concentration was 1 hour for male mice that received 120 mg/kg oxymetholone by gavage (Table J5). The maximum mean concentration was 0.820 mg/L for 30 mg/kg male rats and the maximum mean concentration ranged from 1.13 to 1.61 mg/L for 120 mg/kg males rats administered oxymetholone by gavage. The maximum mean concentration for male mice administered 120 mg/kg by gavage was 0.18 mg/L (Table J5). No time to maximum mean

concentration or maximum mean concentration were calculated for female rats in the gavage study. The elimination half-life for male rats administered 20 mg/kg by intravenous injection ranged from 0.61 to 2.27 hours; the elimination half-life for male rats administered 120 mg/kg by gavage ranged from 3.26 to 3.83 hours. The elimination half-life for 30 mg/kg male rats in the gavage study was 5.56 hours. The greatest concentration of oxymetholone in plasma 2 hours after dosing was in male rats administered 120 mg/kg by gavage.

TABLE J1
Plasma Concentrations of Oxymetholone in Male F344/N Rats after a Single Intravenous Dose of 20 mg/kg Oxymetholone[a]

Time after Dosing (minutes)	Concentration (mg/L)
5	20.6
10	5.51
20	4.27
30	2.07
60	1.49
120	0.619
5	14.4
10	8.04
20	2.21
30	1.72
60	0.881
120	0.914
240	0.496
5	20.3
10	6.51
20	3.01
30	2.19
60	1.21
120	0.846
240	0.376

[a] One animal was bled at each time point.

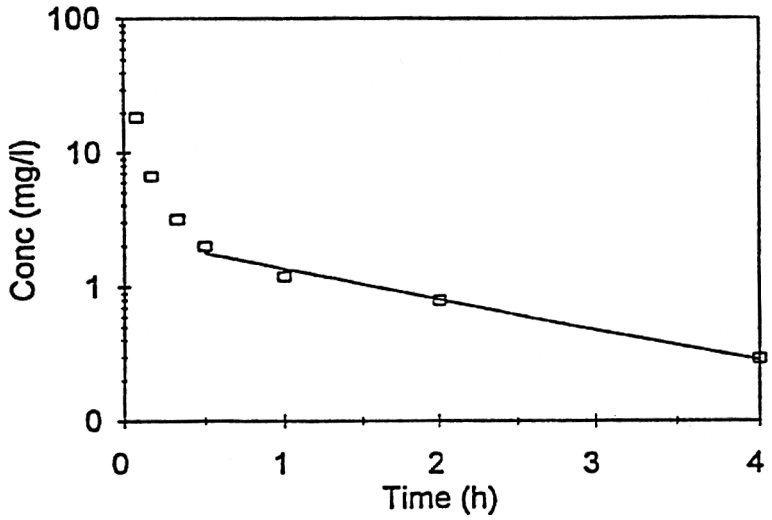

FIGURE J1
Plasma Concentrations of Oxymetholone in Male F344/N Rats after a Single Intravenous Dose of 20 mg/kg Oxymetholone

TABLE J2
Plasma Concentrations of Oxymetholone in Male and Female F344/N Rats Following Gavage Administration[a]

Dose (mg/kg)	Time after Dosing (minutes)	Concentration (mg/L)	Mean ± Standard Deviation
Male			
30	40	0.564	
	40	0.641	
	40	0.629	0.611 ± 0.041
	120	0.875	
	120	0.875	
	120	0.711	0.820 ± 0.095
	240	0.427	
	240	0.466	
	240	0.316	0.403 ± 0.078
120	10	0.626	
	20	0.788	
	40	0.684	
	60	0.999	
	90	0.616	
	120	1.13	
	180	0.925	—[b]
120	10	0.666	
	40	0.733	
	60	0.952	
	120	1.61	
	180	1.07	
	240	0.977	
	300	0.527	
	360	0.806	—
120	10	0.319	
	40	0.675	
	60	0.739	
	120	1.33	
	180	1.08	
	240	0.910	
	300	0.600	
	360	0.462	—
120	480	0.428	
	480	0.339	
	480	0.203	0.323 ± 0.113
	720	0.091[c]	
	720	0.208	
	720	0.255	0.185 ± 0.084
	1,440	<LOD	
	1,440	<LOD	<LOD

