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TOXICOLOGY AND CARCINOGENESIS STUDIES OF *alpha*-METHYLDOPA SESQUIHYDRATE

(CAS NO. 41372-08-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *alpha*-METHYLDOPA SESQUIHYDRATE

(CAS NO. 41372-08-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public peer review.

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

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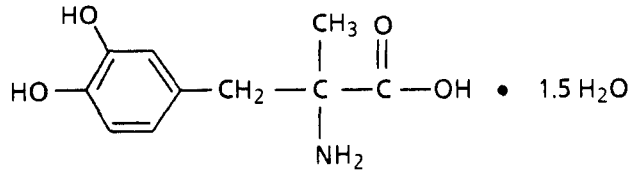

α-METHYLDOPA SESQUIHYDRATE
(3-Hydroxy-α-methyl-L-tyrosine sesquihydrate)

CAS No. 41372-08-1

$C_{10}H_{13}NO_4 \cdot 1.5\,H_2O$ Molecular weight 238.24

Synonyms for α-methyldopa or α-methyldopa sesquihydrate: L-(α-MD); α-methyl-L-3,4-dihydroxyphenylalanine; L(-)-β-(3,4-dihydroxyphenyl)-α-methylalanine; L-(-)-3-(3,4-dihydroxyphenyl)-2-methylalanine; L-α-methyl-3,4-dihydroxyphenylalanine; α-methyl-β-(3,4-dihydroxyphenyl)-L-alanine; L-(-)-α-methyl-β-(3,4-dihydroxyphenyl)alanine; (-)-methyldopa; L-methyldopa; L-α-methyldopa; α-methyl-L-dopa

Trade names for α-methyldopa or α-methyldopa sesquihydrate: Aldomet; Aldometil; Aldomin; α-Medopa; AMD; Bayer 1440 L; Baypresol; Dopamet; Dopatec; Dopegyt; Hyperpax; Medomet; Medopren; Methoplain; MK. B51; MK-351; Presinol; Presolisin; Sedometil; Sembrina

ABSTRACT

α-Methyldopa sesquihydrate is used in the treatment of hypertension; over 20 million prescriptions are written annually for α-methyldopa or α-methyldopa sesquihydrate in the United States. α-Methyldopa sesquihydrate (USP grade, greater than 99% pure) was selected for study because of widespread human exposure and the lack of carcinogenicity studies on this compound.

Fourteen-day, 13-week, and 2-year studies were conducted in F344/N rats and B6C3F$_1$ mice. The chemical was administered in feed because human exposure is primarily by the oral route. Short-term studies were performed in bacteria and mammalian cells to evaluate the potential for genetic damage.

Fourteen-Day and Thirteen-Week Studies: In the 14-day studies, the chemical was administered at dietary concentrations of 0 and 6,250-100,000 ppm. All rats receiving 100,000 ppm and 2/5 female rats receiving 50,000 ppm died. All mice lived until the end of the studies. Final mean body weights of dosed male rats were 14%-43% lower than that of controls, and those of dosed female rats were 9%-24% lower. Feed consumption by dosed male and female rats was reduced. Final mean body weights of dosed mice were generally within 10% of those of controls; feed consumption by dosed groups was lower than that by controls during the first week of the studies.

In the 13-week studies, the chemical was administered at dietary concentrations of 0 and 3,100-50,000 ppm. Deaths occurred in 4/10 male rats, 7/10 female rats, and 2/10 female mice at 50,000 ppm and in 1/10 female rats at 25,000 ppm. Final mean body weights of dosed rats were 6%-46% lower than those of controls. Feed consumption by dosed rat groups was lower than that by controls. Final mean body weights of male mice at 25,000 and 50,000 ppm and female mice at 50,000 ppm were reduced 12%-19%. Feed consumption by dosed and control mice was comparable.

Rats and mice receiving 25,000 and 50,000 ppm exhibited clinical signs of toxicity including lethargy, hyperexcitability, ocular discharge, and rough hair coats. Clinical signs of toxicity were judged to be more severe in dosed male mice than in female mice. Minimal to moderate kidney tubular cell regeneration was seen in male and female rats at 12,500, 25,000, and 50,000 ppm. Bone marrow

hypoplasia occurred in male rats at 25,000 and 50,000 ppm and in female rats at 6,300 ppm and higher. Nuclear enlargement (karyomegaly) of the renal cortical tubular epithelium was observed in male and female mice administered 12,500-50,000 ppm; these kidney lesions were judged to be more severe and occurred more frequently at concentrations of 25,000 ppm and higher.

Because of kidney lesions, bone marrow responses, and body weight effects at 12,500 ppm and higher and increased deaths and clinical signs at 25,000 and 50,000 ppm, dietary concentrations selected for male and female rats in the 2-year studies were 0, 3,100, and 6,300 ppm. Based on clinical signs, kidney effects, and body weight decreases at 25,000 and 50,000 ppm, dietary concentrations selected for male and female mice in the 2-year studies were 0, 6,300, and 12,500 ppm. Diets containing the chemical at these concentrations were fed to groups of 50 male and 50 female rats and 50 male and 50 female mice for 103 weeks.

Body Weight and Survival in the Two-Year Studies: Mean body weights of dosed rats were generally 8%-17% lower than those of controls, and mean body weights of dosed mice were generally 5%-22% lower than those of controls throughout the studies. The average amount of α-methyldopa sesquihydrate consumed per day was approximately 110-120 or 230-240 mg/kg per day by low and high dose rats and 830-890 or 1,760-1,800 mg/kg by low and high dose mice. Survival was comparable among dosed and control groups (male rats: control, 28/50; low dose, 26/50; high dose, 27/50; female rats: 35/50; 34/50; 29/50; male mice: 44/50; 42/50; 39/50; female mice: 42/50; 40/50; 38/50). Clinical signs considered to be dose-related included fighting in male rats, irritability in male mice, and rough hair coats in female mice.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Several lesions of the forestomach, including edema, chronic inflammation, epithelial hyperplasia, and ulcers, were seen at low incidences in high dose rats. No forestomach neoplasms occurred. No neoplastic lesions were observed in either male or female rats which were considered related to α-methyldopa sesquihydrate exposure.

Nephropathy (control, 3/50; low dose, 21/50; high dose, 32/50), karyomegaly (nuclear enlargement) of cells of the tubular epithelium (0/50; 46/50; 44/50), and cysts (2/50; 10/50; 10/50) were observed in the kidney of dosed female mice. Low incidences of tubular cell hyperplasia (0/50; 1/50; 1/50), tubular cell adenomas (0/50; 2/50; 0/50), and tubular cell adenocarcinomas (0/50; 0/50; 1/50) were observed in male mice. Tubular cell adenomas (3/2,029, 0.15%) and tubular cell adenocarcinomas (3/2,029, 0.15%) are uncommon in untreated control male B6C3F_1 mice. No neoplastic lesions in female mice were considered related to α-methyldopa sesquihydrate exposure.

Decreased incidences of several site-specific neoplasms were observed in dosed rats and mice; these decreases might have been due in part to decreased weight gain in dosed groups. The decreases occurred in the adrenal medulla of male rats (pheochromocytomas or malignant pheochromocytomas, combined: 21/49; 3/49; 10/50), uterus of female rats (endometrial stromal polyps: 15/50; 5/49; 1/50), liver of male and female mice (hepatocellular adenomas or carcinomas, combined--male: 15/50; 5/50; 6/50; female: 4/50; 1/50; 0/50), and anterior pituitary gland of female mice (adenoma: 9/49; 4/40; 2/50). The incidences of malignant tumors (male: 19/50; 9/50; 8/50; female: 21/50; 16/50; 12/50) and benign or malignant tumors (combined) (male: 32/50; 15/50; 17/50; female: 33/50; 22/50; 21/50) were reduced in dosed mice.

Reproductive Studies: α-Methyldopa sesquihydrate was administered to male F344/N rats in corn oil by gavage 5 days per week for 65 days at doses of 0, 50, 100, 200, or 400 mg/kg. Decreased body weight was seen in dosed animals. Male rats were mated to untreated female F344/N rats on days 57-61, necropsies were performed on days 65-67, and reproductive toxicity was measured by sperm count, sperm motility, organ weights, hormone levels, and histologic evaluation of the testis. Decreased fertility was observed in males dosed with α-methyldopa sesquihydrate at 200 or 400 mg/kg. Decreases

were also seen in sperm count, sperm motility, apparent number of late spermatids, and plasma testosterone levels in males in the 200 and 400 mg/kg groups. This alteration of reproductive function in male rats was found to be reversible after a 13-week recovery period (without dosing). The decreased fertility observed after α-methyldopa sesquihydrate administration was probably due in part to the decreases in plasma testosterone levels.

Genetic Toxicology: α-Methyldopa sesquihydrate was not mutagenic when tested with or without exogenous metabolic activation with a preincubation protocol in four strains of *Salmonella typhimurium* (TA97, TA98, TA100, or TA1535). No increase in chromosomal aberrations or sister chromatid exchanges was observed in Chinese hamster ovary (CHO) cells exposed to α-methyldopa sesquihydrate with or without S9.

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

Conclusions: Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of α-methyldopa sesquihydrate for male or female F344/N rats fed diets containing 3,100 or 6,300 ppm. There was *equivocal evidence of carcinogenic activity* of α-methyldopa sesquihydrate for male $B6C3F_1$ mice, as shown by three dosed mice having uncommon tubular cell tumors of the kidney. There was *no evidence of carcinogenic activity* of α-methyldopa sesquihydrate for female $B6C3F_1$ mice fed diets containing 6,300 or 12,500 ppm. Nonneoplastic lesions of the kidney including karyomegaly were observed in dosed female mice.

Decreased incidences of several tumor types (in the adrenal gland in male rats, uterus in female rats, liver in male and female mice, and anterior pituitary gland in female mice) were considered related to α-methyldopa sesquihydrate exposure.

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

SUMMARY OF THE TWO-YEAR FEED AND GENETIC TOXICOLOGY STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Dietary concentrations			
0, 3,100, or 6,300 ppm α-methyldopa sesquihydrate in feed	0, 3,100, or 6,300 ppm α-methyldopa sesquihydrate in feed	0, 6,300, or 12,500 ppm α-methyldopa sesquihydrate in feed	0, 6,300, or 12,500 ppm α-methyldopa sesquihydrate in feed
Body weights in the 2-year study			
Reduced 8%-17% in dosed animals	Reduced 5%-12% in dosed animals	Reduced 5%-17% in dosed animals	Reduced 8%-22% in dosed animals
Survival rates in the 2-year study			
28/50; 26/50; 27/50	35/50; 34/50; 29/50	44/50; 42/50; 39/50	42/50; 40/50; 38/50
Nonneoplastic effects			
None	None	None	Renal karyomegaly, nephropathy, and cysts
Neoplastic effects			
None	None	Renal tubular cell adenomas or adenocarcinomas (combined)	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	Equivocal	No evidence
Other considerations			
Decreased tumor incidences in adrenal gland	Decreased tumor incidences in uterus	Decreased tumor incidences in liver	Decreased tumor incidences in liver and pituitary gland
Genetic toxicology			
Salmonella		CHO Cells in Vitro	
Gene Mutation		SCE	Aberration
Negative with and without S9		Negative with and without S9	Negative with and without S9

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

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

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

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic 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 incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of α-Methyldopa Sesquihydrate is based on the 13-week studies that began in July 1980 and ended in October 1980 and on the 2-year studies that began in August 1981 and ended in August 1983 at Physiological Research Laboratories (Minneapolis, Minnesota).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on α-methyldopa sesquihydrate on November 6, 1987, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF α-METHYLDOPA SESQUIHYDRATE

On November 6, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of α-methyldopa sesquihydrate received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J.K. Dunnick, NIEHS, NTP, introduced the toxicology and carcinogenesis studies by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats, equivocal evidence of carcinogenic activity for male mice, no evidence of carcinogenic activity for female mice).

Dr. Hughes, a principal reviewer, agreed with the conclusions. He thought that the concentrations used in the short-term studies, up to 100,000 ppm or 10% of the diet, were excessive and that the use of concentrations that high should be discouraged. Dr. Dunnick noted that NTP guidelines allowed a maximum concentration of 5% for 2-year studies. The higher concentration was used in the 14-day studies to help identify potential target organ toxicity.

Dr. Chinchilli, the second principal reviewer, was unable to attend. Dr. L. Hart, NIEHS, read his review, in which Dr. Chinchilli agreed in principle with the conclusions. However, he felt that a statistical analysis incorporating historical control data should be conducted for the tubular cell tumors of the kidney in male mice. He said that it was difficult to put in perspective the relevance of incidences in the current study (control, 0/50; low dose, 2/50; high dose, 1/50) when they were compared with the historical control incidence of 0.3% (6/2,029). He felt that results of such an analysis would not drastically affect the stated conclusions. Dr. J. Haseman, NIEHS, stated that the NTP does not generally use historical control data in a formal testing framework, due in part to changing incidences over time, particularly for the more common tumors. If the historical control incidence was used as the basis for comparison, then there would be a significant ($P<0.05$) increase in tumor incidence in the low dose group but not in the high dose group.

Dr. Perera, the third principal reviewer, agreed with the conclusions. She asked for discussion of the relationship between tubular cell hyperplasia and tubular cell adenomas and adenocarcinomas in the kidney of male mice. She also asked if there was a rationale for combining these endpoints as has been done for hyperplasia and tumors at other sites. Dr. Dunnick said that the Discussion would be expanded [see page 57] and references cited along with NTP results which support the progression of hyperplasia to neoplasia in renal tubular cells.

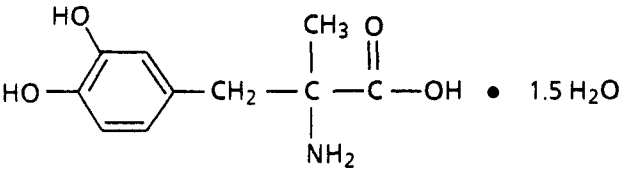
Dr. Sivak commented that the inclusion of a comparison of doses given to animals with the usual doses used therapeutically for humans was useful and important information. Dr. Popp requested that the nephropathy and cysts observed in dosed female mice be included under nonneoplastic effects in the summary table. Dr. Dunnick agreed that these effects were both biologically and statistically significant and would be added to the table [see page 7].

Dr. Hughes moved that the Technical Report on α-methyldopa sesquihydrate be accepted with revisions as discussed and with the conclusions as written for male and female rats and female mice, no evidence of carcinogenic activity, and for male mice, equivocal evidence of carcinogenic activity. Dr. Capen seconded the motion. Dr. Perera proposed an amendment that a statement be included after the conclusion for male mice that there was an increase in hyperplasia in the dosed groups. The amended motion was not seconded. The original motion then was approved unanimously with nine votes.

I. INTRODUCTION

Production and Use
Metabolism and Distribution
Mechanism of Action
Toxicity in Animals
Effects on the Reproductive System
Fetal and Teratologic Effects
Genetic Toxicology
Study Rationale

I. INTRODUCTION



α-METHYLDOPA SESQUIHYDRATE
(3-Hydroxy-α-methyl-L-tyrosine sesquihydrate)

CAS No. 41372-08-1

$C_{10}H_{13}NO_4 \cdot 1.5\,H_2O$ Molecular weight 238.24

Synonyms for α-methyldopa or α-methyldopa sesquihydrate: L-(α-MD); α-methyl-L-3,4-dihydroxyphenylalanine; L(-)-β-(3,4-dihydroxyphenyl)-α-methylalanine; L-(-)-3-(3,4-dihydroxyphenyl)-2-methylalanine; L-α-methyl-3,4-dihydroxyphenylalanine; α-methyl-β-(3,4-dihydroxyphenyl)-L-alanine; L-(-)-α-methyl-β-(3,4-dihydroxyphenyl)alanine; (-)-methyldopa; L-methyldopa; L-α-methyldopa; α-methyl-L-dopa

Trade names for α-methyldopa or α-methyldopa sesquihydrate: Aldomet; Aldometil; Aldomin; α-Medopa; AMD; Bayer 1440 L; Baypresol; Dopamet; Dopatec; Dopegyt; Hyperpax; Medomet; Medopren; Methoplain; MK. B51; MK-351; Presinol; Presolisin; Sedometil; Sembrina

Production and Use

α-Methyldopa sesquihydrate is used for the treatment of hypertension (Rudd and Blaschke, 1985) and is one of the most widely used drugs in the United States; approximately 21.2 million prescriptions for α-methyldopa sesquihydrate or α-methyldopa were written in 1982 (FDA, 1983). The blood pressure-reducing effects of α-methyldopa were first recognized in 1959; the D-isomer was found to be inactive, whereas the L-isomer had full pharmacologic activity (Oates et al., 1960). α-Methyldopa was introduced into clinical practice for the treatment of hypertension in the early 1960s (Reid and Elliott, 1984).

α-Methyldopa sesquihydrate is supplied as 125, 250, or 500 mg tablets that are taken two to four times per day; the hydrochloride of the ethyl ester (α-methyldopate hydrochloride) is used for intravenous injection; a combination of methyldopa and hydrochlorothiazide is available as tablets (USP, 1985; Remington's, 1985; PDR, 1988). Use of α-methyldopa may produce headache, dizziness, sedation, cardiovascular effects (such as bradycardia), nausea and vomiting, liver toxicity, and hematologic side effects (as noted by a positive Coombs' test and hemolytic anemia) (PDR, 1988). A multicenter, randomized, double-blind clinical trial comparing the effects of three major antihypertensive agents, captopril, methyldopa, and propranolol, indicated that the methyldopa treatment gave the highest incidence of side effects including fatigue, lethargy, and sexual disorders; all three drugs exhibited similar blood pressure control (Croog et al., 1986). In a study of 78 patients taking methyldopa, 61% were found to have biochemical evidence of liver damage, including increased serum levels of γ-glutamylpeptidase, aminoaspartate transaminase, and alkaline phosphatase (Stanley and Mijch, 1986). Twenty percent of persons taking α-methyldopa form IgG autoantibodies against red blood cells (Kelton, 1985). α-Methyldopa treatment has also been shown to decrease serum high-density lipoprotein cholesterol, although the mechanism for this is unknown (Ames and Hill, 1982). Some patients have taken methyldopa for up to 15 years (Dollery et al., 1984).

Metabolism and Distribution

The metabolism and distribution of α-methyldopa have been studied in humans. After oral administration, an average of 25% of the dose is absorbed in 36 hours (range, 8%-62%) (Kwan et al., 1976; Myhre et al., 1982). Maximum plasma concentration occurs after 2-3 hours, with a plasma half-life of 2 hours (Barnett et al., 1977). The

primary route of metabolism (probably in the gut wall or liver) is via sulfate conjugation to form methyldopa-*O*-sulfate (Kwan et al., 1976), catalyzed by phenol sulfotransferase (Campbell et al., 1985). A minor pathway of metabolism involves *O*-methylation catalyzed by catechol-*O*-methyltransferease. α-Methyldopa and its metabolites identified in urine after an oral dose to humans included α-methyldopa (25%), α-methyldopa sulfate (51%), α-methyldopamine (9%), α-methyldopamine sulfate (5%), and 3-*O*-methyl-α-methyldopa (10%). Metabolites identified in serum after oral administration to humans included methyldopa, norepinephrine, dihydroxybenzylamine, dopamine, and methyldopamine (Cooper et al., 1979). The metabolites identified in urine of rats given 1.9 mmol of α-methyldopa intraperitoneally included α-methyldopa, methoxymethyldopa, α-methyldopamine, and glucuronide conjugates of methoxymethyldopa and methoxymethyldopamine (Young and Edwards, 1964). Based on studies with perfused segments of rat intestine, Amidon et al. (1986) suggested that α-methyldopa is transported by a carrier-mediated mechanism through the intestinal wall. Free α-methyldopa has low permeability at the intestinal pH of 7.4.

α-Methyldopa can be metabolized in the brain to methylnorepinephrine and methylepinephrine, and the production of these metabolites may be responsible for the effects of methyldopa on the central nervous system and subsequently for its ability to lower blood pressure by reducing total peripheral resistance (Robertson et al., 1984; Freed et al., 1984; Bobik et al., 1986). α-Methyldopa has been detected in the milk of lactating women (Hoskins and Holliday, 1982; White et al., 1985).

Mechanism of Action

α-Methyldopa is an inhibitor of aromatic-L-amino acid decarboxylase, an enzyme that catalyzes the synthesis of epinephrine, and it was first thought that the mechanism for lowering blood pressure was due to the inhibition of the decarboxylase or that the therapeutic action of α-methyldopa was produced by interference with neurotransmission in peripheral sympathetic nerves by displacing norepinephrine (Young and Edwards, 1964; Reid and Elliott, 1984; Rudd and Blaschke, 1985). The hypotensive effect of α-methyldopa in cats was not blocked when a peripheral dopa decarboxylase inhibitor was given with methyldopa (Henning and Van Zwieten, 1968; Henning, 1969a,b). It is now generally recognized that methyldopa exerts its hypotensive effect by being converted in the central nervous system to α-methylnorepinephrine or to other metabolites that act as α_2-adrenergic agonists. Methyldopa is thought to enter central adrenergic neurons and form α-methylnorepinephrine, which stimulates α_2-adrenergic receptors and inhibits sympathetic outflow (Reid and Elliott, 1984; Rudd and Blaschke, 1985; Gillis et al., 1985). α-Methylepinephrine is eightfold more potent than α-methylnorepinephrine as an antihypertensive agent in rats (Robertson et al., 1984), and it might be the metabolite responsible for the therapeutic effects.

Toxicity in Animals

The LD_{50} values for α-methyldopa (milligrams racemic base/kilogram body weight) given in dilute hydrochloric acid or 1% aqueous methylcellulose have been reported as follows: albino female mice (Carworth CF1 strain), base in hydrochloric acid after intravenous administration, 1,760; after oral administration, 5,370; after intraperitoneal administration, 1,690; base in methylcellulose after oral administration, greater than 15,000; after intraperitoneal injection, 14,000 (Merck Institute, 1962).

The LD_{50} values in Sprague Dawley rats after the racemic base was administered in hydrochloric acid by oral administration were 5,800 mg/kg in females and 5,710 mg/kg in males and after intraperitoneal injection, 564 mg/kg in females and 430 mg/kg in males (Merck Institute, 1962). As was seen in mice, when α-methyldopa was administered in 1% methylcellulose, the LD_{50} values increased and were greater than 9,000 mg/kg in both male and female rats after intraperitoneal injection and greater than 15,000 mg/kg after oral administration.

One-year toxicity studies of α-methyldopa were conducted in male and female Sprague Dawley rats (Merck Institute, 1962). Groups of 25 male and 25 female rats were administered 0, 250, 500, or 1,000 mg racemic α-methyldopa/kg body

weight by oral gavage as a 1% aqueous methylcellulose suspension, 5 days per week. A necropsy was performed on 129 rats; the remaining rats were not examined because of autolysis. After the fourth week, all dosed groups became sedated; effects varied from slight sedation for 3 hours at 250 mg/kg to moderate to heavy sedation for 4-6 hours at 1,000 mg/kg. Sedation was more apparent in males than in females. The 1,000 mg/kg groups of animals were flaccid on the dosing days. Animals appeared normal on Monday following a weekend without being dosed. The feces of all dosed rats were black as a result of the presence of oxidized drug. Adipsia was seen in the 1,000 mg/kg group; rats at this dose drank approximately one-third less water than did controls. The average body weight gain was similar among groups, except for the 1,000 mg/kg male rats; this group had a 10%-13% reduction in body weight gain which was considered to be related to decreased feed intake as a result of sedation. The death of 144/200 animals before the end of the studies was attributed to chronic pneumonia. No compound-related histopathologic changes were found.

α-Methyldopa administration can increase serum prolactin levels in humans (Turkington, 1972; Steiner et al., 1976) and in rats (Muller et al., 1967; Wiggins et al., 1980; Forman et al., 1981). α-Methyldopa has been found to increase the growth of DMBA-induced mammary tumors in Sprague Dawley rats; this increase was attributed to increased prolactin levels because L-dopa, a compound that decreases prolactin levels, inhibited the growth of the mammary tumors (Quadri et al., 1973). Prolactin has been shown to stimulate the growth of human mammary carcinoma cells in vitro (Simon et al., 1984). Prolactin induced lactose synthetase activity and DNA synthesis in nitrosomethylurea-induced mammary tumors in organ cultures (Edery et al., 1983).

Effects on the Reproductive System

One of the potential side effects from α-methyldopa treatment is sexual dysfunction in men (Alexander and Evans, 1975; Pillay, 1976; Taylor et al., 1981; Croog et al., 1986). α-Methyldopa sesquihydrate administered to male F344/N rats by gavage 5 days per week for 65 days at doses of 0, 50, 100, 200, or 400 mg/kg was toxic to the reproductive system at 200 and 400 mg/kg as measured by decreased fertility, decreased sperm count, decreased sperm motility, and apparent number of late spermatids (Dunnick et al., 1986; Appendix I). The fertility index (number of males with pregnant females/number of males mated) was 62%, 81%, 67%, 14%, and 5% for the 0, 50, 100, 200, and 400 mg/kg groups, respectively. Decreased weight gain was also seen at these doses. Plasma testosterone levels were reduced but returned to the levels of the corresponding vehicle controls within 1 day of cessation of chemical administration. Following a 13-week recovery period without dosing, reproductive functions were similar to those in the concurrent control group. Decreased sexual function (copulation frequency, penile reflexes, and tissue catecholamines) was seen in Long-Evans male rats administered α-methyldopa at 300 mg/kg by intraperitoneal injection for 12 days (Melman et al., 1983, 1984). Sprague Dawley male rats administered α-methyldopa (100 mg/kg every 12 hours for 36 days) showed decreased serum testosterone levels, but these hormone levels returned to normal after a 36-day recovery period (Greening, 1978).

A single subcutaneous injection of α-methyldopa (300 mg/kg) suppressed ovulation in female Sherman rats after stimulation with pregnant mare serum (Coppola et al., 1966). Microinjections of α-methyldopa into the hypothalamus resulted in decreased ovulation in immature Sprague Dawley rats (Kordon, 1971).

Fetal and Teratologic Effects

α-Methyldopa may be used during pregnancy to control maternal hypertension. In one study, no long-term sequelae were reported in infants (from dosed mothers) followed for up to 7 years (Naden and Redman, 1985). In another study, boys born to mothers taking α-methyldopa were found to have a smaller head circumference at birth and at ages 4 and 7, but this decreased head size was not associated with any apparent effects on mean intelligence quotients (Cockburn et al., 1982). When α-methyldopa was administered to the mother, maternal and newborn infant drug levels were comparable (Jones et al., 1979).

When α-methyldopa was given by gavage to pregnant CD-1 mice (0, 100, 250, 500, or 750 mg/kg) on days 6-17 of gestation and to pregnant CD rats (0, 50, 100, 250, or 500 mg/kg) on days 6-20 of gestation, the number of malformations in fetuses per litter was marginally increased at the highest doses; α-methyldopa at these high doses also was severely toxic (as measured by body weight gain depression and deaths) to the mother (Sleet et al., 1987). No fetal abnormalities were seen at levels at which maternal toxicity was mild. α-Methyldopa administered by gavage to pregnant Sprague Dawley rats on days 1-21 of gestation (100 mg/kg per day) caused an increased incidence of hemorrhage in the interscapular brown fat of the offspring; this effect was observable within 3 days of birth (Kitchin and DiStefano, 1976).

In a three-generation study in Sharpe and Dohme mice, α-methyldopa was administered in feed at concentrations that delivered an estimated dose of 0, 25, 100, 500, or 1,000 mg methyldopa/kg body weight (Peck et al., 1965). No evidence of toxicity or fetal abnormalities was seen in any of the generations. Changes seen in the 1,000 mg/kg group, including a slight decrease in the percentage of pregnancies, a decrease in the average weight of the pups, and a decrease in the percentage of animals weaned, were considered to be related to the sedative effects of the drug.

In a two-litter reproductive study in rats (strain unspecified), α-methyldopa was administered in feed at concentrations that delivered an estimated dose of 0 or 100 mg/kg per day, and normal parturition was permitted (Peck et al., 1965). No fetal abnormalities were seen, although survival of pups to the fourth day was decreased in the exposed group.

When α-methyldopa was given to pregnant New Zealand White rabbits from day 20 to 28 of gestation (term is 31 days), cardiac norepinephrine was found to be depressed in the offspring 1 and 2 weeks after birth, but at 4 weeks there were no significant differences between control and dosed groups (Hoskins and Friedman, 1980). The authors hypothesize that decreased cardiac levels of norepinephrine might diminish the capacity to maintain cardiovascular homeostasis in response to stressful stimuli.

Genetic Toxicology

The limited data on the genotoxic activity of α-methyldopa in vitro indicate that α-methyldopa is not mutagenic. α-Methyldopa was not mutagenic in several strains of *Salmonella typhimurium* when tested without exogenous metabolic activation by the plate incorporation procedure (Dybing, 1977; White et al., 1977) or by preincubation followed by plating (Ishidate et al., 1981). α-Methyldopa sesquihydrate was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, or TA1535 when tested by the NTP in a preincubation protocol in the absence or presence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Table E1).

Ishidate et al. (1981) tested the ability of α-methyldopa to induce chromosomal aberrations in Chinese hamster lung fibroblast cells in vitro with a 5-hour exposure time in the absence of S9 followed by cell harvest at 24 and 48 hours total culture time. Data were not presented in the report, but the authors stated that doses included a 50% growth inhibition dose. Defining a positive response as the induction of chromosomal abnormalities (polyploidy or structural aberrations) in at least 10% of examined cells (two times the background frequency), the authors concluded that methyldopa was clastogenic. In contrast, NTP cytogenetic tests with cultured Chinese hamster ovary cells demonstrated no induction of chromosomal aberrations or sister chromatid exchanges by α-methyldopa sesquihydrate (at doses up to those that are lethal) in either the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Tables E2 and E3). Cell harvest in the NTP chromosomal aberration assay occurs approximately 12 hours (one cell cycle) after culture initiation, and chemical treatment time, in the absence of S9, is for the duration of the culture.

I. INTRODUCTION

Study Rationale

α-Methyldopa was nominated by the National Cancer Institute for toxicity and carcinogenicity studies in rodents because it is a commonly used drug for which no carcinogenicity studies were available. The USP grade of the drug (α-methyldopa sesquihydrate; USP, 1985) was selected for toxicologic evaluation. The oral route was chosen because the drug is given orally for the treatment of hypertension.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF α-METHYLDOPA SESQUIHYDRATE

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF α-METHYLDOPA SESQUIHYDRATE

α-Methyldopa sesquihydrate was obtained in three lots from Merck Sharpe and Dohme (Table 1). Purity and identity determinations were conducted on all lots at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on the analyses performed in support of the α-methyldopa sesquihydrate studies are on file at NIEHS.

All lots of the study chemical were identified as α-methyldopa sesquihydrate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared spectra were consistent with the literature spectra (Aldrich Library of Infrared Spectra); the nuclear magnetic resonance spectra were consistent with that expected for α-methyldopa sesquihydrate (representative infrared and nuclear magnetic resonance spectra are presented in Figures 1 and 2).

The purity of all lots was determined by elemental analysis, Karl Fischer water analysis, nonaqueous potentiometric titration of the amine group with 0.1 N perchloric acid in glacial acetic acid, nonaqueous (dimethylformamide solution) titration of the carboxyl group with 0.1 N tetrabutylammonium hydroxide in isopropanol:methanol (9:1), thin-layer chromatography, and high-performance liquid chromatography. Thin-layer chromatography was performed on lot no. M021981 and lot no. M122782 with silica gel plates and *n*-butanol:water:glacial acetic acid (60:20:20) (solvent system 1) and with chloroform:methanol:water:glacial acetic acid (40:40:10:10) (solvent system 2). Lot no. 89693 was analyzed with methanol:acetonitrile:glacial acetic acid (70:25:1) (solvent system 1) and isopropanol:water:pH 4 phthalate buffer (70:25:5) (solvent system 2). High-performance liquid chromatography was performed with a Waters μBondapak C_{18} column and a Whatman CO:PELL ODS guard system. The solvent system was aqueous 5 mM sodium lauryl sulfate containing 2% (v/v) glacial acetic acid:5 mM sodium lauryl sulfate in methanol containing 2% (v/v) glacial acetic acid. The solvent ratios were 60:40 and 40:60 for lot no. 89693, 45:55 for lot no. M021981, and 48:52 for lot no. M122782.

Results of elemental analyses agreed with the theoretical values for lot nos. 89693 and M122782; results of analysis of lot no. M021981 were slightly high for carbon. The water content of lot no. 89693 was 11.4%, that of lot no. M021981 was 12.7%, and that of lot no. M122782 was 11.4%. By titration of the amine group, lot no. 89693 was 99.3% pure, lot no. M021981 was 100.3% pure, and lot no. M122782 was 99.4% pure. By titration of the carboxyl group, lot no. 89693 was found to be 99.1% pure; lot no. M021981, 101.7% pure; and lot no. M122782, 99.3% pure. A single spot was detected by thin-layer chromatography of lot no. M122782 with both systems. For lot no. M021981, solvent system 1 indicated a major spot and a trace impurity, whereas system 2 gave a single spot only.

TABLE 1. IDENTITY AND SOURCE OF α-METHYLDOPA SESQUIHYDRATE USED IN THE FEED STUDIES

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Number		
89693	89693	M021981; M122782
Date of Initial Use		
8/15/79	7/7/80	M021981--8/11/81; M122782--1/6/83
Supplier		
Merck Sharp and Dohme (West Point, PA)	Merck Sharp and Dohme (West Point, PA)	Merck Sharp and Dohme (West Point, PA)

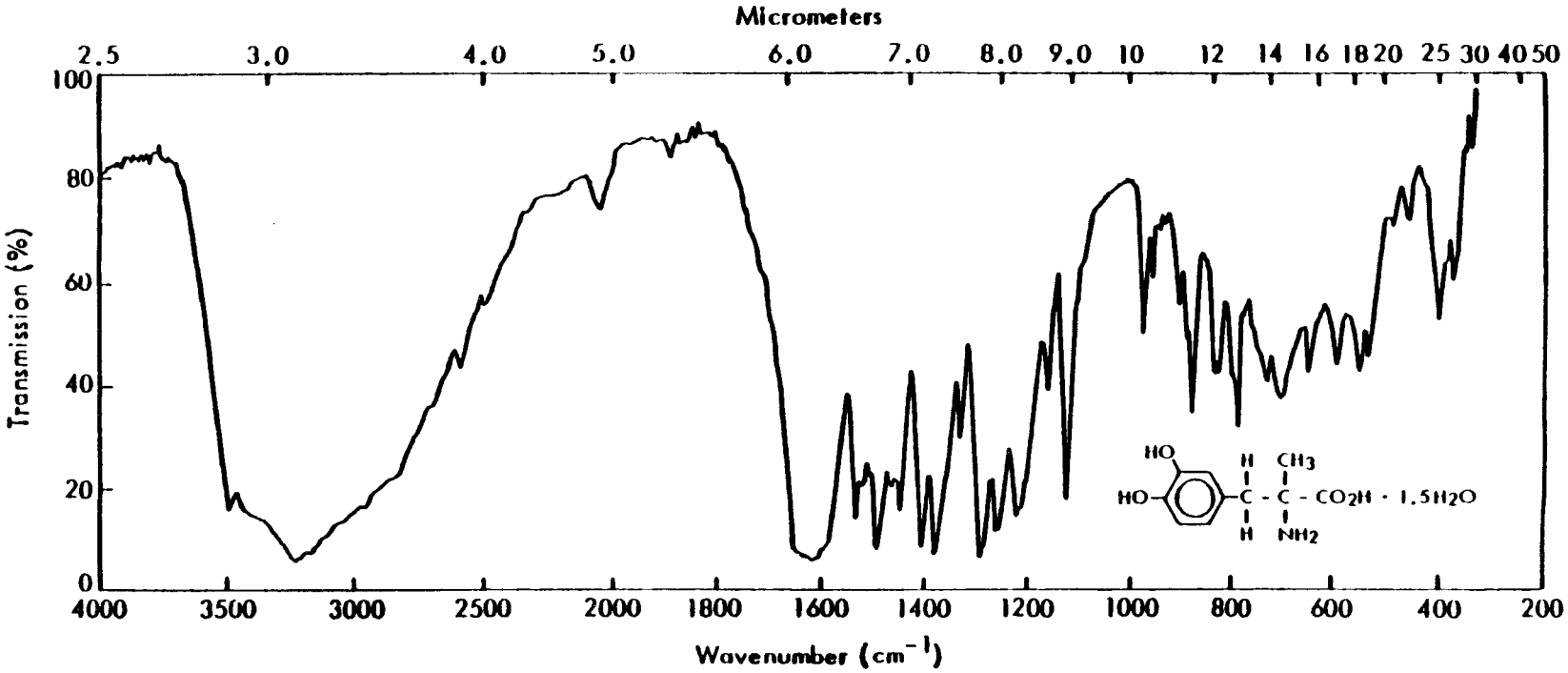


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF α-METHYLDOPA SESQUIHYDRATE (LOT NO. M021981)

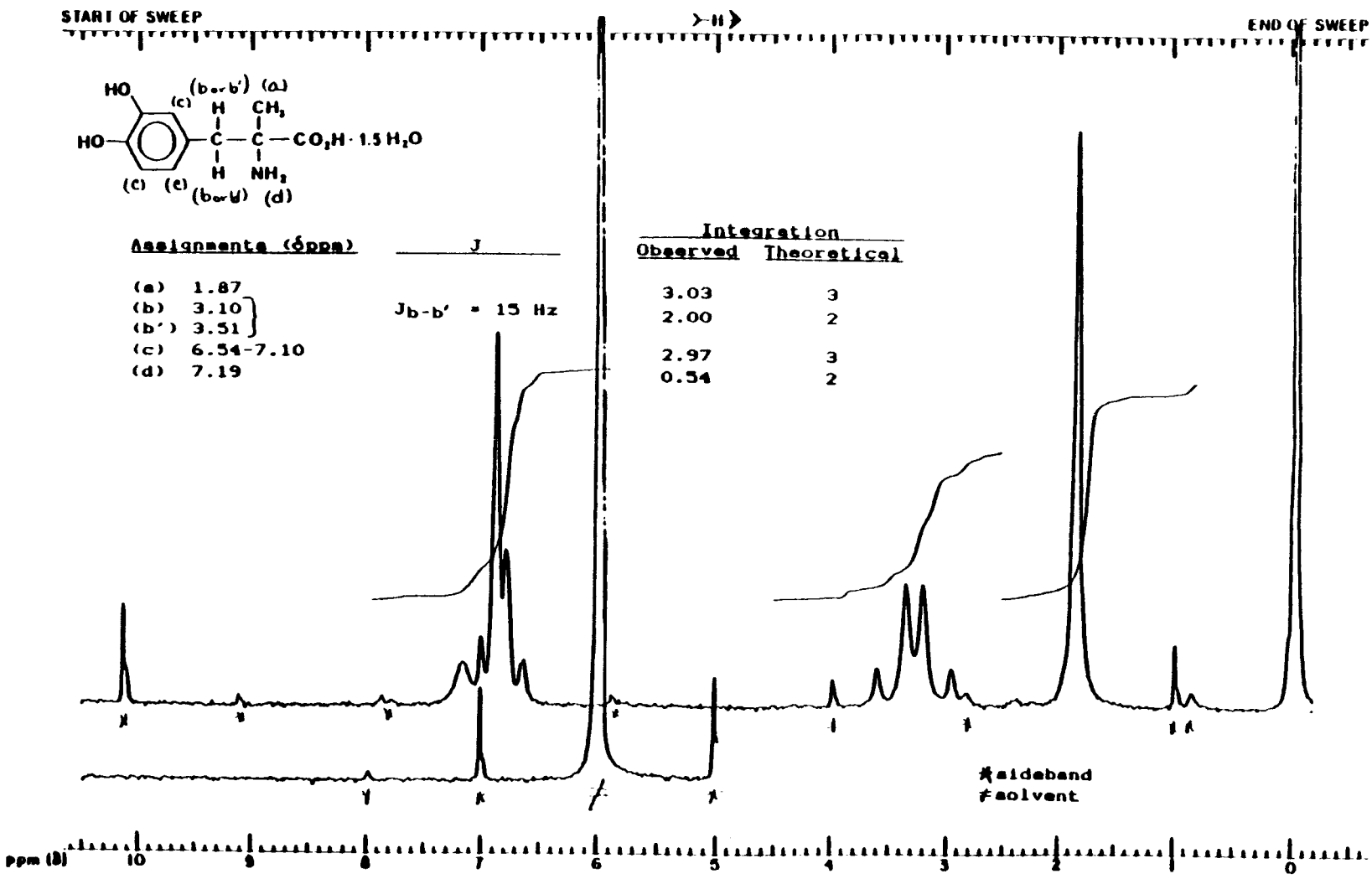


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF α-METHYLDOPA SESQUIHYDRATE (LOT NO. M122782)

Identical patterns of decomposition with streaking were observed for both lot no. 89693 and a USP standard in each of the two solvent systems. High-performance liquid chromatography indicated that lot no. 89693 contained four impurities, none with an area greater than 0.42% that of the major peak; none of the impurities detected in lot nos. M021981 and M122782 had areas greater than 0.1% that of the major peak. The purity of lot no. M122782 was 99.9% relative to a USP sample by comparison of major peaks after high-performance liquid chromatography. Cumulative data indicated that the purity of all three lots was greater than 99%.

The study material used in the 2-year studies (lot nos. M021981 and M122782) met all USP requirements including infrared and ultraviolet spectra, color change in the presence of triketohydrindene hydrate, specific rotation ($[\alpha]_D$ at 28° C of −25.82° [lot no. M021981] or −25.7° [lot no. M122782]; the USP standard is between −25° and −28°), acidity, water content, residue on ignition, heavy metal content, 3-*O*-methylmethyldopa content, and a purity of at least 98% as indicated by titration with perchloric acid in glacial acetic acid. The specific rotation of lot no. 89693, $[\alpha]_D$ at 28° C, was −24.4°, slightly lower than USP specifications.

Stability studies conducted by high-performance liquid chromatography, with the same column as described previously and a solvent system of water with 5 mM heptanesulfonic acid and 1% (v/v) acetic acid:methanol with 5 mM heptanesulfonic acid and 1% (v/v) acetic acid (60:40) and with 1.615 mg/ml propiophenone as the internal standard, indicated that α-methyldopa sesquihydrate was stable as a bulk chemical for 2 weeks at temperatures up to 60° C in the dark. α-Methyldopa sesquihydrate was stored at 5° C during the studies. Confirmation of the stability of the bulk chemical during the studies was obtained by infrared spectroscopy and high-performance liquid chromatography. No deterioration of the study material was seen over the course of the studies.

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

Formulated diets were shown to be homogeneous by sampling a feed blend containing 5,000 ppm α-methyldopa sesquihydrate at three locations within the blender. The mean concentration of α-methyldopa sesquihydrate at each location of the blender varied less than 1% from the target concentration. The stability of 5,000 ppm α-methyldopa in feed was determined by high-performance liquid chromatography after extraction with methanol:water:acetic acid (49.5:49.5:1; v/v/v). The column was the same as described previously, the internal standard was acetanilide, and the solvent ratio was 70% 5 mM aqueous heptanesulfonic acid:acetic acid (97:3) to 30% 5 mM heptanesulfonic acid in methanol:acetic acid (97:3). α-Methyldopa sesquihydrate was found to be stable in feed when stored for 2 weeks at temperatures up to 25° C. Formulated diets were prepared by adding a dry premix (approximately equal amounts of feed and α-methyldopa) to feed. The mixture then was blended for 15 minutes (Table 2). Analysis for α-methyldopa in feed mixtures was performed to confirm that correct concentrations were administered to animals. Formulated diets were analyzed once at the study laboratory during the 13-week studies. The results ranged between 98% and 105% of the target concentrations (Table 3). During the 2-year studies, the formulated diets were analyzed at approximately 8-week intervals. Data on the number of times that the concentrations were within specifications can be extrapolated to indicate the frequency with which diets were formulated within the specified ±10% of the target concentrations. For the α-methyldopa sesquihydrate studies, the diets were formulated within ±10% of the target concentrations 100% (56/56) of the time throughout the studies (Table 4). Referee analyses were periodically performed by the analytical chemistry laboratory. Good agreement generally was found between the analytical chemistry and study laboratories (Table 5).

TABLE 2. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Mixing was conducted in a Patterson-Kelly 8-qt Twin-Shell® blender for 5 min with intensifer bar followed by 10 min without intensifier bar.	α-Methyldopa sesquihydrate and feed were mixed in a beaker with a spatula. The premix and remaining feed were mixed in a Patterson-Kelly blender for 5 min with intensifier bar followed by 10 min without intensifier bar.	Similar to 13-wk studies
Maximum Storage Time		
14 d	14 d	14 d
Storage Conditions		
4° C in the dark	10° C	25° C in opaque containers

TABLE 3. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Date Mixed	Concentration of α-Methyldopa Sesquihydrate (ppm) (a)		Determined as a Percent of Target
	Target	Determined	
07/15/80	3,100	3,200	103.2
	6,300	6,200	98.4
	12,500	13,100	104.8
	25,000	25,100	100.0
	50,000	48,800	97.6
09/09/80	3,100	(b,c) 2,925	94.4

(a) Results of duplicate analysis
(b) Performed by analytical chemistry laboratory
(c) Results of triplicate analysis

TABLE 4. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Date Mixed	Concentration of α-Methyldopa Sesquihydrate in Feed for Target Concentration (ppm) (a)			
	3,100	6,300 (b)	6,300 (c)	12,500
08/04/81	3,200	6,300	6,400	12,500
09/09/81	3,130	6,420	6,450	12,700
10/22/81	3,100	6,500	6,800	13,000
12/10/81	3,040	6,370	6,270	12,500
01/28/82	3,110	6,480	6,340	12,800
04/29/82	3,200	6,700	6,800	13,300
07/01/82	3,130	6,240	6,450	12,600
08/19/82	3,120	6,000	6,300	12,500
10/07/82	3,200	6,000	6,000	12,900
12/09/82	3,160	6,220	6,190	12,700
12/23/82	3,060	6,350	6,600	13,200
03/10/83	2,980	5,970	6,120	12,490
05/18/83	3,180	6,030	6,380	12,500
07/12/83	3,150	6,660	6,610	13,100
Mean (ppm)	3,126	6,303	6,408	12,771
Standard deviation	65.1	241.1	235.6	284.8
Coefficient of variation (percent)	2.1	3.8	3.7	2.2
Range (ppm)	2,980-3,200	5,970-6,700	6,000-6,800	12,490-13,300
Number of samples	14	14	14	14

(a) Results of duplicate analysis
(b) Used for rats
(c) Used for mice

TABLE 5. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
08/04/81	6,300	(c) 6,400 (e) 6,300	(d) 6,800
04/29/82	3,100	3,200	3,200
10/07/82	12,500	12,900	12,600
05/18/83	6,300	(c) 6,380 (e) 6,030	(d) 6,310

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) Formulation for mice
(d) Mouse or rat formulation not specified
(e) Formulation for rats

II. MATERIALS AND METHODS

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 2 weeks before the studies began. Rats were 6 weeks old when placed on study, and mice were 6-8 weeks old. Groups of five males and five females were fed diets containing 0, 6,250, 12,500, 25,000, 50,000, or 100,000 ppm α-methyldopa sesquihydrate for 14 days. Rats and mice were observed once per day and were weighed on days 1, 8, and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 6.