TABLE J2
Plasma Concentrations of Oxymetholone in Male and Female F344/N Rats Following Gavage Administration

Dose (mg/kg)	Time after Dosing (minutes)	Concentration (mg/L)	Mean ± Standard Deviation
Female			
30	120	0.266	
	120	0.231	
	120	0.276	0.258 ± 0.024
120	120	0.687	
	120	1.02	
	120	0.918	0.875 ± 0.171

[a] One animal was bled at each time point; LOD = limit of detection (0.005 mg/L).
[b] No means were calculated because only one measurement was taken per time point.
[c] Estimated concentration above the LOD but below the estimated limit of quantitation (0.100 mg/L)

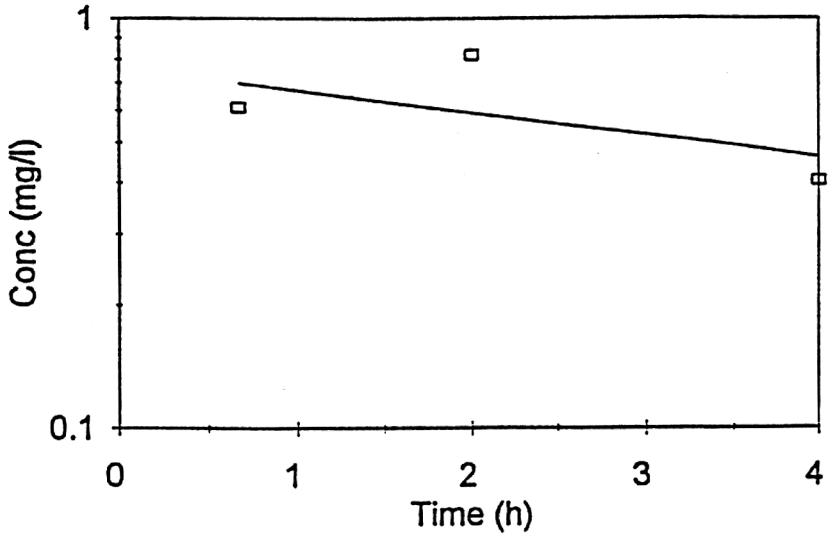

FIGURE J2
Plasma Concentrations of Oxymetholone in Male F344/N Rats after a Single Gavage Dose of 30 mg/kg Oxymetholone