THIRTEEN-WEEK STUDIES

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

Four-week-old male and female F344/N rats and 5-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 20 days (rats) or 19 days (mice). Animals with weights within ±10%-15% of the estimated mean body weight were randomly assigned individual numbers and to cages. Diets containing 0, 3,100, 6,300, 12,500, 25,000, or 50,000 ppm α-methyldopa sesquihydrate were fed to groups of 10 rats and 10 mice of each sex for 13 weeks.

Animals were housed five per cage. Formulated diets, control diets, and water were available ad libitum. Animals were checked two times per day; moribund animals were killed. Feed consumption was measured once per week by cage. Individual animal weights were recorded once per week. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 6.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 3,100, or 6,300 ppm α-methyldopa sesquihydrate were fed to groups of 50 male and 50 female rats for 103 weeks. Diets containing 0, 6,300, or 12,500 ppm α-methyldopa sesquihydrate were fed to groups of 50 male and 50 female mice for 103 weeks.

Source and Specifications of Animals

The male and female F344/N rats and the male and female B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Frederick Cancer Research Center under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 5-6 weeks of age and mice, at 5 weeks of age. The rats were quarantined at the study facility for 13 days and the mice, for 14 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. Male rats were 8 weeks old when placed on study, and female rats and mice were 7 weeks old. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

Animal Maintenance

Male and female rats and female mice were housed by sex five per cage; male mice were housed individually. Cages were not rotated during the studies. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 6.

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
0, 6,250, 12,500, 25,000, 50,000, or 100,000 ppm α-methyldopa sesquihydrate in feed	0, 3,100, 6,300, 12,500, 25,000, or 50,000 ppm α-methyldopa sesquihydrate in feed	Rats--0, 3,100, or 6,300 ppm α-methyldopa sesquihydrate in feed; mice--0, 6,300, or 12,500 ppm
Date of First Dose		
8/15/79	7/7/80	Rats--8/11/81; mice--8/26/81
Date of Last Dose		
8/28/79	10/5/80	Rats--8/1/83; mice--8/16/83
Duration of Dosing		
14 consecutive d	13 wk	103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter; feed consumption measured 1 × wk	Same as 14-d studies	Observed 2 × d; weighed 1 × wk for 13 wk and then 1 × mo; feed consumption measured 1 × mo
Necropsy and Histologic Examination		
Necropsy performed on all animals; approximately 10% of the animals were examined histologically	Necropsy performed on all animals; histologic exam performed on all controls, all dosed animals dying before the scheduled kill, all animals in the highest dose groups, and all dosed animals in which lesions were found at necropsy. Tissues examined include: adrenal glands, bone marrow, brain, colon, esophagus, eyes, femur, gallbladder (mice), gross lesions, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes/seminal vesicles or ovaries/uterus, regional lymph nodes, salivary glands, skin, small intestine, spinal cord if neurologic signs present, spleen, sternebrae or femur or vertebrae, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Kidneys and bone marrow of all rats, testes of male rats, uterus of female rats, and kidneys of mice at 12,500 ppm or more were examined; liver weighed at necropsy	Necropsy performed on all animals; the following tissues examined histologically for control and high dose groups: adrenal glands, brain, cecum, colon, costochondral junction, duodenum, esophagus, eyes, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, pancreas, parathyroids, pharynx, pituitary gland, prostate/testes or ovaries/uterus, rectum, regional lymph nodes, salivary glands, skin, spleen, sternebrae or vertebrae or femur including marrow, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder; tissues examined for low dose groups--male rats: adrenal glands, liver, stomach, and testis; female rats: adrenal glands, liver, stomach, and uterus; male mice: brain, kidneys, liver, spleen, and stomach; female mice: brain, kidneys, liver, pituitary gland, spleen, stomach, kidneys, and uterus
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Rats--Charles River Breeding Laboratories (Portage, MI); mice--Charles River Breeding Laboratories (Kingston, NY)	Frederick Cancer Research Center (Frederick, MD)

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Study Laboratory Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
Method of Animal Identification Rats--tail mark; mice--ear punch	Toe clip	Toe clip and ear notch
Time Held Before Study 14 d	Rats--20 d; mice--19 d	Rats--13 d; mice--14 d
Age When Placed on Study Rats--6 wk; mice--6-8 wk	Rats-- 7 wk; mice--8 wk	Rats--male: 8 wk; female: 7 wk; mice--7 wk
Age When Killed Rats--8 wk; mice--8-10 wk	Rats--20 wk; mice--21 wk	Rats--male: 112 wk; female: 111 wk; mice--111 wk
Necropsy Dates 8/30/79-8/31/79	Rats--10/6/80; mice--10/7/80	Rats--8/8/83-8/10/83; mice--8/22/83-8/25/83
Method of Animal Distribution Animals within ±10%-15% of estimated mean body weight randomly given individual numbers and assigned to cages	Same as 14-d studies	Same as 14-d studies
Feed Rodent Laboratory 5001 Meal® (Ralston Purina Co., St. Louis, MO)	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding Aspen wood chips (Minnesota Sawdust and Shavings Co., Anoka, MN)	Same as 14-d studies	Aspen wood shavings (Minnesota Sawdust and Shavings Co., Anoka, MN)
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum; softened through sodium zeolite to < 1 grain/gal; filtered through spun polyethylene	Same as 14-d studies	Same as 14-d studies
Cages Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
Cage Filters Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as 14-d studies	Same as 14-d studies
Animals per Cage 5	5	5, except for male mice that were housed individually
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--18.9°-22.2° C; hum--52%-68%; light 12 h/d	Temp--20.0°-25.5° C; hum--37%-74%; light 12 h/d	Temp--21.1°-24.4° C; hum--30%-72%; fluorescent light 12 h/d; 15 room air changes/h

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 6) were performed on all high dose and control animals and on low dose animals dying through month 21 of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically. If mortality in the highest dose group exceeded that in the control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

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

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathology results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the

survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

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

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

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

Fisher Exact/Cochran-Armitage Trend Analyses--In addition to survival-adjusted methods, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

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

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

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III. RESULTS: RATS

FOURTEEN-DAY STUDIES

All rats that received 100,000 ppm and 2/5 females that received 50,000 ppm α-methyldopa sesquihydrate died before the end of the studies (Table 7). Final mean body weights of dosed male rats were 14%-43% lower than that of the controls; final mean body weights of dosed female rats were 9%-24% lower. Female rats that received 50,000 ppm lost weight. Feed consumption by male rats that received 50,000 or 100,000 ppm and female rats that received 12,500 ppm or more was less than that by controls. Animals in the two highest dose groups were lethargic.

THIRTEEN-WEEK STUDIES

Four of 10 males and 7/10 females that received 50,000 ppm and 1/10 females that received 25,000 ppm died before the end of the studies (Table 8). Final mean body weights of rats that received 25,000 or 50,000 ppm were 22% and 46% lower than that of controls for males and 26% and 43% lower than that of controls for females. Feed consumption by dosed groups was lower than that by controls. Compound-related clinical signs of toxicity, which were more severe at levels of 12,500 ppm or higher, included lethargy, hyperexcitability, ocular discharge, and rough hair coats. Liver weight to body weight ratios for male rats that received 12,500 or 25,000 ppm were significantly lower than that for controls (Table 9). Minimal to moderate tubular cell regeneration of the renal inner cortex occurred in exposed rats of each sex; severe pyelonephritis was present in the kidney of four high dose male rats. Bone marrow hypoplasia in males and females, moderate to severe seminal vesicle and testicular hypoplasia, and minimal to moderate uterine hypoplasia were also considered to be compound related (Table 10).

TABLE 7. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	121 ± 2	191 ± 3	+70 ± 3		13	15
6,250	5/5	114 ± 7	164 ± 5	+50 ± 4	86	12	11
12,500	5/5	110 ± 8	162 ± 3	+52 ± 7	85	12	12
25,000	(e) 4/5	107 ± 10	148 ± 6	+32 ± 5	77	10	11
50,000	5/5	95 ± 7	108 ± 11	+13 ± 6	57	6	7
100,000	(f) 0/5	100 ± 11	(g)	(g)	(g)	4	3
FEMALE							
0	5/5	100 ± 1	131 ± 2	+31 ± 1		11	10
6,250	5/5	100 ± 1	118 ± 2	+18 ± 2	90	13	7
12,500	5/5	99 ± 2	115 ± 2	+16 ± 1	88	8	7
25,000	5/5	99 ± 2	119 ± 5	+20 ± 3	91	8	8
50,000	(h) 3/5	99 ± 2	99 ± 1	−2 ± 2	76	4	6
100,000	(i) 0/5	100 ± 1	(g)	(g)	(g)	4	3

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Day of death: 5
(f) Day of death: 9,14,14,14,14
(g) No data are reported due to the 100% mortality in this group.
(h) Day of death: 3,14
(i) Day of death: 4,6,14,14,14

TABLE 8. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	156 ± 2	349 ± 3	+193 ± 3		16	15
3,100	10/10	143 ± 2	317 ± 6	+174 ± 6	91	14	13
6,300	10/10	139 ± 2	314 ± 4	+175 ± 4	90	13	13
12,500	10/10	144 ± 2	311 ± 4	+167 ± 4	89	13	12
25,000	10/10	135 ± 3	273 ± 6	+138 ± 5	78	11	11
50,000	(e) 6/10	115 ± 2	189 ± 5	+73 ± 6	54	6	8
FEMALE							
0	10/10	118 ± 2	208 ± 3	+90 ± 2		11	11
3,100	10/10	116 ± 2	189 ± 2	+73 ± 2	91	9	9
6,300	10/10	113 ± 2	188 ± 4	+75 ± 3	90	8	9
12,500	10/10	117 ± 3	196 ± 4	+79 ± 3	94	9	9
25,000	(f) 9/10	111 ± 2	154 ± 5	+43 ± 4	74	5	6
50,000	(g) 3/10	96 ± 1	119 ± 6	+24 ± 5	57	3	5

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Week of death: 3,4,9,9
(f) Week of death: 1
(g) Week of death: 3,3,3,3,3,9,9

TABLE 9. ANALYSIS OF LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE (a)

Concentration (ppm)	Number Weighed	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Final Body Weight (mg/g)
MALE				
0	10	349 ± 3.2	14,574 ± 763	41.8 ± 2.31
3,100	10	(b) 317 ± 6.5	13,905 ± 469	43.8 ± 1.02
6,300	10	(b) 314 ± 3.9	(b) 11,527 ± 287	36.8 ± 1.02
12,500	10	(b) 311 ± 3.8	(b) 10,391 ± 281	(b) 33.5 ± 1.14
25,000	10	(b) 273 ± 5.7	(b) 8,856 ± 404	(b) 32.5 ± 1.38
50,000	6	(b) 189 ± 5.5	(b) 7,410 ± 509	39.0 ± 1.97
FEMALE				
0	10	208 ± 3.2	8,045 ± 471	38.5 ± 1.95
3,100	10	(b) 189 ± 2.3	(b) 6,459 ± 125	34.2 ± 0.56
6,300	10	(b) 188 ± 4.4	(b) 6,586 ± 183	35.1 ± 0.76
12,500	10	196 ± 3.9	(c) 6,808 ± 247	34.7 ± 0.98
25,000	9	(b) 154 ± 4.6	(b) 5,557 ± 248	36.1 ± 0.87
50,000	3	(b) 119 ± 5.7	(b) 4,840 ± 246	41.1 ± 3.96

(a) Mean ± standard error; P values vs. controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.01$
(c) $P<0.05$

TABLE 10. NUMBER OF RATS WITH SELECTED LESIONS IN THE THIRTEEN-WEEK FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Site/Lesion	Male (ppm)						Female (ppm)					
	0	3,100	6,300	12,500	25,000	50,000	0	3,100	6,300	12,500	25,000	50,000
Number examined	10	10	10	10	10	10	10	10	10	10	10	10
Kidney												
Tubular cell regeneration	0	0	0	3	10	9	0	0	0	4	7	10
Pyelonephritis	0	0	0	0	0	4	0	0	0	0	0	0
Bone marrow												
Hypoplasia, hematopoietic	0	0	0	0	9	4	0	0	3	7	6	7
Seminal vesicles												
Hypoplasia	0	0	0	0	0	4	--	--	--	--	--	--
Testis												
Hypoplasia	0	0	0	0	0	4	--	--	--	--	--	--
Uterus												
Hypoplasia	--	--	--	--	--	--	0	0	2	6	8	8

Dose Selection Rationale: Based on the number of deaths at 25,000 ppm (one female) and 50,000 ppm (4/10 males and 7/10 females) and the reduced body weight gain and kidney lesions seen at 12,500 ppm or higher, the dietary concentrations selected for rats in the 2-year studies were 3,100 and 6,300 ppm.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of dosed male rats were 14%-16% lower than those of controls by week 2 and were generally 8%-17% lower than those of controls throughout the studies (Table 11 and Figure 3). The mean body weights of the dosed female rats were generally 5%-12% lower than those of the controls throughout the studies. The average daily feed consumption was 93% that of controls for dosed males and 90% and 88% for low and high dose females (Tables G1 and G2). The average amount of α-methyldopa sesquihydrate consumed per day was approximately 110 or 230 mg/kg for low dose or high dose male rats and 120 or 240 mg/kg for low dose or high dose female rats. Fighting was observed among male rats and occurred more frequently in dosed groups than in the control group.

TABLE 11. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Weeks on Study	Control		3,100 ppm			6,300 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	149	50	142	95	50	145	97	50
1	165	50	159	96	50	163	99	50
2	216	50	185	86	50	181	84	50
3	244	50	208	85	50	204	84	50
4	260	50	226	87	50	218	84	50
5	276	50	242	88	50	231	84	50
6	290	50	258	89	50	243	84	50
7	302	50	270	89	50	252	83	50
8	309	50	275	89	50	264	85	50
9	320	50	289	90	50	281	88	50
10	330	50	301	91	50	290	88	50
11	344	50	312	91	50	302	88	50
12	352	50	321	91	50	311	88	50
15	371	50	346	93	50	336	91	49
18	386	50	355	92	50	344	89	49
24	403	50	366	91	50	362	90	49
28	414	50	379	92	50	373	90	49
31	420	50	375	89	50	372	89	49
36	420	50	373	89	50	371	88	49
40	429	50	381	89	49	379	88	49
44	432	50	387	90	49	381	88	49
48	440	49	390	89	49	384	87	49
53	444	49	399	90	49	394	89	49
57	446	49	407	91	49	396	89	49
62	451	48	410	91	49	401	89	49
66	450	47	412	92	49	400	89	48
70	451	47	405	90	49	404	90	47
74	442	47	408	92	49	405	92	47
79	440	47	405	92	46	409	93	46
83	435	44	401	92	44	396	91	45
87	423	44	403	95	43	396	94	43
92	427	40	402	94	41	388	91	41
96	423	36	396	94	40	388	92	36
101	424	32	388	92	32	377	89	29
103	436	28	387	89	26	365	84	27
FEMALE								
0	127	50	126	99	50	130	102	50
1	141	50	134	95	50	135	96	50
2	155	50	140	90	50	140	90	50
3	165	50	150	91	50	148	90	50
4	169	50	156	92	50	154	91	50
5	175	50	163	93	50	158	90	50
6	180	50	168	93	50	161	89	50
7	186	50	173	93	50	164	88	50
8	186	50	177	95	50	164	88	50
9	190	50	180	95	50	170	89	50
10	193	50	182	94	50	174	90	50
11	200	50	187	94	50	178	89	50
12	203	50	192	95	50	183	90	50
15	219	50	206	94	50	194	89	50
18	221	50	213	96	50	202	91	50
24	224	50	218	97	50	213	95	50
28	234	50	226	97	50	224	96	50
31	239	50	226	95	50	233	97	50
36	239	50	234	98	50	236	99	50
40	244	50	234	96	50	247	101	50
44	253	50	240	95	50	252	100	50
48	262	50	244	93	49	259	99	49
53	278	50	259	93	49	267	96	49
57	287	50	263	92	49	271	94	49
62	301	50	272	90	49	279	93	48
66	307	50	274	89	49	282	92	48
70	316	50	278	88	49	286	91	47
74	315	50	281	89	49	291	92	47
79	331	47	291	88	47	295	89	47
83	319	44	290	91	47	292	92	45
87	329	42	295	90	45	301	91	44
92	332	40	296	89	41	307	92	41
96	331	39	299	90	38	308	93	38
101	340	35	304	89	35	308	91	33
103	338	35	300	89	34	301	89	29

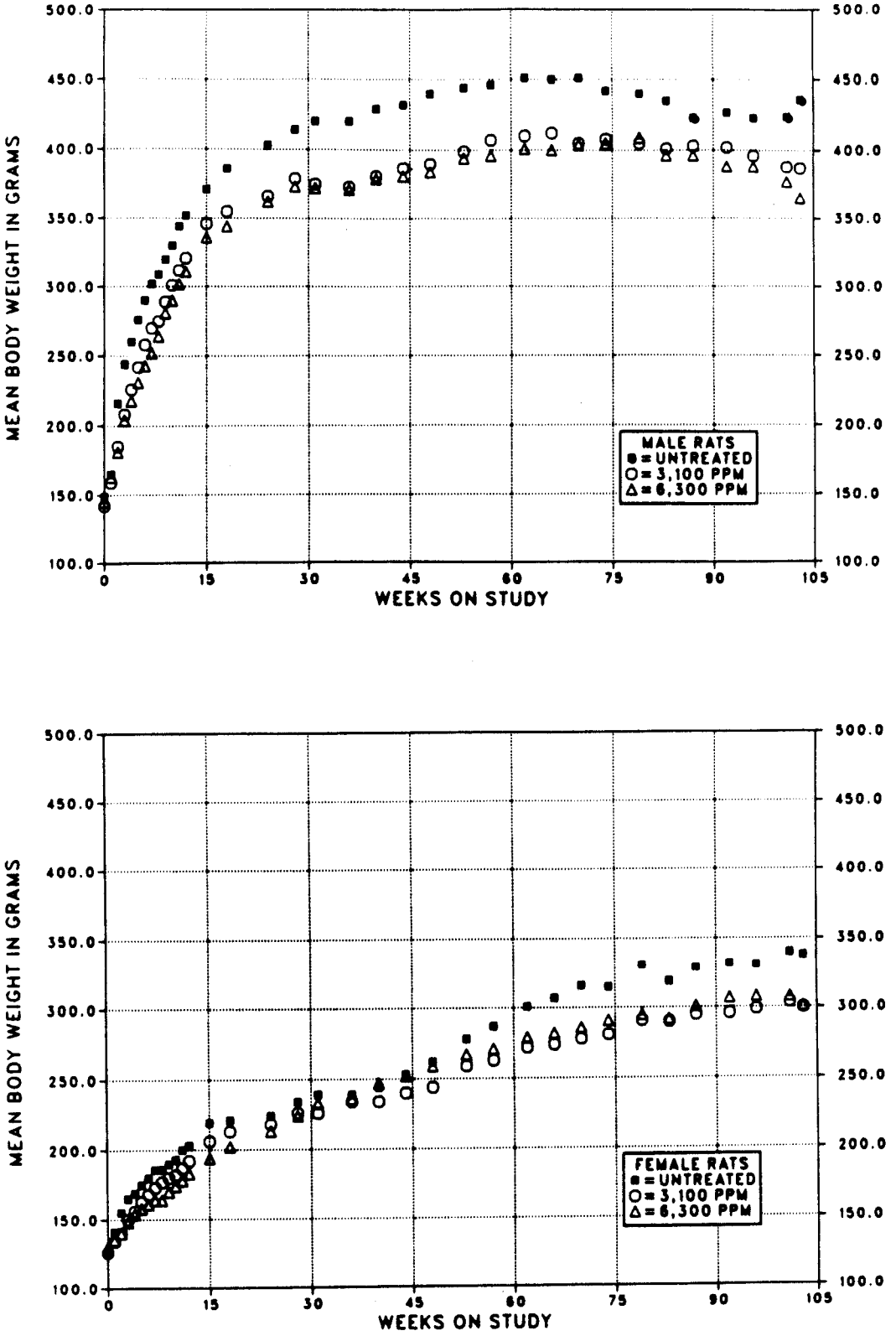

FIGURE 3. GROWTH CURVES FOR RATS FED DIETS CONTAINING α-METHYLDOPA SESQUIHYDRATE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing α-methyldopa sesquihydrate at the concentrations used in these studies and for controls are shown in Table 12 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the Zymbal gland, adrenal gland, forestomach, uterus, and eye.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Historical incidences of tumors in control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

TABLE 12. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

	Control	3,100 ppm	6,300 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	24	23
Killed at termination	28	26	27
Survival P values (c)	0.916	0.940	0.984
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	15	16	21
Killed at termination	34	34	29
Died during termination period	1	0	0
Survival P values (c)	0.317	0.883	0.365

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

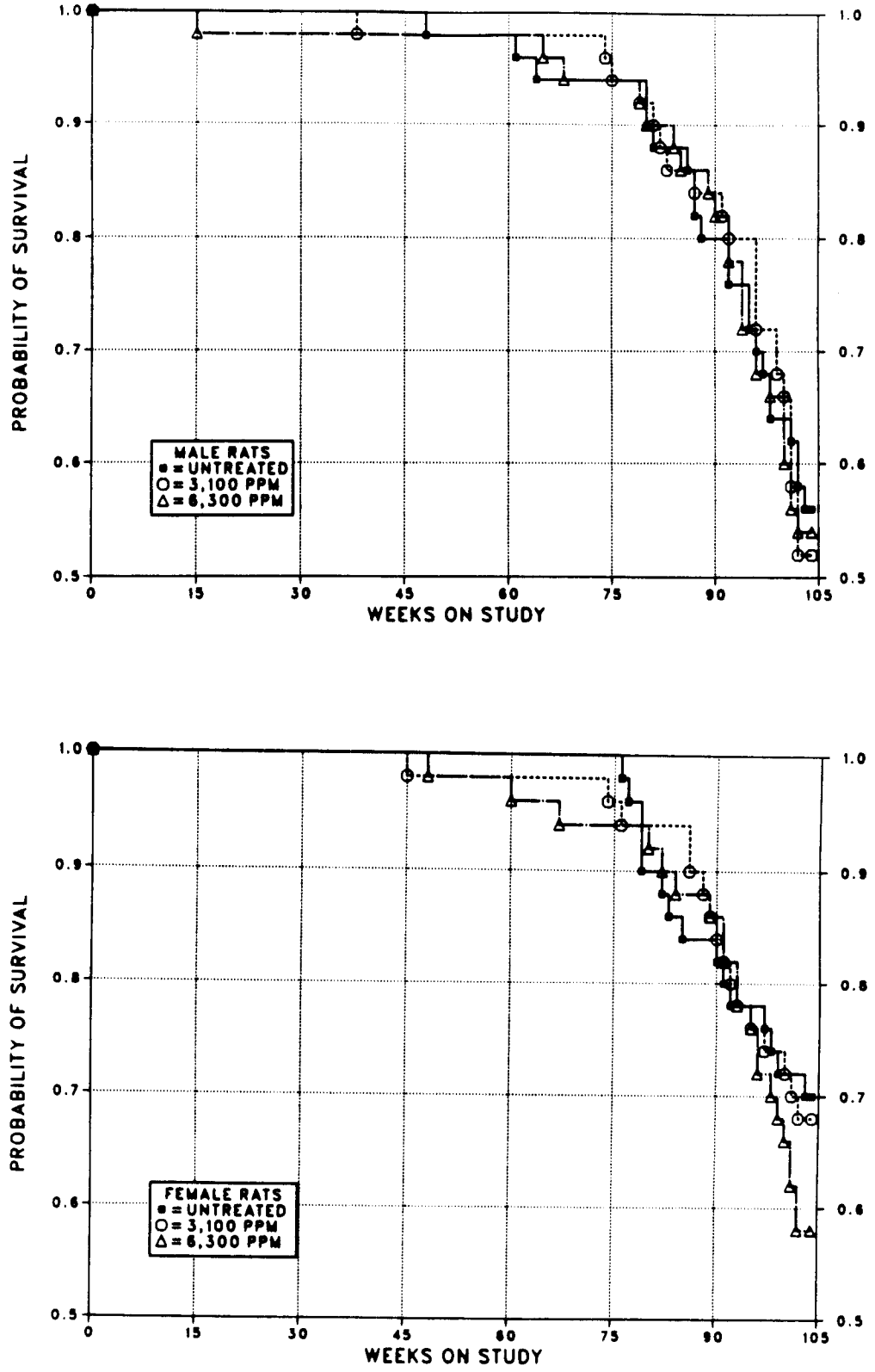

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING α-METHYLDOPA SESQUIHYDRATE FOR TWO YEARS

Zymbal Gland: Squamous cell carcinomas occurred in the Zymbal gland of 3/50 low dose male rats. The Zymbal gland consists of collections of sebaceous glands associated with the external ear canal. These small glands are not routinely examined microscopically in all animals in NTP studies, and the tumors in the low dose group were identified by gross examination at necropsy and then characterized by microscopic examination. The historical incidence of Zymbal gland neoplasms in untreated control male F344/N rats is 15/1,937; the highest observed incidence in a control group is 3/50. These neoplasms were not considered to be related to chemical exposure.

Adrenal Gland: The incidence of focal hyperplasia of the cortex in low dose male rats was greater than that in controls (male: control, 13/49; low dose, 26/49; high dose, 16/50; female: 34/50; 37/50; 25/50). Pheochromocytomas and pheochromocytomas or malignant pheochromocytomas (combined) in male rats occurred with significant negative trends; the incidences in the dosed groups were significantly lower than those in the controls (Table 13).

Forestomach: Edema, chronic inflammation, ulcers, and epithelial hyperplasia were observed at increased incidences in high dose rats (Table 14). No neoplasms of the forestomach were diagnosed in male or female rats.

Uterus: Endometrial stromal polyps in female rats occurred with a significant negative trend; the incidences in the dosed groups were significantly lower than that in controls (Table 15).

Eye: Retinal atrophy and cataracts of the lens were observed at increased incidences in low dose female rats (retinal atrophy--male: control, 1/49; low dose, 5/50; high dose, 1/50; female: 6/50; 18/50; 12/50; cataracts--male: 1/49; 3/50; 1/50; female: 7/50; 17/50; 10/50). The low dose groups were on the top two tiers of the racks, and this proximity to the fluorescent light source was the probable cause of increased cataracts in these groups.

TABLE 13. ANALYSIS OF ADRENAL GLAND MEDULLARY LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (a)

	Control	3,100 ppm (b)	6,300 ppm (b)
Focal Hyperplasia			
Overall Rates	14/49 (29%)	7/49 (14%)	6/50 (12%)
Pheochromocytoma			
Overall Rates	18/49 (37%)	2/49 (4%)	6/50 (12%)
Adjusted Rates	52.1%	5.9%	19.2%
Terminal Rates	12/28 (43%)	0/26 (0%)	4/27 (15%)
Week of First Observation	81	100	92
Life Table Tests	P=0.002N	P<0.001N	P=0.008N
Incidental Tumor Tests	P=0.001N	P<0.001N	P=0.004N
Malignant Pheochromocytoma			
Overall Rates	3/49 (6%)	1/49 (2%)	4/50 (8%)
Pheochromocytoma or Malignant Pheochromocytoma (c)			
Overall Rates	21/49 (43%)	3/49 (6%)	10/50 (20%)
Adjusted Rates	61.1%	7.9%	28.3%
Terminal Rates	15/28 (54%)	0/26 (0%)	5/27 (19%)
Week of First Observation	81	81	68
Life Table Tests	P=0.012N	P<0.001N	P=0.026N
Incidental Tumor Tests	P=0.006N	P<0.001N	P=0.012N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes).
(b) The estimated dose in milligrams per kilograms per day is given in Chapter III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix G.
(c) Historical incidence at study laboratory (mean ± SD): 36/149 (24% ± 4%); historical incidence in NTP studies: 460/1,913 (24% ± 13%)

TABLE 14. NUMBER OF RATS WITH LESIONS OF THE FORESTOMACH IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Lesion	Male (ppm)			Female (ppm)		
	0	3,100	6,300	0	3,100	6,300
No. examined	49	49	50	50	50	49
Edema	2	1	9	1	1	4
Chronic inflammation	2	3	8	0	3	7
Ulcer	0	2	6	0	1	2
Epithelial hyperplasia	1	2	6	0	1	6

TABLE 15. ANALYSIS OF UTERINE ENDOMETRIAL STROMAL POLYPS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (a)

	Control	3,100 ppm	6,300 ppm
Overall Rates	15/50 (30%)	5/49 (10%)	1/50 (2%)
Adjusted Rates	35.7%	12.7%	3.4%
Terminal Rates	9/35 (26%)	2/34 (6%)	1/29 (3%)
Week of First Observation	79	86	104
Life Table Tests	P<0.001N	P=0.019N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.014N	P<0.001N

(a) Historical incidence at study laboratory (mean ± SD): 33/149 (22% ± 8%); historical incidence in NTP studies: 424/1,963 (22% ± 8%)

FOURTEEN-DAY STUDIES

All the mice lived to the end of the studies (Table 16). All groups of males, including controls, lost weight during the studies. The final mean body weight of female mice that received 100,000 ppm was 91% that of controls. Feed consumption by dosed mice was lower than that by controls during week 1 of the studies but was comparable during week 2. Rough hair coats and excitability were considered to be compound-related effects.

THIRTEEN-WEEK STUDIES

The incidence of deaths in the various groups is given in Table 17. Fighting was observed in all groups of dosed male mice. Final mean body weights of mice that received 25,000 or 50,000 ppm were 12% and 19% lower than that of controls for males and 8% and 12% lower for females. Feed consumption was not affected by incorporation of α-methyldopa sesquihydrate in feed. Compound-related clinical signs of toxicity in males were indicated by irritability, hyperexcitability, and greater tendency toward fighting. Ocular discharge was noted for mice of each sex at all concentrations.

TABLE 16. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Day 7	Day 13
MALE							
0	5/5	25.7 ± 1.3	25.6 ± 1.4	−0.1 ± 1.5		3.2	3.1
6,250	5/5	25.3 ± 0.9	25.0 ± 1.0	−0.3 ± 0.4	97.7	2.8	3.6
12,500	5/5	25.5 ± 0.7	20.0 ± 1.0	−5.5 ± 1.0	78.1	2.6	3.2
25,000	5/5	26.8 ± 1.6	24.9 ± 1.8	−1.9 ± 0.8	97.3	2.2	3.6
50,000	5/5	25.2 ± 0.7	24.8 ± 0.8	−0.4 ± 0.5	96.9	2.0	3.3
100,000	5/5	27.7 ± 0.7	23.8 ± 0.7	−3.9 ± 0.2	93.0	1.9	2.8
FEMALE							
0	5/5	20.3 ± 0.6	21.9 ± 0.6	+1.6 ± 0.2		3.0	3.1
6,250	5/5	20.7 ± 0.5	22.4 ± 0.4	+1.7 ± 0.3	102.3	2.3	2.9
12,500	5/5	21.0 ± 0.7	21.9 ± 0.5	+0.9 ± 0.2	100.0	2.2	3.0
25,000	5/5	21.3 ± 0.4	20.5 ± 0.7	−0.8 ± 0.6	93.6	2.1	3.2
50,000	5/5	21.3 ± 1.2	21.1 ± 1.2	−0.2 ± 0.3	96.3	1.7	3.0
100,000	5/5	20.4 ± 0.9	20.0 ± 0.9	−0.4 ± 0.4	91.3	1.7	3.1

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

TABLE 17. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	24.5 ± 0.4	32.6 ± 0.5	+8.1 ± 0.5		3.6	3.8
3,100	(e) 8/10	22.2 ± 0.5	30.2 ± 0.6	+7.8 ± 0.7	92.6	3.9	3.5
6,300	(f) 7/10	21.4 ± 0.5	29.5 ± 0.8	+8.0 ± 0.5	90.5	3.4	3.5
12,500	(g) 7/10	20.9 ± 0.3	29.8 ± 0.7	+9.0 ± 0.6	91.4	3.4	3.8
25,000	(h) 8/10	21.0 ± 0.5	28.6 ± 0.5	+7.8 ± 0.4	87.7	3.6	3.5
50,000	10/10	21.0 ± 0.3	26.3 ± 0.4	+5.3 ± 0.3	80.7	3.6	3.5
FEMALE							
0	10/10	19.5 ± 0.4	25.1 ± 0.7	+5.6 ± 0.5		3.1	3.1
3,100	10/10	19.5 ± 0.2	25.8 ± 0.5	+6.3 ± 0.5	102.8	2.9	3.2
6,300	10/10	18.9 ± 0.3	24.0 ± 0.5	+5.1 ± 0.3	95.6	3.1	3.3
12,500	10/10	18.7 ± 0.2	23.0 ± 0.5	+4.3 ± 0.4	91.6	3.2	3.4
25,000	10/10	16.6 ± 0.4	23.1 ± 0.3	+6.5 ± 0.4	92.0	3.2	3.1
50,000	(i) 8/10	16.1 ± 0.5	22.0 ± 0.5	+5.5 ± 0.6	87.6	4.3	3.8

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Week of death: 5,7
(f) Week of death: 3,7,7
(g) Week of death: 6,7,8
(h) Week of death: 4,9
(i) Week of death: both 1

Mice of each sex receiving concentrations above 12,500 ppm were lethargic. Liver weight to body weight ratios for dosed mice were not significantly different from those for controls (Table 18). Minimal to mild nuclear enlargement (karyomegaly) of the renal cortical tubular epithelium was observed in all females that received 12,500 ppm or more and in 5/10 males that received 12,500 ppm, 9/10 males that received 25,000 ppm, and 10/10 males that received 50,000 ppm. The severity was greater at 25,000 and 50,000 ppm than at lower concentrations.

Dose Selection Rationale: Because of kidney lesions and the severity of clinical signs in dosed mice at 25,000 ppm or higher, dietary concentrations selected for mice for the 2-year studies were 6,300 and 12,500 ppm α-methyldopa sesquihydrate. Male mice were individually housed during the 2-year study because dosed males in the 13-week study were observed fighting.

TABLE 18. ANALYSIS OF LIVER WEIGHTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE (a)

Concentration (ppm)	Number Weighed	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Final Body Weight (mg/g)
MALE				
0	10	32.6 ± 0.5	1,799 ± 81	55.4 ± 2.69
3,100	8	(b) 30.2 ± 0.6	1,699 ± 69	56.3 ± 1.83
6,300	7	(c) 29.5 ± 0.8	1,680 ± 88	56.8 ± 2.15
12,500	7	(c) 29.8 ± 0.7	1,799 ± 124	60.3 ± 3.95
25,000	8	(c) 28.6 ± 0.5	1,649 ± 44	57.7 ± 1.13
50,000	10	(c) 26.3 ± 0.4	(c) 1,281 ± 15	48.7 ± 0.86
FEMALE				
0	10	25.1 ± 0.7	1,243 ± 25	49.9 ± 1.50
3,100	10	25.8 ± 0.5	1,213 ± 37	47.0 ± 0.87
6,300	10	24.0 ± 0.5	(b) 1,097 ± 39	45.8 ± 1.33
12,500	10	(b) 23.0 ± 0.5	(c) 1,072 ± 36	46.6 ± 1.15
25,000	10	(b) 23.1 ± 0.3	1,172 ± 34	50.8 ± 1.05
50,000	8	(c) 22.0 ± 0.5	1,185 ± 33	53.9 ± 0.56

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.05$
(c) $P<0.01$

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of dosed mice were 5%-22% lower than those of controls throughout the studies (Table 19 and Figure 5). The average daily feed consumption by low and high dose mice was 109% and 104% that by controls for males and 105% and 108% for females (Tables G3 and G4). The average amount of α-methyldopa sesquihydrate consumed per day was approximately 830-890 or 1,760-1,800 mg/kg for low dose or high dose mice. Compound-related clinical signs included a cough reflex (through month 8) and irritability in males and rough hair coats in females.

TABLE 19. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Weeks on Study	Control Av. Wt. (grams)	Control No. of Survivors	6,300 ppm Av. Wt. (grams)	6,300 ppm Wt. (percent of controls)	6,300 ppm No. of Survivors	12,500 ppm Av. Wt. (grams)	12,500 ppm Wt. (percent of controls)	12,500 ppm No. of Survivors
MALE								
1	20.4	50	22.0	108	50	21.3	104	50
2	23.5	50	23.3	99	49	22.2	94	50
3	25.0	50	24.1	96	49	22.6	90	50
4	26.2	50	24.6	94	49	23.4	89	50
5	26.2	50	25.4	97	49	23.8	91	50
6	26.6	50	26.8	101	49	24.5	92	50
7	27.5	50	26.9	98	49	25.2	92	50
8	28.4	50	27.0	95	49	25.6	90	50
9	28.7	50	27.3	95	49	26.0	91	49
10	29.2	50	28.1	96	49	26.1	89	49
11	29.4	50	28.7	98	49	27.6	94	49
12	29.8	50	28.7	96	49	28.1	94	49
13	31.6	50	30.6	97	49	28.7	91	49
16	32.3	50	31.5	98	49	30.0	93	49
21	33.0	50	32.0	97	49	30.3	92	46
25	34.3	50	32.7	95	49	31.1	91	46
30	34.9	50	33.9	97	49	32.2	92	45
32	--	--	--	--	--	32.4	--	45
33	36.9	50	33.7	91	49	--	--	--
38	36.6	50	35.2	96	49	34.9	95	45
43	37.8	50	36.1	96	49	34.5	91	45
46	38.7	49	36.1	93	49	34.4	89	44
51	38.4	49	37.3	97	49	35.7	93	44
55	39.3	49	37.9	96	49	36.2	92	44
59	40.4	49	37.8	94	49	36.9	91	44
64	41.6	49	38.8	93	49	36.9	89	44
68	42.2	49	39.6	94	49	36.8	87	44
72	42.8	49	39.1	91	49	35.9	84	42
77	43.2	48	40.1	93	48	38.1	88	41
81	43.3	48	39.7	92	47	38.0	88	40
85	44.3	46	41.7	94	47	38.7	87	39
90	44.5	46	40.6	91	47	39.1	88	39
94	43.0	45	39.8	93	47	38.4	89	39
99	43.3	45	39.8	92	45	38.3	88	39
103	42.0	44	36.8	88	42	34.8	83	39
FEMALE								
1	18.3	50	17.0	93	50	17.0	93	50
2	19.0	50	18.0	95	50	17.3	91	50
3	20.1	50	18.9	94	50	18.4	92	50
4	20.6	50	18.6	90	50	19.0	92	50
5	21.6	50	20.7	96	50	20.0	93	50
6	22.3	50	21.3	96	50	20.2	91	50
7	23.0	50	22.0	96	50	21.1	92	50
8	23.4	50	22.6	97	50	22.3	95	50
9	23.5	50	22.8	97	50	22.5	96	50
10	23.8	50	23.7	100	50	22.8	96	50
11	24.6	50	23.6	96	50	23.2	94	50
12	24.2	50	23.6	98	50	23.3	96	50
13	24.3	50	23.9	98	50	23.6	97	50
16	26.2	50	25.0	95	50	24.7	94	50
20	26.7	50	26.1	98	50	25.3	95	50
25	28.2	50	26.5	94	49	24.8	88	49
30	28.9	50	26.6	92	49	26.0	90	48
33	29.6	50	26.8	91	49	26.1	88	48
38	31.8	50	28.1	88	49	27.6	87	48
43	32.7	50	29.1	89	49	28.2	86	45
46	33.7	50	29.3	87	49	28.2	84	45
51	35.1	50	30.6	87	49	29.7	85	45
55	35.0	50	30.9	88	48	29.2	83	45
59	37.2	49	32.4	87	48	29.9	80	45
64	39.7	49	32.9	83	48	32.0	81	45
68	40.3	49	33.3	83	48	31.4	78	45
72	40.7	49	33.2	82	48	32.0	79	45
77	40.6	48	34.4	85	48	33.3	82	45
81	42.4	47	34.9	82	47	33.3	79	44
85	43.0	47	35.8	83	46	34.0	79	43
90	43.0	47	37.3	87	44	35.0	81	41
94	43.4	46	36.5	84	42	35.2	81	40
99	43.8	45	37.1	85	42	35.3	81	39
103	43.8	43	37.5	86	40	35.4	81	38

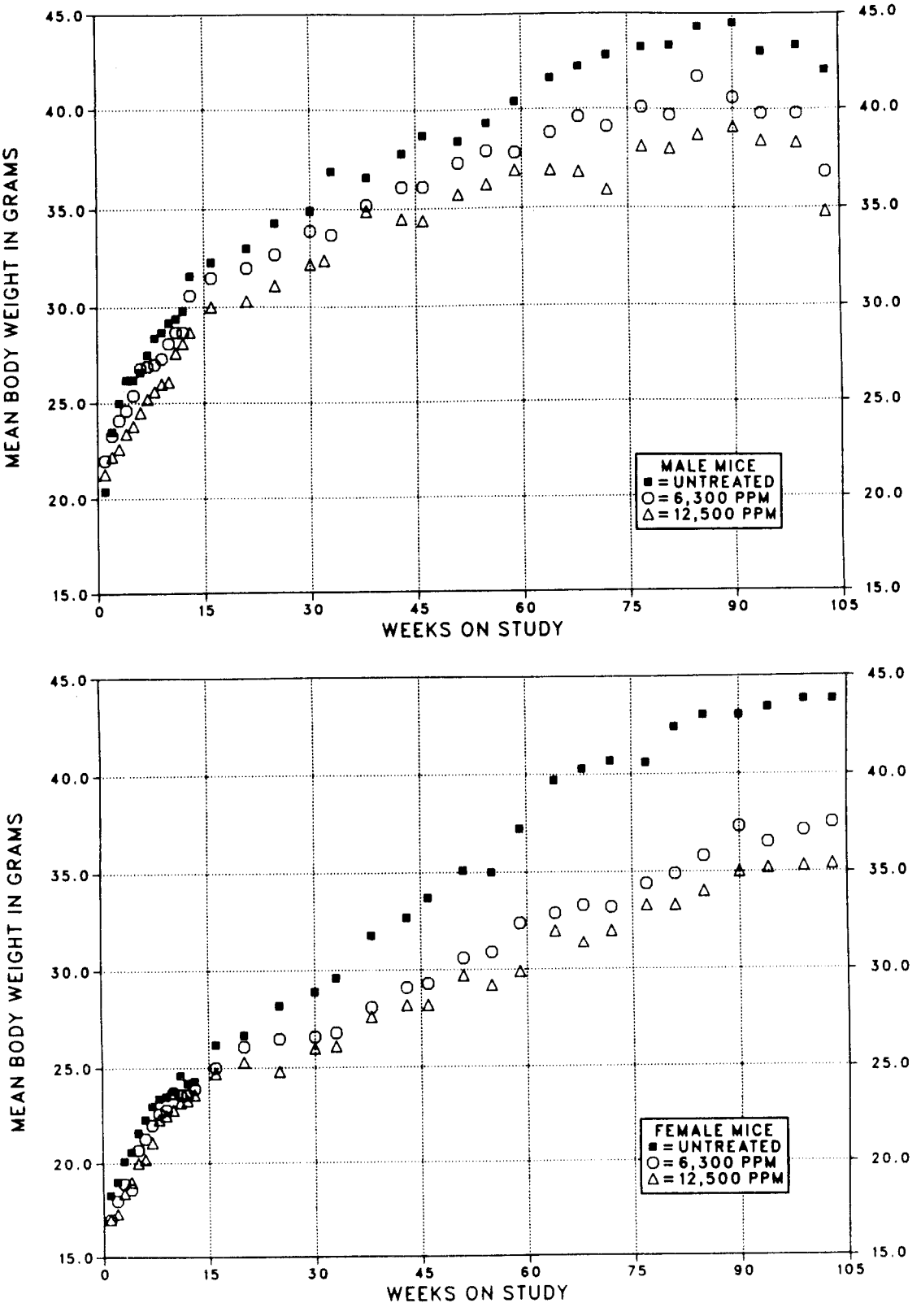

FIGURE 5. GROWTH CURVES FOR MICE FED DIETS CONTAINING α-METHYLDOPA SESQUIHYDRATE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing α-methyldopa sesquihydrate at the concentrations used in these studies and for controls are shown in Table 20 and in the Kaplan and Meier curves in Figure 5. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the kidney, glandular stomach, liver, anterior pituitary gland, uterus, ovary, bone, and nasal mucosa.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Historical incidences of tumors in control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Historical incidences of tumors in control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

TABLE 20. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

	Control	6,300 ppm	12,500 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	6	8	7
Accidentally killed	0	0	4
Killed at termination	44	42	39
Survival P values (c)	0.702	0.787	0.800
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	8	10	8
Accidentally killed	0	0	4
Killed at termination	42	40	38
Survival P values (c)	0.931	0.933	0.841