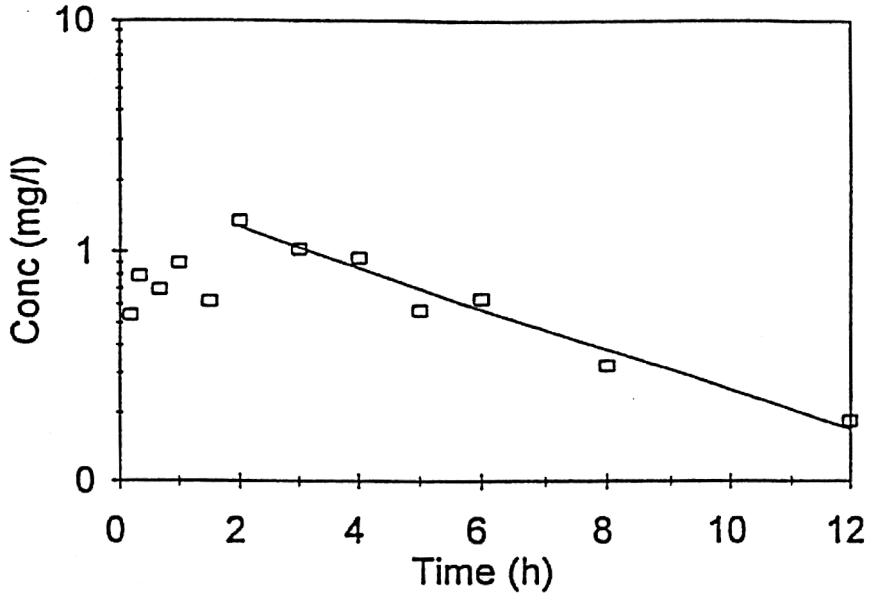

FIGURE J3
Plasma Concentrations of Oxymetholone in Male F344/N Rats after a Single Gavage Dose of 120 mg/kg Oxymetholone

TABLE J3
Plasma Concentrations of Oxymetholone in Male B6C3F$_1$ Mice after a Single Intravenous Dose of 20 mg/kg Oxymetholone[a]

Time after Dosing (minutes)	Concentration (mg/L)	Mean ± Standard Deviation
5	3.52	
5	2.85	
5	2.79	3.05 ± 0.41
10	1.79	
10	1.79	
10	1.67	1.75 ± 0.07
20	0.366	
20	0.446	
20	1.11	0.641 ± 0.408
30	1.37	
30	0.801	
30	0.469	0.880 ± 0.456
60	0.190	
60	0.606	
60	0.553	0.450 ± 0.226
120	0.524	
120	0.865	
120	0.143	0.511 ± 0.361
240	0.385	
240	0.516	
240	0.334	0.412 ± 0.094

[a] Data are given in mg/L as the mean for three values.

TABLE J4
Plasma Concentrations of Oxymetholone in Male B6C3F$_1$ Mice after a Single Gavage Dose of 120 mg/kg Oxymetholone[a]

Time after Dosing (minutes)	Concentration (mg/L)	Mean ± Standard Deviation
10	<LOD	
10	<LOD	
10	<LOD	<LOD
40	<LOD	
40	0.116	
40	0.140	0.085 ± 0.075
60	0.259	
60	0.151	
60	0.156	0.189 ± 0.061
120	0.130	
120	0.134	
120	0.118	0.127 ± 0.008
240	0.152	
240	0.157	
240	0.130	0.146 ± 0.014
360	0.183	
360	0.158	
360	0.186	0.176 ± 0.015

[a] Data are given in mg/L as the mean for three values; LOD=limit of detection (0.005 mg/L).

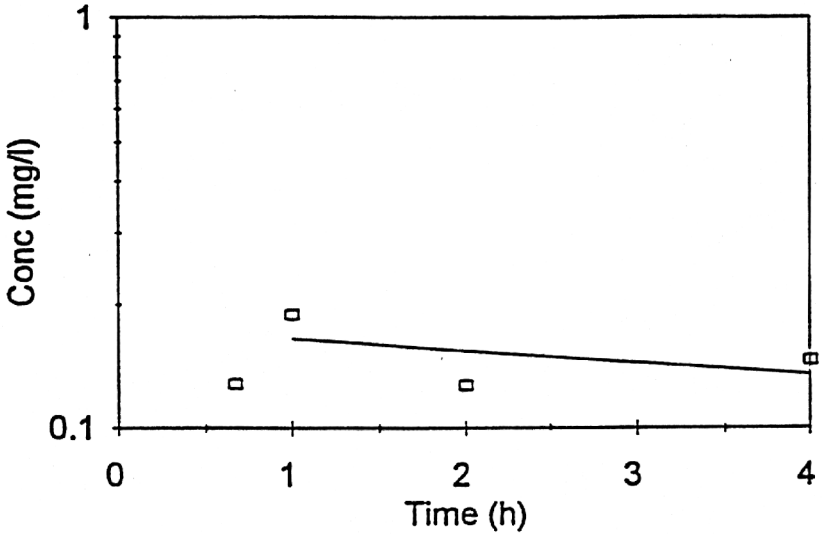

FIGURE J4
Plasma Concentrations of Oxymetholone in Male B6C3F$_1$ Rats after a Single Intravenous Dose of 20 mg/kg Oxymetholone