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

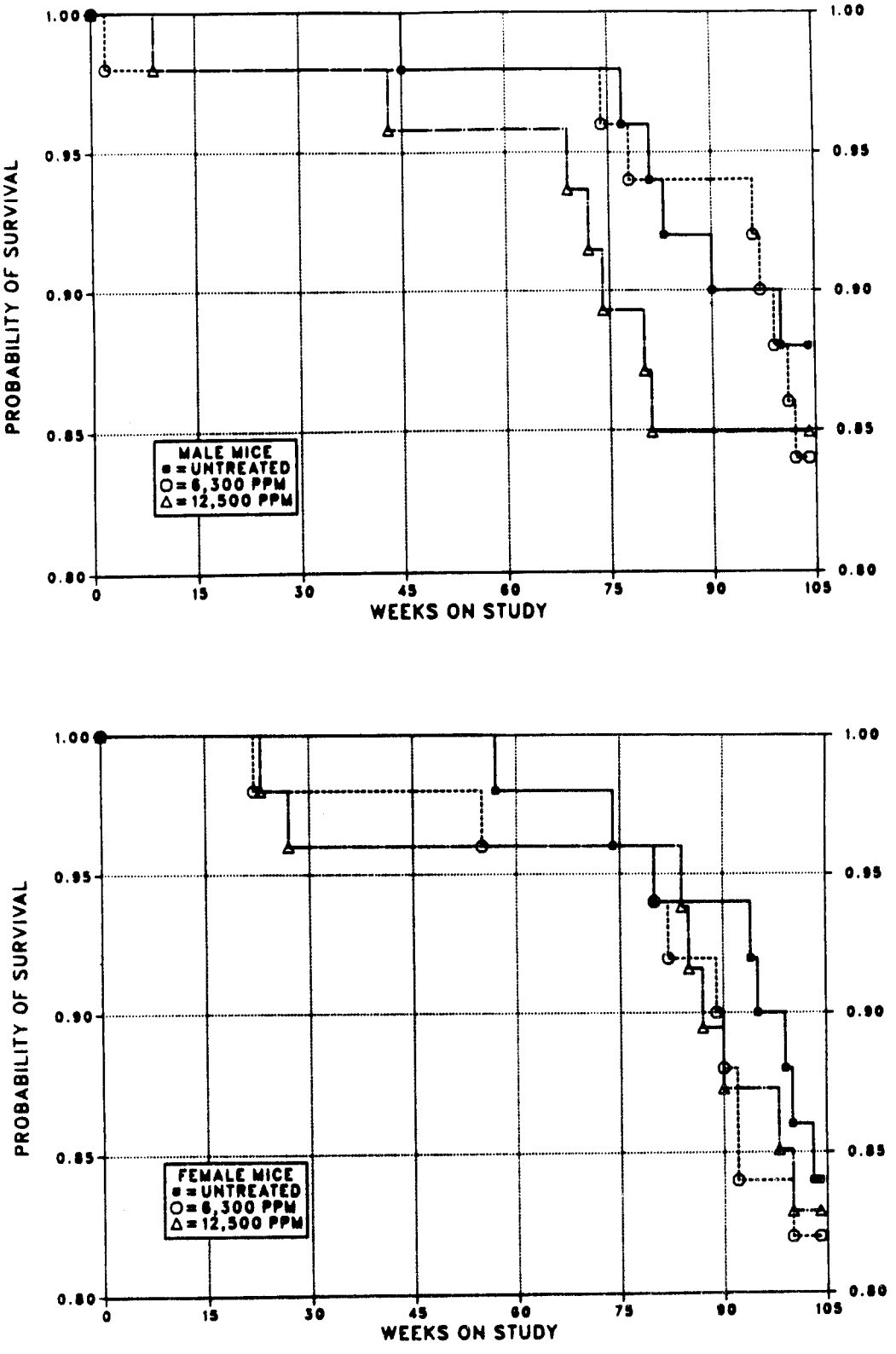

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING α-METHYLDOPA SESQUIHYDRATE FOR TWO YEARS

Kidney: Cysts, nephropathy, and nuclear enlargement (karyomegaly) occurred with increased incidences in dosed female mice (Table 21). Nephropathy is an age-related change characterized by degeneration and regeneration of the tubular epithelium in the renal cortex and variable degrees of glomerulosclerosis. Cysts consist of greatly dilated tubules and are part of the complex process diagnosed as nephropathy. Karyomegaly consisted of nuclear enlargement (up to 3-4 times normal size) in the tubular epithelium, primarily in the outer stripe of the outer medulla and inner cortex. Tubular cell hyperplasia was seen in 0/50 control, 1/50 low dose, and 1/50 high dose male mice. Tubular cell adenomas were seen in 2/50 low dose male mice, and a tubular cell adenocarcinoma was seen in 1/50 high dose male mice. Tubular cell hyperplasia consists of one or several adjacent cross-sections of the renal tubules with stratified epithelium. Tubular cell tumors are circumscribed masses of tubular cells exhibiting loss of normal architectural features and arranged in small clusters that are separated by delicate fibrovascular stroma or complex papillary formations. Adenocarcinomas are differentiated from adenomas primarily on the basis of the degree of cellular atypia and pleomorphism and the size of the tumor. Tubular cell adenomas have been observed in 3/2,029 (0.15%) historical untreated control male $B6C3F_1$ mice, and tubular cell adenocarcinomas have been observed in 3/2,029 (0.15%) historical untreated control male $B6C3F_1$ mice. No more than one tubular cell neoplasm has been observed in any untreated control group.

TABLE 21. NUMBER OF MICE WITH RENAL LESIONS IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Lesion	Control	6,300 ppm (a)	12,500 ppm (a)
MALE			
Number examined	50	50	50
Nephropathy	47	46	41
Karyomegaly in the tubular epithelium	0	0	0
Cysts	8	11	10
Tubular cell hyperplasia	0	1	1
Tubular cell adenoma (b)	0	2	0
Tubular cell adenocarcinoma (b)	0	0	1
FEMALE			
Number examined	50	50	50
Nephropathy	3	(c) 21	(c) 32
Karyomegaly in the tubular epithelium	0	(c) 46	(c) 44
Cysts	2	(d) 10	(d) 10
Tubular cell hyperplasia	1	0	0

(a) The estimated dose in milligrams per kilograms per day is given in Chapter III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix G.
(b) Historical incidence of tubular cell adenomas in NTP studies (mean): 3/2,029 (0.15%); historical incidence of adenomas or adenocarcinomas (combined): 6/2,029 (0.3%); no renal tubular cell neoplasms have been observed in 150 untreated controls at the study laboratory.
(c) $P<0.01$ vs. control group
(d) $P<0.05$ vs. control group

Glandular Stomach: Cysts, inflammation, epithelial hyperplasia, and eosinophilic cytoplasmic change occurred at increased incidences in low dose female mice (Table 22). There was an increase in the depth of the mucosal epithelium including the surface epithelium of the gastric pits, the mucous neck cells, and parietal cells (hyperplasia), a few greatly dilated glands lined by attenuated epithelium (cysts), and variable infiltration of the lamina propria with acute and chronic inflammatory cells. A few epithelial cells in the gastric pits were enlarged and had homogeneous eosinophilic cytoplasm. These changes may be attributed to the retention of secretory products in the cytoplasm of the cell and generally were minimal to mild in severity.

Liver: Necrosis was observed at increased incidences in dosed female mice (Table 23). Hepatocellular carcinomas and adenomas or carcinomas (combined) in male mice and hepatocellular adenomas or carcinomas (combined) in female mice occurred with significant negative trends. The incidences of hepatocellular carcinomas in high dose male mice and hepatocellular adenomas or carcinomas (combined) in dosed male mice were significantly lower than those in controls.

TABLE 22. NUMBER OF MICE WITH GLANDULAR STOMACH LESIONS IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Lesion	Control	6,300 ppm (a)	12,500 ppm (a)
MALE			
Number examined	49	48	50
Cysts	5	7	7
Inflammation	11	9	9
Epithelial hyperplasia	11	12	5
Eosinophilic cytoplasmic change	8	7	5
FEMALE			
Number examined	49	49	49
Cysts	8	14	9
Inflammation	12	20	11
Epithelial hyperplasia	3	22	6
Eosinophilic cytoplasmic change	11	24	16

TABLE 23. ANALYSIS OF HEPATOCELLULAR LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE (a)

	Control	6,300 ppm	12,500 ppm
MALE			
Necrosis			
Overall Rates	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adenoma			
Overall Rates	7/50 (14%)	3/50 (6%)	6/50 (12%)
Carcinoma			
Overall Rates	8/50 (16%)	3/50 (6%)	0/50 (0%)
Adjusted Rates	17.3%	6.9%	0.0%
Terminal Rates	6/44 (14%)	2/42 (5%)	0/39 (0%)
Week of First Observation	81	101	
Life Table Tests	P=0.004N	P=0.118N	P=0.010N
Incidental Tumor Tests	P=0.005N	P=0.189N	P=0.009N
Adenoma or Carcinoma (b)			
Overall Rates	15/50 (30%)	5/50 (10%)	6/50 (12%)
Adjusted Rates	31.8%	11.6%	14.8%
Terminal Rates	12/44 (27%)	4/42 (10%)	5/39 (13%)
Week of First Observation	77	101	69
Life Table Tests	P=0.027N	P=0.019N	P=0.056N
Incidental Tumor Tests	P=0.019N	P=0.023N	P=0.029N
FEMALE			
Necrosis			
Overall Rates	8/50 (16%)	13/50 (26%)	15/50 (30%)
Adenoma			
Overall Rates	3/50 (6%)	1/50 (2%)	0/50 (0%)
Carcinoma			
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adenoma or Carcinoma (c)			
Overall Rates	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted Rates	9.5%	2.4%	0.0%
Terminal Rates	4/42 (10%)	1/41 (2%)	0/38 (0%)
Week of First Observation	104	104	
Life Table Tests	P=0.031N	P=0.187N	P=0.076N
Incidental Tumor Tests	P=0.031N	P=0.187N	P=0.076N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes).
(b) Historical incidence at study laboratory (mean ± SD): 52/150 (35% ± 4%); historical incidence in NTP studies: 609/2,032 (30% ± 8%)
(c) Historical incidence at study laboratory (mean ± SD): 18/149 (12% ± 6%); historical incidence in NTP studies: 177/2,033 (9% ± 5%)

Anterior Pituitary Gland: Adenomas in female mice occurred with a significant negative trend; the incidence in the high dose group was significantly lower than that in the controls (Table 24).

Uterus: Endometrial cystic hyperplasia was observed at decreased incidences in dosed female mice (control, 44/50; low dose, 21/49; high dose, 20/49).

Ovary: The incidence of cysts was decreased in high dose female mice (control, 15/47; low dose, 7/15; high dose, 3/47; $P<0.01$).

Bone: The incidence of myelofibrosis was lower in high dose female mice than in controls (control, 26/50; low dose, 0/7; high dose, 13/50).

Nasal Mucosa: Eosinophilic cytoplasmic change was observed at a decreased incidence in dosed female mice (control, 36/50; low dose, 0/50; high dose, 18/50; $P<0.01$).

TABLE 24. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control	6,300 ppm	12,500 ppm
Focal Hyperplasia			
Overall Rates	11/49 (22%)	2/40 (5%)	9/50 (18%)
Adenoma (a)			
Overall Rates	9/49 (18%)	4/40 (10%)	2/50 (4%)
Adjusted Rates	21.4%	12.1%	5.3%
Terminal Rates	9/42 (21%)	4/33 (12%)	2/38 (5%)
Week of First Observation	104	104	104
Life Table Tests	P=0.025N	P=0.228N	P=0.039N
Incidental Tumor Tests	P=0.025N	P=0.228N	P=0.039N

(a) Historical incidence of adenomas or carcinomas (combined) at study laboratory (mean ± SD): 26/146 (18% ± 16%); historical incidence in NTP studies: 204/1,764 (12% ± 10%)

IV. DISCUSSION AND CONCLUSIONS

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α-Methyldopa sesquihydrate (USP grade) is widely used in the United States for the treatment of hypertension; however, studies to determine its long-term toxicity and carcinogenicity in rodents had not been performed. Because of this, 14-day, 13-week, and 2-year studies were conducted by administering α-methyldopa sesquihydrate to F344/N rats and B6C3F$_1$ mice in feed. The oral route was chosen because the drug is used orally in humans. In addition, short-term in vitro genetic toxicology studies were performed.

The genetic toxicology studies, which included tests for mutation induction in Salmonella and cytogenetic tests for induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, were uniformly negative. Published reports from other bacterial mutation studies also indicate no mutagenicity caused by α-methyldopa (Dybing, 1977; White et al., 1977; Ishidate et al., 1981). However, based on the induction of chromosomal aberrations in cultured Chinese hamster lung fibroblasts, Ishidate et al. (1981) concluded that α-methyldopa, in the absence of S9, was clastogenic, inducing polyploidy or structural aberrations.

In the 14-day studies, α-methyldopa sesquihydrate was administered in feed at concentrations up to 100,000 ppm. All rats administered 100,000 ppm and 2/5 female rats administered 50,000 ppm died. All mice lived until the end of the studies. Final mean body weights of dosed rats were 10%-43% lower than those of controls, but final mean body weights of dosed mice were generally within 10% of control mean body weights.

In the 13-week studies, α-methyldopa sesquihydrate was administered at concentrations up to 50,000 ppm. Deaths occurred in rats at 25,000 and 50,000 ppm and in female mice at 50,000 ppm. Final mean body weights of dosed rats were 6%-46% lower than those of controls, and final mean body weights of male mice at 25,000 and 50,000 ppm and female mice at 50,000 ppm were 12%-19% lower than those of controls. Compound-related clinical signs of toxicity were most marked in rats and mice at concentrations of 25,000 and 50,000 ppm and included lethargy, hyperexcitability, ocular discharge, and rough hair coats. Increased fighting was observed among dosed male mice.

The kidney of dosed rats and mice appeared to be the principal organ affected. Kidney tubular cell regeneration was seen in male and female rats at 12,500 ppm or higher, and nuclear enlargement (karyomegaly) of the renal cortical tubular epithelium was seen in male and female mice at 12,500 ppm or higher. Kidney toxicity is not often reported as a side effect of α-methyldopa treatment in humans (Croog et al., 1986; PDR, 1986).

Based on clinical signs, kidney lesions, and body weight effects at concentrations of 12,500 ppm or higher, dietary concentrations selected for the 2-year studies in rats were 0, 3,100, and 6,300 ppm. Dietary concentrations selected for mice were 0, 6,300, and 12,500 ppm, twice those for rats, because of clinical signs of toxicity, kidney lesions, and body weight effects at 25,000 and 50,000 ppm. These concentrations correspond to average daily α-methyldopa sesquihydrate doses of 110 or 240 mg/kg for rats and 830 or 1,800 mg/kg for mice. Calculations according to Freireich et al. (1966) indicate that the dose in milligrams per square meter surface area for rats would be 572-1,248 and for mice, 2,490-5,400. In comparison, a 70-kg man taking four 250-mg α-methyldopa tablets per day for the treatment of hypertension would receive a dose of 15 mg/kg, or 450 mg/m^2. The maximum maintenance dose for children is 65 mg/kg, or 2,000 mg/m^2 (Remington's, 1985).

In the 2-year studies, survival was comparable among dosed and control animals; final mean body weights of dosed rats and mice were 11%-19% lower than those of controls. The clinical signs observed for rats and mice in the 2-year studies were not as severe as those observed in the 13-week studies at 25,000 and 50,000 ppm. Notable clinical signs included fighting among group-housed dosed male rats, irritability in the individually housed dosed male mice, and rough hair coats in the dosed female mice.

Low incidences of nonneoplastic lesions were seen in the forestomach of high dose rats, but no chemical-related neoplasms were seen in this organ.

In the 2-year study, nonneoplastic lesions of the kidney were seen at increased incidences in female mice only, in contrast to the occurrence of nonneoplastic lesions of the kidney in both species and sexes in the 13-week studies. The kidney lesions seen at increased incidences in dosed female mice included nephropathy, nuclear enlargement of the cells of the tubular epithelium (karyomegaly), and cysts.

Equivocal evidence of carcinogenic activity was seen in the kidney of male mice. Tubular cell hyperplasia was seen in one low dose and one high dose male mouse but not in controls. Tubular cell adenomas were seen in two low dose male mice, and a tubular cell adenocarcinoma was seen in one high dose male mouse. Other experimental studies in rats (Hiasa et al., 1979; Dees et al., 1980; Kurokawa et al., 1983, 1985, 1987) have shown that tubular cell hyperplasia may sometimes precede and be associated with the development of tubular cell tumors. Tubular cell adenomas (3/2,029, 0.15%) and tubular cell adenocarcinomas (3/2,029, 0.15%) are uncommon tumors in untreated control male $B6C3F_1$ mice, and the incidences of kidney tumors seen in this 2-year study of α-methyldopa sesquihydrate in male mice are greater than the historical control incidences.

Further studies are needed to help explain kidney tumor formation in male mice. Because this response is limited to a single species and sex, sex-related factors, perhaps hormonal influences, might have contributed to this tumor development in the kidney. A kidney tumor response in male mice after chemical exposure is an unusual finding (Haseman et al., 1984b).

Decreased incidences of neoplasms were seen in the adrenal medulla of male rats, uterus of female rats, liver of male and female mice, and anterior pituitary gland of female mice (Table 25). These decreases might have been due in part to decreased body weights of dosed rats and mice. Rao et al. (1987) have reported that body weights of up to 20% lower than normal are associated with a decrease in the incidences of mammary gland and anterior pituitary gland neoplasms in untreated control female rats. However, the broad spectrum of decreases in naturally occurring tumors in these α-methyldopa sesquihydrate studies in rats and mice suggests that these effects may also have been due to chemical exposure.

α-Methyldopa sesquihydrate was toxic to the reproductive system of the male rat at 200 and 400 mg/kg (Appendix I; Dunnick et al., 1986). Body weight gains were also depressed in rats at these doses. Reproductive toxicity was measured by decreased fertility, decreased sperm count and percentage motile sperm, increased percentage abnormal sperm, and decreased reproductive and accessory sex organ weights. No compound-related differences were seen in these measures of reproductive toxicity after the recovery period. In the 13-week studies, hypoplasia of the testis was observed in male F344/N rats given 50,000 ppm α-methyldopa sesquihydrate in feed. In the reproductive study, α-methyldopa sesquihydrate decreased plasma testosterone levels within 1 day of compound administration, but testosterone levels rebounded within 2-3 days after cessation of compound administration. These hormonal alterations may have contributed to the reproductive toxic effects of α-methyldopa sesquihydrate. Dose-related histopathologic abnormalities of the testis were seen after 65 days of dosing, characterized by increased numbers of basally located spermatid heads, an apparent decrease in the number of late-stage spermatids, and a reduction in germ cell number.

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

TABLE 25. COMPOUND-RELATED DECREASES OF LESIONS IN RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE

Site/Lesion	Control	3,100 ppm	6,300 ppm	12,500 ppm
MALE RATS				
Adrenal medulla				
Pheochromocytoma or malignant pheochromocytoma (combined)	21/49	(a) 3/49	(b)10/50	
FEMALE RATS				
Uterus				
Endometrial stromal polyp	15/50	(b) 5/49	(a) 1/50	
MALE MICE				
Liver				
Adenoma or carcinoma (combined)	15/50		(b) 5/50	(b) 6/50
Malignant tumors (all types)	19/50		(b) 9/50	(b) 8/50
Benign or malignant tumors (combined) (all types)	32/50		(a)15/50	(a)17/50
FEMALE MICE				
Liver				
Adenoma or carcinoma (combined)	4/50		1/50	0/50
Anterior pituitary gland				
Adenoma	9/49		4/40	(b) 2/50
Bone				
Myelofibrosis	26/50		--	(b)13/50
Ovary				
Cysts	15/47		--	(a) 3/47
Uterus/endometrium				
Cystic hyperplasia	44/50		(a)21/49	(a)20/49
Nasal mucosa				
Eosinophilic cytoplasmic change	36/50		--	(a)18/50
Malignant tumors (all types)	21/50		16/50	12/50
Benign or malignant tumors (combined) (all types)	33/50		(b)22/50	(b)21/50

(a) $P<0.01$ vs. controls
(b) $P<0.05$ vs. controls

Conclusions: Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of α-methyldopa sesquihydrate for male or female F344/N rats fed diets containing 3,100 or 6,300 ppm. There was *equivocal evidence of carcinogenic activity* of α-methyldopa sesquihydrate for male $B6C3F_1$ mice, as shown by three dosed mice having uncommon tubular cell tumors of the kidney. There was *no evidence of carcinogenic activity* of α-methyldopa sesquihydrate for female $B6C3F_1$ mice fed diets containing 6,300 or 12,500 ppm.

Nonneoplastic lesions of the kidney including karyomegaly were observed in dosed female mice. Decreased incidences of several tumor types (in the adrenal gland in male rats, uterus in female rats, liver in male and female mice, and anterior pituitary gland in female mice) were considered related to α-methyldopa sesquihydrate exposure.

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

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *alpha*-METHYLDOPA SESQUIHYDRATE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Squamous cell papilloma	1 (2%)		1 (2%)
Keratoacanthoma	1 (2%)		
*Subcutaneous tissue	(49)	(50)	(50)
Fibroma	3 (6%)	3 (6%)	2 (4%)
Fibrosarcoma			1 (2%)
Lipoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(49)	(22)	(50)
Carcinoma, NOS, metastatic		1 (5%)	
Squamous cell carcinoma, metastatic		1 (5%)	
Pheochromocytoma, metastatic			2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Leukemia, mononuclear cell	20 (41%)	15 (30%)	19 (38%)
#Spleen	(49)	(26)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma		1 (4%)	
Leukemia, mononuclear cell	6 (12%)		3 (6%)
#Lymph node	(49)	(12)	(50)
C-cell carcinoma, metastatic			1 (2%)
CIRCULATORY SYSTEM			
#Myocardium	(49)	(12)	(50)
Hemangiosarcoma	1 (2%)		
*Vein of neck	(49)	(50)	(50)
Pheochromocytoma, metastatic	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(49)	(50)	(50)
Squamous cell papilloma			1 (2%)
#Liver	(49)	(50)	(50)
Neoplastic nodule	6 (12%)	2 (4%)	
Hepatocellular carcinoma		1 (2%)	1 (2%)
#Duodenum	(49)	(8)	(49)
Leiomyosarcoma			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(18)	(48)
Adenoma, NOS		1 (6%)	
#Anterior pituitary	(49)	(18)	(48)
Adenoma, NOS	8 (16%)	8 (44%)	13 (27%)
#Adrenal	(49)	(49)	(50)
Cortical adenoma		2 (4%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(49)	(49)	(50)
Pheochromocytoma	18 (37%)	2 (4%)	6 (12%)
Pheochromocytoma, malignant	3 (6%)	1 (2%)	4 (8%)
#Thyroid	(49)	(9)	(48)
Follicular cell adenoma			1 (2%)
Follicular cell carcinoma			1 (2%)
C-cell adenoma	3 (6%)		2 (4%)
C-cell carcinoma			2 (4%)
#Parathyroid	(36)	(5)	(39)
Adenoma, NOS	1 (3%)		
#Pancreatic islets	(49)	(6)	(49)
Islet cell adenoma	1 (2%)		1 (2%)
Islet cell carcinoma	2 (4%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Fibroadenoma	2 (4%)		
*Preputial gland	(49)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	2 (4%)
Adenoma, NOS	7 (14%)	3 (6%)	5 (10%)
#Testis	(49)	(46)	(50)
Interstitial cell tumor	44 (90%)	43 (93%)	38 (76%)
NERVOUS SYSTEM			
#Cerebral cortex	(49)	(9)	(50)
Astrocytoma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(49)	(50)	(50)
Squamous cell carcinoma		3 (6%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(49)	(50)	(50)
Osteosarcoma			1 (2%)
BODY CAVITIES			
*Tunica vaginalis	(49)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Sarcoma, NOS, metastatic		1 (2%)	
Fibrosarcoma	1 (2%)		
Mesothelioma, malignant	1 (2%)		
Osteosarcoma, metastatic			1 (2%)
Thigh			
Sarcoma, NOS		1	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	3	4
Moribund sacrifice	19	21	19
Terminal sacrifice	28	26	27

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	49	49	48
Total primary tumors	132	89	107
Total animals with benign tumors	47	48	45
Total benign tumors	89	64	70
Total animals with malignant tumors	31	22	32
Total malignant tumors	36	23	37
Total animals with secondary tumors##	1	3	4
Total secondary tumors	1	3	4
Total animals with tumors uncertain--benign or malignant	7	2	
Total uncertain tumors	7	2	

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE: UNTREATED CONTROL

ANIMAL NUMBER	11101	11401	11225	11006	11110	11117	11221	11222	11322	11334	11220	11335	11008	11226	11337	11330	11133	11336	11338	11001	11119	11141	11002	11033	11004
WEEKS ON STUDY	04808	06161	06404	08800	08800	08816	08866	08877	08887	08888	09292	09292	09595	09596	09696	09797	09898	09898	10101	10202	10202	10303	10404	10404	10404
INTEGUMENTARY SYSTEM																									
Skin	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X								
Keratoacanthoma																									
Subcutaneous tissue	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma				X																		X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Leukemia, mononuclear cell				X													X								
Lymph nodes	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	A	+	+	+	+	+	−	+	−	+	+	+	+	−	+	−	+	−	−	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Blood vessels	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pheochromocytoma, metastatic																									X
DIGESTIVE SYSTEM																									
Salivary gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X					X				X												
Adrenal	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X								X				X	X	X	X		X	X	
Pheochromocytoma, malignant																									X
Thyroid	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma											X														
Parathyroid	+	−	A	+	+	+	+	+	−	+	−	+	+	+	−	−	−	+	+	+	−	+	+	+	+
Adenoma, NOS						X																			
Pancreatic islets	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																	X								
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	A	N	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Fibroadenoma																			X						
Testis	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X		X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS															X										
Adenoma, NOS		X						X											X			X			
NERVOUS SYSTEM																									
Brain	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Tunica vaginalis	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																					X				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma																					X				
Mesothelioma, malignant											X														
Leukemia, mononuclear cell	X						X	X		X		X	X	X		X	X			X		X			X

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	105	107	109	112	115	116	118	123	124	127	128	129	131	133	139	141	142	143	144	145	146	147	148	149	150	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Squamous cell papilloma																										1
Keratoacanthoma												X														1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibroma		X																								3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS														X												1
Leukemia, mononuclear cell				X	X						X				X											6
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	–	+	–	–	+	–	+	–	+	+	–	+	–	+	+	–	+	–	+	+	+	+	–	–	–	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma												X														1
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Pheochromocytoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule				X				X	X		X			X								X				6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X		X	X				X							X									8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma	X			X						X		X	X		X		X			X			X		X	18
Pheochromocytoma, malignant					X													X								3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma																X			X							3
Parathyroid	+	–	–	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	36
Adenoma, NOS																										1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma												X														1
Islet cell carcinoma																		X								2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibroadenoma								X																		2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Carcinoma, NOS																										1
Adenoma, NOS	X				X								X													7
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Fibrosarcoma																										1
Mesothelioma, malignant																										1
Leukemia, mononuclear cell									X	X			X	X			X		X				X		X	20

* Animals necropsied

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

ANIMAL NUMBER	00007	00004	00233	01188	04499	00909	00808	01707	02808	01010	00202	01303	01109	02707	00101	03707	04606	00303	03000	03606	03909	01606	04141	04404	00505
WEEKS ON STUDY	03808	07704	07505	07909	08101	08802	08803	08707	09101	09902	09906	09906	09906	09906	09909	09909	10000	10101	10101	10101	10101	10102	10202	10202	10404
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	N	N	N	N	+	N	N	+	+	N	N	N	N	N	N
Fibroma															X			X							
Lipoma																			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	+	+	+	−	+	+	+	+
Carcinoma, NOS, metastatic								X																	
Squamous cell carcinoma, metastatic						X																			
Trachea	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	+	+	+	+	−	+	+	+	+	+
Fibroma																		X							
Lymph nodes	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	+	+	+
Thymus	+	+	+	+	−	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	−	−	+	+	−	−	−	−	+	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule												X													
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Large intestine	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	+	−	−	−	−	+	+	−	−	−
Urinary bladder	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	−	−	−	−	−	+	+	+	−	−	-	−	−	−	+	+
Adenoma, NOS		X				@X		X									X								X
Adrenal	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma														X											
Pheochromocytoma																	X		X						
Pheochromocytoma, malignant					X																				
Thyroid	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	-	−	−	−	−	−	−	−	−
Parathyroid	−	−	+	+	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−
Interstitial cell tumor			X	X	X	X	X		X	X	X		X	X	X	X	X	X		X	X	X	X	X	
Prostate	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X																	X					
Adenoma, NOS									X	X															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	N
Squamous cell carcinoma						X							X					X							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic																			X						
Leukemia, mononuclear cell				X			X		X					X		X	X		X		X	X	X	X	X
Thigh, NOS																									
Sarcoma, NOS																			X						

@ Multiple occurrence of morphology

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

ANIMAL NUMBER	00 06	01 11	01 12	01 14	01 15	02 20	02 21	02 22	02 24	02 25	02 26	02 29	03 31	03 32	03 33	03 34	03 35	03 38	04 40	04 42	04 43	04 45	04 47	04 48	05 50	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	+	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	*50
Fibroma								X																		3
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	+	+	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	+	–	–	+	22
Carcinoma, NOS, metastatic																										1
Squamous cell carcinoma, metastatic																										1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Spleen	+	–	–	–	–	–	+	+	+	–	–	–	+	–	–	+	–	–	–	–	–	–	–	–	–	26
Fibroma																										1
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	12
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																		X								2
Hepatocellular carcinoma	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
ENDOCRINE SYSTEM																										
Pituitary	+	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–	18
Adenoma, NOS	X				X															X						8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma											X															2
Pheochromocytoma																										2
Pheochromocytoma, malignant																										1
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	9
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Interstitial cell tumor	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Prostate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Adenoma, NOS	X																									3
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, metastatic																										1
Leukemia, mononuclear cell							X		X		X															15
Thigh, NOS																										
Sarcoma, NOS																										1

* Animals necropsied

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

ANIMAL NUMBER	0054	0088	0051	0084	0069	0667	0663	0092	0999	0664	0855	0557	0887	0996	0866	0993	0555	0611	0944	1100	0522	0977	0753	0553	0566
WEEKS ON STUDY	0155	0665	0688	0799	0800	0844	0855	0899	0900	0922	0922	0944	0944	0944	0966	0966	0988	1000	1000	1000	1011	1011	1022	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																				X	X				
Fibrosarcoma						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic			X																	X					
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																									
Thymus	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	−	−	+	−	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																X									
Large intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X				X	X				X						X		X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma											X					X									
Pheochromocytoma, malignant			X				X													X					
Thyroid	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C-cell adenoma																									X
C-cell carcinoma																							X		
Parathyroid	−	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																							X		
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor						X	X	X	X			X	X		X	X	X		X	X	X		X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS												X													
Adenoma, NOS																				.		X			X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma				X																					
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma, metastatic																									
Leukemia, mononuclear cell				X				X		X	X		X		X	X	X	X	X			X	X		

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

ANIMAL NUMBER	058	059	060	062	065	066	068	070	071	072	073	074	076	077	078	079	080	081	082	083	089	090	091	095	098	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma							X																			1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, metastatic																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell				X	X									X												3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																			X							1
Thymus	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma		X																								1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	48
Adenoma, NOS								X	X		X			X	X	X							X			13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma					X	X													X					X		6
Pheochromocytoma, malignant															X											4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma										X																1
Follicular cell carcinoma									X																	1
C-cell adenoma														X												2
C-cell carcinoma																			X							2
Parathyroid	+	−	+	+	+	+	~	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	~	−	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																							X			1
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	38
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																					X					2
Adenoma, NOS				X											X									X		5
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																				X						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma, metastatic																				X						1
Leukemia, mononuclear cell	X					X	X				X							X		X					X	19

* *Animals necropsied*

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control	3,100 ppm	6,300 ppm
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/49 (6%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	9.1%	9.3%	6.3%
Terminal Rates (c)	2/28 (7%)	1/26 (4%)	0/27 (0%)
Week of First Observation	80	99	100
Life Table Tests (d)	P=0.425N	P=0.653	P=0.511N
Incidental Tumor Tests (d)	P=0.387N	P=0.647N	P=0.484N
Cochran-Armitage Trend Test (d)	P=0.403N		
Fisher Exact Test (d)		P=0.651N	P=0.490N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/49 (6%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	9.1%	9.3%	8.3%
Terminal Rates (c)	2/28 (7%)	1/26 (4%)	0/27 (0%)
Week of First Observation	80	99	84
Life Table Tests (d)	P=0.573	P=0.653	P=0.651
Incidental Tumor Tests (d)	P=0.569N	P=0.647N	P=0.658N
Cochran-Armitage Trend Test (d)	P=0.575N		
Fisher Exact Test (d)		P=0.651N	P=0.651N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	26/49 (53%)	(e,f) 15/50 (30%)	22/50 (44%)
Adjusted Rates (b)	62.2%		55.2%
Terminal Rates (c)	13/28 (46%)		10/27 (37%)
Week of First Observation	48		79
Life Table Test (d)			P=0.346N
Incidental Tumor Test (d)			P=0.243N
Fisher Exact Test (d)			P=0.242N
Liver: Neoplastic Nodule			
Overall Rates (a)	6/49 (12%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	21.4%	6.3%	0.0%
Terminal Rates (c)	6/28 (21%)	1/26 (4%)	0/27 (0%)
Week of First Observation	104	96	
Life Table Tests (d)	P=0.008N	P=0.149N	P=0.018N
Incidental Tumor Tests (d)	P=0.007N	P=0.139N	P=0.018N
Cochran-Armitage Trend Test (d)	P=0.007N		
Fisher Exact Test (d)		P=0.128N	P=0.012N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	6/49 (12%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	21.4%	10.0%	3.7%
Terminal Rates (c)	6/28 (21%)	2/26 (8%)	1/27 (4%)
Week of First Observation	104	96	104
Life Table Tests (d)	P=0.039N	P=0.266N	P=0.060N
Incidental Tumor Tests (d)	P=0.036N	P=0.253N	P=0.060N
Cochran-Armitage Trend Test (d)	P=0.034N		
Fisher Exact Test (d)		P=0.233N	P=0.053N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	8/49 (16%)	(e) 8/18 (44%)	13/48 (27%)
Adjusted Rates (b)	23.5%		38.7%
Terminal Rates (c)	5/28 (18%)		7/25 (28%)
Week of First Observation	80		80
Life Table Test (d)			P=0.137
Incidental Tumor Test (d)			P=0.129
Fisher Exact Test (d)			P=0.149

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Control	3,100 ppm	6,300 ppm
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	18/49 (37%)	2/49 (4%)	6/50 (12%)
Adjusted Rates (b)	52.1%	5.9%	19.2%
Terminal Rates (c)	12/28 (43%)	0/26 (0%)	4/27 (15%)
Week of First Observation	81	100	92
Life Table Tests (d)	P=0.002N	P<0.001N	P=0.008N
Incidental Tumor Tests (d)	P=0.001N	P<0.001N	P=0.004N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P<0.001N	P=0.004N
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	3/49 (6%)	1/49 (2%)	4/50 (8%)
Adjusted Rates (b)	10.7%	2.2%	10.6%
Terminal Rates (c)	3/28 (11%)	0/26 (0%)	1/27 (4%)
Week of First Observation	104	81	68
Life Table Tests (d)	P=0.405	P=0.324N	P=0.493
Incidental Tumor Tests (d)	P=0.431	P=0.349N	P=0.545
Cochran-Armitage Trend Test (d)	P=0.418		
Fisher Exact Test (d)		P=0.309N	P=0.511
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	21/49 (43%)	3/49 (6%)	10/50 (20%)
Adjusted Rates (b)	61.1%	7.9%	28.3%
Terminal Rates (c)	15/28 (54%)	0/26 (0%)	5/27 (19%)
Week of First Observation	81	81	68
Life Table Tests (d)	P=0.012N	P<0.001N	P=0.026N
Incidental Tumor Tests (d)	P=0.006N	P<0.001N	P=0.012N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P<0.001N	P=0.013N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/49 (6%)	(e) 0/9 (0%)	2/48 (4%)
Adjusted Rates (b)	9.5%		7.4%
Terminal Rates (c)	2/28 (7%)		2/27 (7%)
Week of First Observation	92		104
Life Table Test (d)			P=0.511N
Incidental Tumor Test (d)			P=0.536N
Fisher Exact Test (d)			P=0.510N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	(e) 0/9 (0%)	4/48 (8%)
Adjusted Rates (b)	9.5%		14.8%
Terminal Rates (c)	2/28 (7%)		4/27 (15%)
Week of First Observation	92		104
Life Table Test (d)			P=0.485
Incidental Tumor Test (d)			P=0.463
Fisher Exact Test (d)			P=0.488
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	(e) 0/6 (0%)	2/49 (4%)
Adjusted Rates (b)	9.9%		7.1%
Terminal Rates (c)	2/28 (7%)		1/27 (4%)
Week of First Observation	98		102
Life Table Test (d)			P=0.519N
Incidental Tumor Test (d)			P=0.477N
Fisher Exact Test (d)			P=0.500N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Control	3,100 ppm	6,300 ppm
Preputial Gland: Adenoma			
Overall Rates (a)	7/49 (14%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	20.6%	8.4%	17.7%
Terminal Rates (c)	4/28 (14%)	1/26 (4%)	4/27 (15%)
Week of First Observation	61	91	101
Life Table Tests (d)	P=0.333N	P=0.178N	P=0.406N
Incidental Tumor Tests (d)	P=0.306N	P=0.164N	P=0.345N
Cochran-Armitage Trend Test (d)	P=0.301N		
Fisher Exact Test (d)		P=0.151N	P=0.365N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	8/49 (16%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	22.8%	13.0%	23.3%
Terminal Rates (c)	4/28 (14%)	1/26 (4%)	5/27 (19%)
Week of First Observation	61	75	94
Life Table Tests (d)	P=0.466N	P=0.292N	P=0.523N
Incidental Tumor Tests (d)	P=0.396N	P=0.213N	P=0.448N
Cochran-Armitage Trend Test (d)	P=0.430N		
Fisher Exact Test (d)		P=0.264N	P=0.483N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	44/49 (90%)	43/46 (93%)	38/50 (76%)
Adjusted Rates (b)	100.0%	100.0%	94.9%
Terminal Rates (c)	28/28 (100%)	24/24 (100%)	25/27 (93%)
Week of First Observation	80	75	84
Life Table Tests (d)	P=0.223N	P=0.385	P=0.243N
Incidental Tumor Tests (d)	P=0.016N	P=0.281	P=0.042N
Cochran-Armitage Trend Test (d)	P=0.031N		
Fisher Exact Test (d)		P=0.393	P=0.060N
Zymbal Gland: Squamous Cell Carcinoma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	7.6%	0.0%
Terminal Rates (c)	0/28 (0%)	0/26 (0%)	0/27 (0%)
Week of First Observation		82	
Life Table Tests (d)	P=0.637N	P=0.134	(g)
Incidental Tumor Tests (d)	P=0.617N	P=0.144	(g)
Cochran-Armitage Trend Test (d)	P=0.628N		
Fisher Exact Test (d)		P=0.125	(g)
All Sites: Benign Tumors			
Overall Rates (a)	47/49 (96%)	48/50 (96%)	45/50 (90%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	28/28 (100%)	26/26 (100%)	27/27 (100%)
Week of First Observation	61	74	80
Life Table Tests (d)	P=0.483N	P=0.402	P=0.513N
Incidental Tumor Tests (d)	P=0.129N	P=0.753	P=0.241N
Cochran-Armitage Trend Test (d)	P=0.151N		
Fisher Exact Test (d)		P=0.683	P=0.227N
All Sites: Malignant Tumors			
Overall Rates (a)	31/49 (63%)	22/50 (44%)	32/50 (64%)
Adjusted Rates (b)	70.0%	50.1%	72.1%
Terminal Rates (c)	15/28 (54%)	5/26 (19%)	15/27 (56%)
Week of First Observation	48	75	68
Life Table Tests (d)	P=0.427	P=0.131N	P=0.461
Incidental Tumor Tests (d)	P=0.527	P=0.020N	P=0.568
Cochran-Armitage Trend Test (d)	P=0.498		
Fisher Exact Test (d)		P=0.043N	P=0.553

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Control	3,100 ppm	6,300 ppm
All Sites: All Tumors			
Overall Rates (a)	49/49 (100%)	49/50 (98%)	48/50 (96%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	28/28 (100%)	26/26 (100%)	27/27 (100%)
Week of First Observation	48	74	68
Life Table Tests (d)	P=0.518	P=0.469	P=0.552
Incidental Tumor Tests (d)	P=0.122N	P=0.500N	P=0.314N
Cochran-Armitage Trend Test (d)	P=0.146N		
Fisher Exact Test (d)		P=0.505N	P=0.253N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues
(f) Only 26 spleens were examined microscopically.
(g) No P value is reported because no tumors were observed in the 6,300-ppm and control groups.

TABLE A4a. HISTORICAL INCIDENCE OF ZYMBAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

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

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

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

Study	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	10/50	0/50	10/50
Phenylephrine hydrochloride	13/49	1/49	14/49
Oxytetracycline hydrochloride	10/50	2/50	12/50
TOTAL	33/149 (22.1%)	3/149 (2.0%)	36/149 (24.2%)
SD (b)	3.77%	2.00%	4.29%
Range (c)			
High	13/49	2/50	14/49
Low	10/50	0/50	10/50
Overall Historical Incidence			
TOTAL	438/1,913 (22.9%)	27/1,913 (1.4%)	460/1,913 (24.0%)
SD (b)	12.70%	1.99%	12.68%
Range (c)			
High	31/49	4/49	(d) 32/49
Low	2/50	0/50	3/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest: 26/50; third highest: 21/49

TABLE A4c. HISTORICAL INCIDENCE OF LIVER TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Hepatocellular Carcinoma
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	1/50	2/50	3/50
Phenylephrine hydrochloride	5/50	1/50	5/50
Oxytetracycline hydrochloride	6/50	0/50	6/50
TOTAL	12/150 (8.0%)	3/150 (2.0%)	14/150 (9.3%)
SD (b)	5.29%	2.00%	3.06%
Range (c)			
High	6/50	2/50	6/50
Low	1/50	0/50	3/50
Overall Historical Incidence			
TOTAL	74/1,929 (3.8%)	20/1,929 (1.0%)	93/1,929 (4.8%)
SD (b)	3.57%	1.45%	3.65%
Range (c)			
High	6/49	3/50	7/49
Low	0/50	0/50	0/50

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

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Epidermal inclusion cyst	1 (2%)	4 (8%)	1 (2%)
Inflammation, active chronic	2 (4%)		
Inflammation, chronic	1 (2%)		
Hyperkeratosis		1 (2%)	1 (2%)
*Subcutaneous tissue	(49)	(50)	(50)
Perivascular cuffing	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(50)
Inflammation, active chronic	3 (6%)	3 (6%)	4 (8%)
Hyperplasia, epithelial	1 (2%)		
#Lung	(49)	(22)	(50)
Congestion, NOS			2 (4%)
Edema, NOS	2 (4%)	2 (9%)	1 (2%)
Hemorrhage		1 (5%)	3 (6%)
Pneumonia, interstitial chronic	6 (12%)	1 (5%)	1 (2%)
Perivascular cuffing	2 (4%)	1 (5%)	3 (6%)
Alveolar macrophages	1 (2%)		1 (2%)
Hyperplasia, adenomatous	1 (2%)		
Metaplasia, osseous		2 (9%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(8)	(50)
Hyperplasia, NOS	34 (69%)	2 (25%)	29 (58%)
Myelofibrosis	2 (4%)		
#Spleen	(49)	(26)	(50)
Fibrosis	5 (10%)	5 (19%)	2 (4%)
Necrosis, NOS	1 (2%)	2 (8%)	
Necrosis, focal	1 (2%)		
Hemosiderosis		1 (4%)	2 (4%)
Hyperplasia, lymphoid	2 (4%)		
Hematopoiesis	1 (2%)	2 (8%)	5 (10%)
#Lymph node	(49)	(12)	(50)
Hemorrhage			1 (2%)
#Mesenteric lymph node	(49)	(12)	(50)
Hemorrhage			3 (6%)
Inflammation, acute/chronic	1 (2%)		
Fibrosis	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
#Thymus	(29)	(9)	(40)
Cyst, NOS	1 (3%)		1 (3%)
Hemorrhage	3 (10%)	1 (11%)	2 (5%)
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(49)	(12)	(50)
Lymphangiectasis	1 (2%)		
#Heart	(49)	(12)	(50)
Fibrosis	1 (2%)		
#Heart/atrium	(49)	(12)	(50)
Thrombosis, NOS	1 (2%)		

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

	Untreated Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Myocardium	(49)	(12)	(50)
Inflammation, chronic	5 (10%)	2 (17%)	6 (12%)
Fibrosis	44 (90%)	9 (75%)	44 (88%)
Degeneration, NOS	5 (10%)	4 (33%)	3 (6%)
#Cardiac valve	(49)	(12)	(50)
Degeneration, mucoid			1 (2%)
*Artery	(49)	(50)	(50)
Periarteritis	2 (4%)		1 (2%)
*Pulmonary artery	(49)	(50)	(50)
Mineralization			1 (2%)
#Liver	(49)	(50)	(50)
Thrombus, fibrin		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(8)	(50)
Inflammation, active chronic			1 (2%)
Inflammation, chronic	1 (2%)		
Degeneration, lipoid		1 (13%)	
Atrophy, NOS	5 (10%)		2 (4%)
#Liver	(49)	(50)	(50)
Hernia, NOS	2 (4%)	2 (4%)	2 (4%)
Inflammation, focal			1 (2%)
Granuloma, NOS	3 (6%)	1 (2%)	4 (8%)
Degeneration, cystic		3 (6%)	
Necrosis, focal	1 (2%)		
Necrosis, diffuse		1 (2%)	
Metamorphosis, fatty		6 (12%)	6 (12%)
Nuclear alteration		1 (2%)	
Cytoplasmic change, NOS	1 (2%)		
Cytoplasmic vacuolization	1 (2%)	1 (2%)	3 (6%)
Basophilic cyto change	29 (59%)	22 (44%)	21 (42%)
Eosinophilic cyto change	3 (6%)		
Clear cell change	12 (24%)	12 (24%)	11 (22%)
Hyperplasia, focal			2 (4%)
Angiectasis	11 (22%)	2 (4%)	3 (6%)
Regenerative nodule		2 (4%)	1 (2%)
#Portal tract	(49)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Bile duct	(49)	(50)	(50)
Hyperplasia, NOS	48 (98%)	43 (86%)	46 (92%)
#Pancreas	(49)	(6)	(49)
Ectopia	1 (2%)		
Inflammation, active chronic	1 (2%)		
#Pancreatic acinus	(49)	(6)	(49)
Basophilic cyto change	1 (2%)		
Atrophy, NOS	20 (41%)	3 (50%)	18 (37%)
Hyperplasia, focal	1 (2%)		
#Esophagus	(48)	(8)	(49)
Inflammation, active chronic		1 (13%)	
Hyperkeratosis	1 (2%)	1 (13%)	5 (10%)
#Glandular stomach	(49)	(49)	(50)
Multiple cysts	37 (76%)	44 (90%)	37 (74%)
#Forestomach	(49)	(49)	(50)
Edema, NOS	2 (4%)	1 (2%)	9 (18%)
Ulcer, NOS		2 (4%)	6 (12%)
Inflammation, acute			3 (6%)
Inflammation, active chronic	2 (4%)	2 (4%)	8 (16%)
Inflammation, chronic		1 (2%)	
Hyperplasia, epithelial	1 (2%)	2 (4%)	6 (12%)
Hyperkeratosis		2 (4%)	