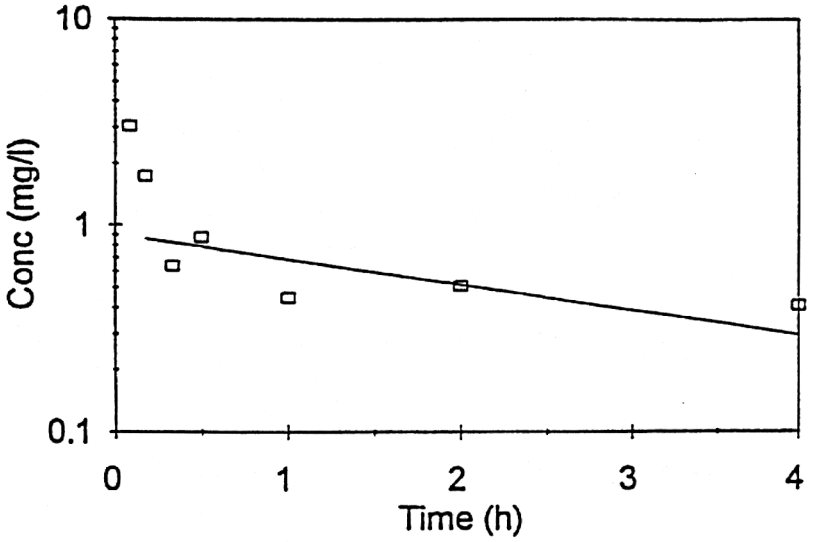

FIGURE J5
Plasma Concentrations of Oxymetholone in Male B6C3F$_1$ Rats after a Single Gavage Dose of 120 mg/kg Oxymetholone

TABLE J5
Summary of Pharmacokinetic Data from Oxymetholone Studies in Male and Female F344/N Rats and Male B6C3F$_1$ Mice[a]

Route	Dose (mg/kg)	T_{max} (hr)	C_{max} (mg/L)	$t_{½}$ (hr)	C (2hr) (mg/L)	AUC_0^∞ (mg hr/L)	AUC_0^∞ (Dose-normalized)	Cl_{tot}[b] (L/hr kg)	V_d[b] (L/kg)
Male Rats									
Intravenous injection	20	NA[c]	NA	0.61	0.620	6.92	0.346		
Intravenous injection	20	NA	NA	2.27	0.914	8.12	0.406		
Intravenous injection	20	NA	NA	1.07	0.846	8.14	0.407		
Mean				1.33		7.68		2.60	4.98
Gavage	30	2.0	0.820	5.56	0.820	6.07	0.202		
Gavage	120	2.0	1.13	3.55	1.13	7.34	0.047		
Gavage	120	2.0	1.61	3.83	1.61	9.10	0.076		
Gavage	120	2.0	1.33	3.26	1.33	7.51	0.063		
Mean				3.43		7.96		15.1	74.7
Female Rats									
Gavage	30	—[d]	—	—	0.258	—	—		
Gavage	120	—	—	—	0.875	—	—		
Male Mice									
Intravenous injection	20	NA	NA	2.46	0.510	3.62	0.181		
Gavage	120	1.0	0.18	10.3	0.127	2.53	0.021		

[a] T_{max}=time of maximum mean concentration; C_{max}=maximum mean concentration; $t_{½}$=elimination half-life; C(2hr)=concentration 2 hours after dosing; AUC_0^∞=area under the curve to infinity; Cl_{tot}=total body clearance; V_d=volume of distribution
[b] Mean data available only for male rats
[c] Not applicable due to intravenous dosing
[d] This data set includes only the 2-hour concentration.