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

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Duodenum	(49)	(8)	(49)
Diverticulum			1 (2%)
#Colonic submucosa	(49)	(8)	(49)
Edema, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(11)	(50)
Cyst, NOS		1 (9%)	
Nephropathy	49 (100%)	9 (82%)	50 (100%)
Atrophy, pressure			1 (2%)
#Kidney/tubule	(49)	(11)	(50)
Degeneration, hyaline			3 (6%)
Necrosis, NOS	1 (2%)		
Metamorphosis, fatty	1 (2%)	1 (9%)	1 (2%)
Pigmentation, NOS	1 (2%)	2 (18%)	4 (8%)
#Urinary bladder	(49)	(8)	(50)
Inflammation, acute hemorrhagic			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary pars tuber	(49)	(18)	(48)
Cyst, NOS	1 (2%)		1 (2%)
#Pituitary intermedia	(49)	(18)	(48)
Cyst, NOS	1 (2%)		
#Anterior pituitary	(49)	(18)	(48)
Cyst, NOS	7 (14%)	3 (17%)	9 (19%)
Hyperplasia, focal	19 (39%)	5 (28%)	20 (42%)
Angiectasis	1 (2%)	2 (11%)	5 (10%)
#Pituitary posterior	(49)	(18)	(48)
Gliosis	2 (4%)	2 (11%)	3 (6%)
#Adrenal cortex	(49)	(49)	(50)
Cyst, NOS	1 (2%)		
Degeneration, lipoid	12 (24%)	11 (22%)	9 (18%)
Hypertrophy, focal	3 (6%)	1 (2%)	4 (8%)
Hyperplasia, focal	13 (27%)	26 (53%)	16 (32%)
Angiectasis	12 (24%)	24 (49%)	18 (36%)
Metaplasia, osseous		1 (2%)	
#Adrenal medulla	(49)	(49)	(50)
Cyst, NOS			1 (2%)
Hyperplasia, focal	14 (29%)	7 (14%)	6 (12%)
#Thyroid	(49)	(9)	(48)
Fibrosis		1 (11%)	
Hyperplasia, C-cell	9 (18%)	1 (11%)	5 (10%)
#Pancreatic islets	(49)	(6)	(49)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Cyst, NOS	2 (4%)		
Hyperplasia, cystic	6 (12%)		5 (10%)
*Preputial gland	(49)	(50)	(50)
Hyperplasia, focal			1 (2%)
#Prostate	(49)	(8)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, active chronic	28 (57%)	6 (75%)	31 (62%)
Hyperplasia, epithelial	4 (8%)		1 (2%)
*Seminal vesicle	(49)	(50)	(50)
Inflammation, acute			1 (2%)

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

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Testis	(49)	(46)	(50)
Infarct, NOS	1 (2%)		
Atrophy, NOS	22 (45%)	10 (22%)	26 (52%)
Hyperplasia, interstitial cell	37 (76%)	39 (85%)	44 (88%)
*Epididymis	(49)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
NERVOUS SYSTEM			
*Brain/neuropil	(49)	(50)	(50)
Cytoplasmic vacuolization	1 (2%)		
#Leptomeninges	(49)	(9)	(50)
Congestion, NOS		1 (11%)	
#Brain	(49)	(9)	(50)
Hydrocephalus, NOS	2 (4%)		5 (10%)
Necrosis, NOS		1 (11%)	
Necrosis, focal			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(49)	(50)	(50)
Hemorrhage	1 (2%)		
*Eye/sclera	(49)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	
*Eye/retina	(49)	(50)	(50)
Atrophy, NOS	1 (2%)	5 (10%)	1 (2%)
*Eye/lens, cortex	(49)	(50)	(50)
Cataract	1 (2%)	3 (6%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(49)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
ALL OTHER SYSTEMS			
Adipose tissue			
Necrosis, fat	10	10	7
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/no necropsy	1		

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *alpha*-METHYLDOPA SESQUIHYDRATE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
Squamous cell carcinoma			1 (2%)
Keratoacanthoma	2 (4%)		
Fibroma	1 (2%)		1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
Fibroma	1 (2%)		2 (4%)
Fibrosarcoma	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(18)	(50)
Alveolar/bronchiolar adenoma			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	11 (22%)	14 (28%)	6 (12%)
#Spleen	(50)	(17)	(50)
Leukemia, mononuclear cell	1 (2%)	1 (6%)	3 (6%)
#Thymus	(35)	(7)	(39)
Histiocytic sarcoma		1 (14%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Liver	(50)	(50)	(50)
Neoplastic nodule		1 (2%)	
#Small intestine	(50)	(8)	(50)
Sarcoma, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(10)	(50)
Histiocytic sarcoma, metastatic		1 (10%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(35)	(50)
Adenoma, NOS		1 (3%)	
#Anterior pituitary	(50)	(35)	(50)
Carcinoma, NOS		2 (6%)	
Adenoma, NOS	23 (46%)	17 (49%)	24 (48%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	2 (4%)	2 (4%)	5 (10%)
#Thyroid	(50)	(12)	(48)
Follicular cell adenoma	1 (2%)		1 (2%)
C-cell adenoma	7 (14%)	1 (8%)	6 (13%)
C-cell carcinoma	1 (2%)	1 (8%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Parathyroid	(39)	(5)	(38)
Adenoma, NOS	1 (3%)		
#Pancreatic islets	(50)	(10)	(49)
Islet cell adenoma		1 (10%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
Papillary carcinoma		2 (4%)	
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS	2 (4%)	1 (2%)	1 (2%)
Fibroadenoma	19 (38%)	14 (28%)	19 (38%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS		2 (4%)	1 (2%)
Adenoma, NOS	10 (20%)	8 (16%)	11 (22%)
#Uterus	(50)	(49)	(50)
Adenoma, NOS	1 (2%)		
Leiomyoma	1 (2%)		
Endometrial stromal polyp	15 (30%)	5 (10%)	1 (2%)
Endometrial stromal sarcoma	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(9)	(50)
Granular cell tumor, NOS			1 (2%)
#Brain	(50)	(9)	(50)
Astrocytoma	1 (2%)		
Oligodendroglioma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	6	2
Moribund sacrifice	14	10	19
Terminal sacrifice	34	34	29

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	44	47	47
Total primary tumors	105	77	89
Total animals with benign tumors	41	36	45
Total benign tumors	85	50	73
Total animals with malignant tumors	16	24	13
Total malignant tumors	20	26	15
Total animals with secondary tumors##	1	1	
Total secondary tumors	1	1	
Total animals with tumors uncertain--benign or malignant		1	1
Total uncertain tumors		1	1

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE: UNTREATED CONTROL

ANIMAL NUMBER	1 4 9	1 2 4	1 3 7	1 4 5	1 4 8	1 1 0	1 2 8	1 4 4	1 1 3	1 4 7	1 0 4	1 1 5	1 1 6	1 0 3	1 4 3	1 0 1	1 0 2	1 0 5	1 0 6	1 0 7	1 0 8	1 0 9	1 1 1	1 1 2	1 1 4
WEEKS ON STUDY	0 7 6	0 7 7	0 7 9	0 7 9	0 7 9	0 8 2	0 8 3	0 8 5	0 9 0	0 9 1	0 9 2	0 9 7	0 9 8	0 9 9	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																				X					
Fibroma																					X				
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																						X			
Fibrosarcoma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	−	+	−	+	−	−	−	+	−	+	−	+	+	+	−	+	+	+	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X	X						X							X	X	X	X	X		X	X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																				X					
Pheochromocytoma																X									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma	X															X			X			X	X		
C-cell carcinoma																									
Parathyroid	+	−	+	+	+	−	+	+	+	+	+	+	−	−	−	+	+	+	+	−	−	+	+	+	+
Adenoma, NOS												X													
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																	X								
Fibroadenoma	X		X	X									X					X	X	X	X				
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS		X	X		X					X								X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X																		
Leiomyoma																									
Endometrial stromal polyp			X		X			X		X		X		X					X	X					X
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma														X											
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic											X														
Leukemia, mononuclear cell			X						X	X		X		X			X								

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
.: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	117	118	119	120	121	122	123	125	126	127	129	130	131	132	133	134	135	136	138	139	140	141	142	146	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma							X																			2
Fibroma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																						X				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	−	+	+	+	+	+	+	+	−	+	+	−	+	+	+	−	+	+	+	+	+	−	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																	X									1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS			X	X		X		X	X		X	X	X						X	X				X	X	23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma							X																			1
C-cell adenoma												X		X												7
C-cell carcinoma																					X					1
Parathyroid	+	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	39
Adenoma, NOS																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS													X													2
Fibroadenoma		X		X		X			X		X			X			X		X		X			X	X	19
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X	X					X										X	X		10
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Leiomyoma										X																1
Endometrial stromal polyp									X	X			X					X					X	X		15
Endometrial stromal sarcoma																							X			1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																X										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, metastatic																										1
Leukemia, mononuclear cell			X	X									X					X					X			11

* Animals necropsied

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

ANIMAL NUMBER	0014	0032	0021	0111	0222	0155	0299	0255	0499	0366	0355	0466	0330	0002	0023	0400	0101	0033	0004	0055	0066	0077	0088	0099	0100
WEEKS ON STUDY	045	074	076	086	086	088	089	090	091	092	093	095	097	100	101	102	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N
Sarcoma, NOS													X												
Fibrosarcoma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	+	−	+	−	−	−	−	−	+	−
Trachea	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	−	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	−	−	−	+	−	−	−	−	−	−
Leukemia, mononuclear cell																			X						
Lymph nodes	+	+	+	+	+	+	+	+	+	−	−	+	−	−	+	+	−	−	−	−	−	−	−	−	−
Thymus	+	−	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Histiocytic sarcoma			X																						
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma						X																			
Salivary gland	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−
Esophagus	−	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Large intestine	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Histiocytic sarcoma, metastatic			X																						
Urinary bladder	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	−	+	−	+	+	+	+	+	+	+
Carcinoma, NOS					X																				
Adenoma, NOS							X		X		X			X	X				X	X	X	X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X														X	
Thyroid	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−
C-cell adenoma																							X		
C-cell carcinoma																									
Parathyroid	−	+	−	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−
Islet cell adenoma																		X							
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	N	N	N	N	+	N	+	+	+	N	N	N	+
Papillary carcinoma									X										X						
Adenocarcinoma, NOS																									
Fibroadenoma					X						X	X					X				X				X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							X																		
Adenoma, NOS				X		X				X				X					X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp				X						X				X											
Ovary	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X	X				X		X		X		X			X	X									

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

ANIMAL NUMBER	012	013	016	017	018	019	020	024	026	027	028	031	033	034	037	038	039	041	042	043	044	045	047	048	050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	+	–	18
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Spleen	+	+	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	17
Leukemia, mononuclear cell																										1
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
Histiocytic sarcoma																										1
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																X										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
URINARY SYSTEM																										
Kidney	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Histiocytic sarcoma, metastatic																										1
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	–	+	–	+	–	+	+	–	–	+	+	+	+	–	+	+	–	–	–	+	35
Carcinoma, NOS							X																			2
Adenoma, NOS		X	X	X					X		X					@X	X			X						17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										2
Thyroid	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	12
C-cell adenoma																										1
C-cell carcinoma																									X	1
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Pancreatic islets	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	N	N	N	+	N	N	+	N	N	N	+	+	+	N	N	+	+	+	+	N	N	N	*50
Papillary carcinoma																										2
Adenocarcinoma, NOS										X																1
Fibroadenoma			X				X							X	X	X			X		X	X				14
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS		X																								2
Adenoma, NOS													X	X								X				8
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp			X									X														5
Ovary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X	X				X		X				X								X						14

* Animals necropsied
@ Multiple occurrence of morphology

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

ANIMAL NUMBER	0066	0069	1000	0091	0068	0077	0062	0096	0098	0053	0063	0071	0055	0099	0086	0072	0065	0078	0088	0084	0097	0051	0052	0054	0056
WEEKS ON STUDY	048	060	067	080	082	084	089	091	091	093	093	095	096	096	098	099	100	101	101	102	102	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																				X					
Fibroma																							X		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma							X			X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell								X																	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	−	−	−	−	+	+	−	+	−	+	+	+	−	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X			X	X			X		X	X	X		X				X	X	X				X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																						X			
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																					X				
Parathyroid	+	+	−	+	−	+	−	+	−	+	+	+	−	+	−	+	+	+	+	+	−	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS								X																	
Adenocarcinoma, NOS														X											
Fibroadenoma				X							X		X	X	X		X		X			X		X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																	X								
Adenoma, NOS			X																				X	X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
Oligodendroglioma																							X		
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell									X			X				X					X		X		

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

ANIMAL NUMBER	0057	0058	0059	0060	0061	0064	0067	0070	0073	0074	0075	0076	0079	0080	0081	0082	0083	0085	0087	0089	0090	0092	0093	0094	0095	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma								X																		1
Squamous cell carcinoma																										1
Fibroma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell										X													X			3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS					X			X		X	X	X							X	X	X	X	X	X	X	24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma				X			X							X					X							5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma							X																			1
C-cell adenoma		X						X							X						X		X			6
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	~	+	–	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Carcinoma, NOS												X														1
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Fibroadenoma					X	X	X	X	X		X				X	X							X		X	19
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS			X	X	X		X	X		X			X				X									11
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS					X																					1
Oligodendroglioma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell												X														6

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control	3,100 ppm	6,300 ppm
Integumentary System: Fibroma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	5.7%	0.0%	7.9%
Terminal Rates (c)	2/35 (6%)	0/34 (0%)	1/29 (3%)
Week of First Observation	104		89
Life Table Tests (d)	P=0.355	P=0.245N	P=0.458
Incidental Tumor Tests (d)	P=0.395	P=0.245N	P=0.503
Cochran-Armitage Trend Test (d)	P=0.386		
Fisher Exact Test (d)		P=0.247N	P=0.500
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	7.7%	2.1%	7.9%
Terminal Rates (c)	2/35 (6%)	0/34 (0%)	1/29 (3%)
Week of First Observation	79	86	89
Life Table Tests (d)	P=0.564	P=0.305N	P=0.622
Incidental Tumor Tests (d)	P=0.550	P=0.356N	P=0.638
Cochran-Armitage Trend Test (d)	P=0.591		
Fisher Exact Test (d)		P=0.309N	P=0.661
Integumentary System: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	7.7%	4.7%	7.9%
Terminal Rates (c)	2/35 (6%)	0/34 (0%)	1/29 (3%)
Week of First Observation	79	86	89
Life Table Tests (d)	P=0.557	P=0.499N	P=0.622
Incidental Tumor Tests (d)	P=0.569N	P=0.514N	P=0.638
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.500N	P=0.661
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	12/50 (24%)	(e,f) 15/50 (30%)	9/50 (18%)
Adjusted Rates (b)	29.3%		24.7%
Terminal Rates (c)	7/35 (20%)		4/29 (14%)
Week of First Observation	79		91
Life Table Test (d)			P=0.421N
Incidental Tumor Test (d)			P=0.264N
Fisher Exact Test (d)			P=0.312N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	23/50 (46%)	(e,g) 17/35 (49%)	24/50 (48%)
Adjusted Rates (b)	58.3%		58.5%
Terminal Rates (c)	19/35 (54%)		13/29 (45%)
Week of First Observation	76		48
Life Table Test (d)			P=0.282
Incidental Tumor Test (d)			P=0.565N
Fisher Exact Test (d)			P=0.500
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	5.7%	5.3%	17.2%
Terminal Rates (c)	2/35 (6%)	1/34 (3%)	5/29 (17%)
Week of First Observation	104	92	104
Life Table Tests (d)	P=0.101	P=0.688	P=0.145
Incidental Tumor Tests (d)	P=0.090	P=0.663	P=0.145
Cochran-Armitage Trend Test (d)	P=0.145		
Fisher Exact Test (d)		P=0.691	P=0.218

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Control	3,100 ppm	6,300 ppm
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	7/50 (14%)	(e) 1/12 (8%)	6/48 (13%)
Adjusted Rates (b)	18.8%		19.9%
Terminal Rates (c)	6/35 (17%)		5/29 (17%)
Week of First Observation	76		102
Life Table Test (d)			P=0.602
Incidental Tumor Test (d)			P=0.607N
Fisher Exact Test (d)			P=0.532N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	(e) 2/12 (17%)	6/48 (13%)
Adjusted Rates (b)	21.6%		19.9%
Terminal Rates (c)	7/35 (20%)		5/29 (17%)
Week of First Observation	76		102
Life Table Test (d)			P=0.527N
Incidental Tumor Test (d)			P=0.499N
Fisher Exact Test (d)			P=0.419N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	19/50 (38%)	14/50 (28%)	19/50 (38%)
Adjusted Rates (b)	47.7%	37.1%	51.5%
Terminal Rates (c)	15/35 (43%)	11/34 (32%)	12/29 (41%)
Week of First Observation	76	86	80
Life Table Tests (d)	P=0.347	P=0.226N	P=0.372
Incidental Tumor Tests (d)	P=0.514N	P=0.207N	P=0.553N
Cochran-Armitage Trend Test (d)	P=0.538		
Fisher Exact Test (d)		P=0.198N	P=0.581
Mammary Gland: Adenocarcinoma, Carcinoma, or Papillary Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	5.7%	8.1%	6.0%
Terminal Rates (c)	2/35 (6%)	2/34 (6%)	1/29 (3%)
Week of First Observation	104	91	96
Life Table Tests (d)	P=0.541	P=0.492	P=0.640
Incidental Tumor Tests (d)	P=0.583	P=0.467	P=0.659N
Cochran-Armitage Trend Test (d)	P=0.593N		
Fisher Exact Test (d)		P=0.500	P=0.691
Mammary Gland: Adenoma, Adenocarcinoma, Carcinoma, or Papillary Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	5.7%	8.1%	8.2%
Terminal Rates (c)	2/35 (6%)	2/34 (6%)	1/29 (3%)
Week of First Observation	104	91	91
Life Table Tests (d)	P=0.366	P=0.492	P=0.451
Incidental Tumor Tests (d)	P=0.376	P=0.467	P=0.503
Cochran-Armitage Trend Test (d)	P=0.414		
Fisher Exact Test (d)		P=0.500	P=0.500
Clitoral Gland: Adenoma			
Overall Rates (a)	10/50 (20%)	8/50 (16%)	11/50 (22%)
Adjusted Rates (b)	24.1%	19.8%	35.8%
Terminal Rates (c)	6/35 (17%)	4/34 (12%)	10/29 (34%)
Week of First Observation	77	86	67
Life Table Tests (d)	P=0.332	P=0.409N	P=0.355
Incidental Tumor Tests (d)	P=0.286	P=0.468N	P=0.299
Cochran-Armitage Trend Test (d)	P=0.448		
Fisher Exact Test (d)		P=0.398N	P=0.500

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Control	3,100 ppm	6,300 ppm
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	10/50 (20%)	12/50 (24%)
Adjusted Rates (b)	24.1%	24.3%	37.7%
Terminal Rates (c)	6/35 (17%)	5/34 (15%)	10/29 (34%)
Week of First Observation	77	86	67
Life Table Tests (d)	P=0.255	P=0.588	P=0.273
Incidental Tumor Tests (d)	P=0.228	P=0.517	P=0.262
Cochran-Armitage Trend Test (d)	P=0.357		
Fisher Exact Test (d)		P=0.598	P=0.405
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	15/50 (30%)	5/49 (10%)	1/50 (2%)
Adjusted Rates (b)	35.7%	12.7%	3.4%
Terminal Rates (c)	9/35 (26%)	2/34 (6%)	1/29 (3%)
Week of First Observation	79	86	104
Life Table Tests (d)	P<0.001N	P=0.019N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.014N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.013N	P<0.001N
All Sites: Benign Tumors			
Overall Rates (a)	41/50 (82%)	36/50 (72%)	45/50 (90%)
Adjusted Rates (b)	87.1%	81.6%	97.8%
Terminal Rates (c)	29/35 (83%)	26/34 (76%)	28/29 (97%)
Week of First Observation	76	86	48
Life Table Tests (d)	P=0.063	P=0.278N	P=0.069
Incidental Tumor Tests (d)	P=0.184	P=0.215N	P=0.293
Cochran-Armitage Trend Test (d)	P=0.180		
Fisher Exact Test (d)		P=0.172N	P=0.194
All Sites: Malignant Tumors			
Overall Rates (a)	16/50 (32%)	24/50 (48%)	13/50 (26%)
Adjusted Rates (b)	38.2%	49.4%	32.7%
Terminal Rates (c)	10/35 (29%)	10/34 (29%)	4/29 (14%)
Week of First Observation	79	45	82
Life Table Tests (d)	P=0.434N	P=0.111	P=0.463N
Incidental Tumor Tests (d)	P=0.181N	P=0.084	P=0.220N
Cochran-Armitage Trend Test (d)	P=0.294N		
Fisher Exact Test (d)		P=0.076	P=0.330N
All Sites: All Tumors			
Overall Rates (a)	44/50 (88%)	47/50 (94%)	47/50 (94%)
Adjusted Rates (b)	91.6%	94.0%	97.9%
Terminal Rates (c)	31/35 (89%)	31/34 (91%)	28/29 (97%)
Week of First Observation	76	45	48
Life Table Tests (d)	P=0.083	P=0.321	P=0.093
Incidental Tumor Tests (d)	P=0.280	P=0.283	P=0.372
Cochran-Armitage Trend Test (d)	P=0.181		
Fisher Exact Test (d)		P=0.243	P=0.243

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues
(f) Only 17 spleens were examined microscopically.
(g) Two carcinomas were also observed.

TABLE B4. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL POLYPS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Physiological Research Laboratories	
Ephedrine sulfate	11/49
Phenylephrine hydrochloride	7/50
Oxytetracycline hydrochloride	15/50
TOTAL	33/149 (22.1%)
SD (b)	8.00%
Range (c)	
High	15/50
Low	7/50
Overall Historical Incidence	
TOTAL	424/1,963 (21.6%)
SD (b)	7.65%
Range (c)	
High	18/49
Low	4/50

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

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Ulcer, NOS		1 (2%)	
Inflammation, active chronic			1 (2%)
Inflammation, chronic necrotizing			1 (2%)
Hyperkeratosis			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, active chronic		1 (2%)	2 (4%)
Infection, fungal			1 (2%)
#Lung	(50)	(18)	(50)
Congestion, NOS		1 (6%)	
Edema, NOS	1 (2%)		
Hemorrhage			1 (2%)
Pneumonia, interstitial chronic	2 (4%)	2 (11%)	4 (8%)
Perivascular cuffing	4 (8%)	2 (11%)	8 (16%)
Alveolar macrophages	1 (2%)		1 (2%)
Hyperplasia, adenomatous	1 (2%)		2 (4%)
#Lung/alveoli	(50)	(18)	(50)
Crystals, NOS		1 (6%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(8)	(50)
Atrophy, NOS			1 (2%)
Hyperplasia, NOS	22 (44%)	4 (50%)	10 (20%)
Myelofibrosis	1 (2%)		
#Spleen	(50)	(17)	(50)
Fibrosis			1 (2%)
Hemosiderosis			2 (4%)
Hyperplasia, nodular		1 (6%)	
Hematopoiesis	5 (10%)	3 (18%)	3 (6%)
#Splenic capsule	(50)	(17)	(50)
Hematoma, NOS		1 (6%)	
#Splenic follicles	(50)	(17)	(50)
Atrophy, NOS			1 (2%)
#Mandibular lymph node	(50)	(12)	(50)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, acute/chronic	1 (2%)		
#Mesenteric lymph node	(50)	(12)	(50)
Hemorrhage	3 (6%)		
#Thymus	(35)	(7)	(39)
Cyst, NOS	4 (11%)		1 (3%)
Hemorrhage			1 (3%)
CIRCULATORY SYSTEM			
#Myocardium	(50)	(9)	(50)
Mineralization	1 (2%)		1 (2%)
Inflammation, chronic	11 (22%)	1 (11%)	16 (32%)
Fibrosis	40 (80%)	4 (44%)	43 (86%)
Degeneration, NOS	2 (4%)		1 (2%)

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

	Untreated Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
*Artery	(50)	(50)	(50)
Periarteritis	1 (2%)		1 (2%)
Arteriosclerosis, NOS	1 (2%)		
*Aorta	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(9)	(50)
Inflammation, chronic			2 (4%)
Atrophy, NOS	2 (4%)		2 (4%)
Hyperplasia, epithelial	1 (2%)		
#Submaxillary duct	(50)	(9)	(50)
Dysplasia, epithelial			1 (2%)
#Liver	(50)	(50)	(50)
Hernia, NOS	9 (18%)	11 (22%)	4 (8%)
Inflammation, acute focal			1 (2%)
Granuloma, NOS	15 (30%)	20 (40%)	22 (44%)
Metamorphosis, fatty			5 (10%)
Nuclear alteration	3 (6%)	2 (4%)	1 (2%)
Cytoplasmic vacuolization	11 (22%)	12 (24%)	9 (18%)
Basophilic cyto change	43 (86%)	42 (84%)	46 (92%)
Clear cell change	7 (14%)	9 (18%)	4 (8%)
Hyperplasia, focal	4 (8%)	5 (10%)	10 (20%)
Angiectasis	2 (4%)	3 (6%)	3 (6%)
Regenerative nodule	1 (2%)		
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, NOS	1 (2%)		
Metamorphosis, fatty	2 (4%)		1 (2%)
#Bile duct	(50)	(50)	(50)
Cyst, NOS	1 (2%)	1 (2%)	
Hyperplasia, NOS	33 (66%)	21 (42%)	27 (54%)
#Pancreas	(50)	(10)	(49)
Ectopia			1 (2%)
Inflammation, chronic	1 (2%)		
#Pancreatic acinus	(50)	(10)	(49)
Atrophy, NOS	13 (26%)	1 (10%)	12 (24%)
#Esophagus	(50)	(8)	(50)
Hyperkeratosis		3 (38%)	3 (6%)
#Glandular stomach	(50)	(50)	(49)
Multiple cysts	33 (66%)	41 (82%)	42 (86%)
#Gastric serosa	(50)	(50)	(49)
Inflammation, active chronic			1 (2%)
#Forestomach	(50)	(50)	(49)
Edema, NOS	1 (2%)	1 (2%)	4 (8%)
Ulcer, NOS		1 (2%)	2 (4%)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, active chronic		1 (2%)	3 (6%)
Inflammation, chronic		2 (4%)	4 (8%)
Hyperplasia, epithelial		1 (2%)	6 (12%)
Hyperkeratosis		1 (2%)	1 (2%)
#Jejunum	(50)	(8)	(50)
Ulcer, NOS	1 (2%)		
#Ileum	(50)	(8)	(50)
Inflammation, granulomatous	1 (2%)		
#Colon	(49)	(8)	(49)
Cyst, NOS			1 (2%)

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

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(10)	(50)
Cyst, NOS		1 (10%)	
Scar	1 (2%)		
Nephropathy	49 (98%)	6 (60%)	42 (84%)
#Kidney/tubule	(50)	(10)	(50)
Degeneration, hyaline	3 (6%)	1 (10%)	
Nephrosis, NOS	1 (2%)		
Metamorphosis, fatty		1 (10%)	2 (4%)
Pigmentation, NOS	2 (4%)		
#Kidney/pelvis	(50)	(10)	(50)
Hemosiderosis			1 (2%)
#Urinary bladder	(49)	(9)	(50)
Hyperplasia, epithelial		1 (11%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(35)	(50)
Angiectasis		1 (3%)	
#Anterior pituitary	(50)	(35)	(50)
Cyst, NOS	30 (60%)	21 (60%)	28 (56%)
Hyperplasia, focal	14 (28%)	8 (23%)	22 (44%)
Angiectasis	8 (16%)	6 (17%)	9 (18%)
#Adrenal cortex	(50)	(50)	(50)
Degeneration, lipoid	21 (42%)	26 (52%)	22 (44%)
Metamorphosis, fatty	2 (4%)	1 (2%)	3 (6%)
Hypertrophy, focal	2 (4%)	10 (20%)	5 (10%)
Hyperplasia, focal	34 (68%)	37 (74%)	25 (50%)
Angiectasis	30 (60%)	36 (72%)	40 (80%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	7 (14%)	7 (14%)	5 (10%)
#Thyroid	(50)	(12)	(48)
Hyperplasia, C-cell	26 (52%)	1 (8%)	24 (50%)
#Pancreatic islets	(50)	(10)	(49)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	2 (4%)	2 (4%)	1 (2%)
Inflammation, granulomatous			1 (2%)
Hyperplasia, NOS	3 (6%)		1 (2%)
Hyperplasia, cystic	40 (80%)	9 (18%)	41 (82%)
*Clitoral gland	(50)	(50)	(50)
Abscess, NOS	1 (2%)	1 (2%)	1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, focal	3 (6%)		1 (2%)
#Uterus	(50)	(49)	(50)
Hydrometra	2 (4%)	1 (2%)	
Hyperplasia, epithelial		2 (4%)	
Polypoid hyperplasia	1 (2%)		
#Endometrial gland	(50)	(49)	(50)
Cyst, NOS	5 (10%)		
#Ovary	(50)	(9)	(50)
Cyst, NOS		1 (11%)	5 (10%)

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

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain	(50)	(9)	(50)
Mineralization	1 (2%)	1 (11%)	
Hydrocephalus, NOS	1 (2%)	1 (11%)	3 (6%)
Inflammation, chronic	1 (2%)		
Gliosis	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage		4 (8%)	1 (2%)
Inflammation, acute			1 (2%)
*Cornea, substantia propria	(50)	(50)	(50)
Vascularization	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	6 (12%)	18 (36%)	12 (24%)
*Eye/lens, cortex	(50)	(50)	(50)
Cataract	7 (14%)	17 (34%)	10 (20%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Mesothelial cyst			1 (2%)
Inflammation, active chronic	1 (2%)		
*Pleural mesothelium	(50)	(50)	(50)
Hyperplasia, NOS			1 (2%)
ALL OTHER SYSTEMS			
Adipose tissue			
Necrosis, fat	5	2	
Renal pelvic cavity			
Hemosiderosis			2
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF *alpha*-METHYLDOPA SESQUIHYDRATE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Sebaceous adenoma			1 (2%)
Malignant melanoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(13)	(49)
Hepatocellular carcinoma, metastatic		1 (8%)	
Alveolar/bronchiolar adenoma	6 (12%)	2 (15%)	3 (6%)
Alveolar/bronchiolar carcinoma	4 (8%)	3 (23%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type	1 (2%)		
Malignant lymphoma, histiocytic type	1 (2%)		
Malignant lymphoma, mixed type	1 (2%)		2 (4%)
#Spleen	(49)	(48)	(50)
Malignant lymphoma, mixed type	1 (2%)		
#Mesenteric lymph node	(49)	(8)	(49)
Malignant lymphoma, undifferentiated type		1 (13%)	
Malignant lymphoma, histiocytic type	1 (2%)		
#Jejunum	(49)	(3)	(50)
Malignant lymphoma, mixed type	1 (2%)		
CIRCULATORY SYSTEM			
#Spleen	(49)	(48)	(50)
Hemangioma	2 (4%)		
Hemangiosarcoma		1 (2%)	
#Liver	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Papilloma, NOS		1 (2%)	
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	7 (14%)	3 (6%)	6 (12%)
Hepatocellular carcinoma	8 (16%)	3 (6%)	
#Forestomach	(49)	(48)	(50)
Papilloma, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		2 (4%)	
Tubular cell adenocarcinoma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(3)	(48)
Adenoma, NOS			1 (2%)
#Adrenal	(50)	(2)	(48)
Cortical adenoma			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(2)	(50)
Follicular cell adenoma			2 (4%)
Follicular cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	1 (2%)
Adenoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrosarcoma		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	5	7
Moribund sacrifice	4	3	
Terminal sacrifice	44	42	39
Accidentally killed, nda			4
TUMOR SUMMARY			
Total animals with primary tumors**	32	15	17
Total primary tumors	39	18	22
Total animals with benign tumors	15	7	12
Total benign tumors	17	8	14
Total animals with malignant tumors	19	9	8
Total malignant tumors	22	10	8
Total animals with secondary tumors##		1	
Total secondary tumors		1	

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

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

ANIMAL NUMBER	10 05	14 49	11 14	11 10	11 18	15 50	10 01	10 02	10 03	10 04	10 06	10 07	10 08	10 09	11 11	11 12	11 13	11 15	11 16	11 17	11 19	12 20	12 21	12 22	12 23
WEEKS ON STUDY	04 5	07 7	08 1	08 3	09 0	10 0	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant melanoma																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X	X					X												
Alveolar/bronchiolar carcinoma				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
Thymus	+	–	+	–	–	–	+	+	+	+	–	+	+	–	–	+	+	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma		X																				X			
Hepatocellular carcinoma			X		X									X					X	X					
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS									X																
Small intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																							X		
Parathyroid	–	+	+	–	+	+	–	+	+	+	+	–	+	+	+	–	–	+	+	+	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS													X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type										X															
Malignant lymphoma, histiocytic type															X										
Malignant lymphoma, mixed type				X																					

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Malignant melanoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X		X		X			6
Alveolar/bronchiolar carcinoma	X									X								X								4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma						X			X																	2
Malignant lymphoma, mixed type		X																								1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, histiocytic type						X																				1
Thymus	+	+	+	+	+	-	+	+	+	+	-	+	-	+	-	-	-	+	+	+	-	+	+	+	-	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma						X						X				X				X					X	7
Hepatocellular carcinoma		X	X										X													8
Hemangiosarcoma					X																					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type													X													1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
Parathyroid	+	+	-	+	-	+	-	+	+	+	-	+	+	-	+	-	-	+	+	+	-	-	+	-	-	28
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS											X															1
Adenoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																										1

* Animals necropsied

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

ANIMAL NUMBER	019	050	038	034	028	026	008	033	001	002	003	004	005	006	007	009	010	011	012	013	014	015	016	017	018
WEEKS ON STUDY	002	074	078	096	097	099	101	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+
Hepatocellular carcinoma, metastatic							X																		
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma			X																				X		
Trachea	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	-	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Spleen	+	-	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Lymph nodes	+	-	+	A	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Malignant lymphoma, undifferentiated type					X																				
Thymus	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CIRCULATORY SYSTEM																									
Heart	+	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS								X																	
Salivary gland	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X																		
Hepatocellular carcinoma							X												X						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	-	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Esophagus	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stomach	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
Small intestine	-	-	+	A	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Large intestine	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																				X					
Urinary bladder	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Adrenal	+	·	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thyroid	+	-	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parathyroid	-	-	-	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prostate	+	+	+	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NERVOUS SYSTEM																									
Brain	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																							X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma							X																		

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

ANIMAL NUMBER	020	021	022	023	024	025	027	029	030	031	032	035	036	037	039	040	041	042	043	044	045	046	047	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	13
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma			X															X								2
Alveolar/bronchiolar carcinoma						X																				3
Trachea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
HEMATOPOIETIC SYSTEM																										
Bone marrow	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymph nodes	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	8
Malig. lymphoma, undifferentiated type																										1
Thymus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
CIRCULATORY SYSTEM																										
Heart	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS																										1
Salivary gland	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X																X							3
Hepatocellular carcinoma																									X	3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
Esophagus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Large intestine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																								X		2
Urinary bladder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	-	6
ENDOCRINE SYSTEM																										
Pituitary	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Adrenal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
Thyroid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
Parathyroid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Prostate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1

* Animals necropsied

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

ANIMAL NUMBER	051	059	066	076	069	080	055	071	072	056	078	052	053	054	057	058	060	061	062	063	064	065	067	068	070
WEEKS ON STUDY	009	019	019	019	028	043	069	072	074	080	081	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											X
Alveolar/bronchiolar carcinoma												X					X								
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	–	–	+	+	+	+	+	+	+	–	–	+	–	+	+	–	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X							X				X					X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																X									
Urinary bladder	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																	X								
Parathyroid	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	–	+	+	+	–	–	+	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																							X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	073	074	075	077	079	081	082	083	084	085	086	087	088	089	090	091	092	093	094	095	096	097	098	099	100	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma																									X	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma						X																				3
Alveolar/bronchiolar carcinoma														X	X											4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	-	+	+	-	+	-	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X									X									6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS					X																					1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma					X																					1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma												X														2
Parathyroid	+	+	-	+	+	+	+	-	-	+	+	+	+	+	-	+	-	+	+	-	+	-	+	-	-	34
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type																									X	2

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control	6,300 ppm	12,500 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/50 (12%)	(b) 2/13 (15%)	3/49 (6%)
Adjusted Rates (c)	13.6%		7.9%
Terminal Rates (d)	6/44 (14%)		3/38 (8%)
Week of First Observation	104		104
Life Table Test (e)			P=0.318N
Incidental Tumor Test (e)			P=0.318N
Fisher Exact Test (e)			P=0.254N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	4/50 (8%)	(b) 3/13 (23%)	4/49 (8%)
Adjusted Rates (c)	8.8%		10.5%
Terminal Rates (d)	3/44 (7%)		4/38 (11%)
Week of First Observation	83		104
Life Table Test (e)			P=0.558
Incidental Tumor Test (e)			P=0.542
Fisher Exact Test (e)			P=0.631
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	(b) 5/13 (38%)	7/49 (14%)
Adjusted Rates (c)	22.1%		18.4%
Terminal Rates (d)	9/44 (20%)		7/38 (18%)
Week of First Observation	83		104
Life Table Test (e)			P=0.422N
Incidental Tumor Test (e)			P=0.433N
Fisher Exact Test (e)			P=0.314N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (c)	6.6%	0.0%	5.1%
Terminal Rates (d)	2/44 (5%)	0/42 (0%)	2/39 (5%)
Week of First Observation	83		104
Life Table Tests (e)	P=0.436N	P=0.129N	P=0.560N
Incidental Tumor Tests (e)	P=0.469N	P=0.249N	P=0.580N
Cochran-Armitage Trend Test (e)	P=0.388N		
Fisher Exact Test (e)		P=0.122N	P=0.500N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	6/50 (12%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (c)	13.2%	2.2%	5.1%
Terminal Rates (d)	5/44 (11%)	0/42 (0%)	2/39 (5%)
Week of First Observation	83	97	104
Life Table Tests (e)	P=0.095N	P=0.067N	P=0.181N
Incidental Tumor Tests (e)	P=0.111N	P=0.062N	P=0.191N
Cochran-Armitage Trend Test (e)	P=0.070N		
Fisher Exact Test (e)		P=0.056N	P=0.135N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (c)	6.8%	2.4%	0.0%
Terminal Rates (d)	3/44 (7%)	1/42 (2%)	0/39 (0%)
Week of First Observation	104	104	
Life Table Tests (e)	P=0.073N	P=0.322N	P=0.143N
Incidental Tumor Tests (e)	P=0.073N	P=0.322N	P=0.143N
Cochran-Armitage Trend Test (e)	P=0.060N		
Fisher Exact Test (e)		P=0.309N	P=0.121N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Control	6,300 ppm	12,500 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (c)	15.4%	6.9%	14.8%
Terminal Rates (d)	6/44 (14%)	2/42 (5%)	5/39 (13%)
Week of First Observation	77	101	69
Life Table Tests (e)	P=0.518N	P=0.179N	P=0.593N
Incidental Tumor Tests (e)	P=0.433N	P=0.099N	P=0.459N
Cochran-Armitage Trend Test (e)	P=0.434N		
Fisher Exact Test (e)		P=0.159N	P=0.500N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	8/50 (16%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (c)	17.3%	6.9%	0.0%
Terminal Rates (d)	6/44 (14%)	2/42 (5%)	0/39 (0%)
Week of First Observation	81	101	
Life Table Tests (e)	P=0.004N	P=0.118N	P=0.010N
Incidental Tumor Tests (e)	P=0.005N	P=0.189N	P=0.009N
Cochran-Armitage Trend Test (e)	P=0.002N		
Fisher Exact Test (e)		P=0.100N	P=0.003N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (c)	31.8%	11.6%	14.8%
Terminal Rates (d)	12/44 (27%)	4/42 (10%)	5/39 (13%)
Week of First Observation	77	101	69
Life Table Tests (e)	P=0.027N	P=0.019N	P=0.056N
Incidental Tumor Tests (e)	P=0.019N	P=0.023N	P=0.029N
Cochran-Armitage Trend Test (e)	P=0.012N		
Fisher Exact Test (e)		P=0.011N	P=0.024N
All Sites: Benign Tumors			
Overall Rates (a)	15/50 (30%)	7/50 (14%)	12/50 (24%)
Adjusted Rates (c)	33.2%	15.9%	29.8%
Terminal Rates (d)	14/44 (32%)	5/42 (12%)	11/39 (28%)
Week of First Observation	77	101	69
Life Table Tests (e)	P=0.392N	P=0.062N	P=0.468N
Incidental Tumor Tests (e)	P=0.340N	P=0.022N	P=0.365N
Cochran-Armitage Trend Test (e)	P=0.273N		
Fisher Exact Test (e)		P=0.045N	P=0.327N
All Sites: Malignant Tumors			
Overall Rates (a)	19/50 (38%)	9/50 (18%)	8/50 (16%)
Adjusted Rates (c)	40.3%	19.4%	20.5%
Terminal Rates (d)	16/44 (36%)	5/42 (12%)	8/39 (21%)
Week of First Observation	81	78	104
Life Table Tests (e)	P=0.020N	P=0.038N	P=0.033N
Incidental Tumor Tests (e)	P=0.019N	P=0.032N	P=0.033N
Cochran-Armitage Trend Test (e)	P=0.007N		
Fisher Exact Test (e)		P=0.022N	P=0.012N
All Sites: All Tumors			
Overall Rates (a)	32/50 (64%)	15/50 (30%)	17/50 (34%)
Adjusted Rates (c)	66.6%	31.9%	42.4%
Terminal Rates (d)	28/44 (64%)	10/42 (24%)	16/39 (41%)
Week of First Observation	77	78	69
Life Table Tests (e)	P=0.011N	P=0.003N	P=0.016N
Incidental Tumor Tests (e)	P=0.006N	P<0.001N	P=0.007N
Cochran-Armitage Trend Test (e)	P=0.002N		
Fisher Exact Test (e)		P<0.001N	P=0.003N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

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

TABLE C4a. HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	No. Examined	No. of Tumors	Diagnosis
Historical Incidence at Physiological Research Laboratories			
	150	0	
Overall Historical Incidence			
		3	Tubular cell adenoma
		1	Adenocarcinoma, NOS
		2	Tubular cell adenocarcinoma
TOTAL	2,029	6 (0.3%)	

(a) Data as of August 7, 1986, for studies of at least 104 weeks; no more than one tumor has been observed in any untreated control group.

TABLE C4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	10/50	13/50	19/50
Phenylephrine hydrochloride	12/50	4/50	15/50
Oxytetracycline hydrochloride	7/50	11/50	18/50
TOTAL	29/150 (19.3%)	28/150 (18.7%)	52/150 (34.7%)
SD (b)	5.03%	9.45%	4.16%
Range (c)			
High	12/50	13/50	19/50
Low	7/50	4/50	15/50
Overall Historical Incidence			
TOTAL	242/2,032 (11.9%)	394/2,032 (19.4%)	609/2,032 (30.0%)
SD (b)	7.44%	6.84%	7.90%
Range (c)			
High	(d) 22/50	16/50	(e) 29/50
Low	0/49	4/50	8/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest: 12/50
(e) Second highest: 20/50

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Edema, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, serous	1 (2%)		
Eosinophilic cyto change	1 (2%)		
*Nasal mucosa	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Inflammation, acute	1 (2%)		
#Lung	(50)	(13)	(49)
Congestion, NOS	3 (6%)		11 (22%)
Hemorrhage	3 (6%)	1 (8%)	5 (10%)
Inflammation, acute/chronic		1 (8%)	
Inflammation, chronic focal	1 (2%)	1 (8%)	4 (8%)
Perivascular cuffing	1 (2%)		4 (8%)
Alveolar macrophages	2 (4%)	1 (8%)	1 (2%)
#Lung/alveoli	(50)	(13)	(49)
Hemorrhage			1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(2)	(50)
Hyperplasia, NOS	1 (2%)		1 (2%)
Angiectasis	1 (2%)		1 (2%)
Hyperplasia, granulocytic	3 (6%)		5 (10%)
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, megakaryocytic	1 (2%)		
#Spleen	(49)	(48)	(50)
Infarct, healed	1 (2%)		
Atrophy, NOS			2 (4%)
Angiectasis	1 (2%)	1 (2%)	
Hyperplasia, reticulum cell	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid	36 (73%)	31 (65%)	23 (46%)
Hematopoiesis	3 (6%)	1 (2%)	2 (4%)
#Splenic follicles	(49)	(48)	(50)
Atrophy, NOS			2 (4%)
#Mandibular lymph node	(49)	(8)	(49)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Mesenteric lymph node	(49)	(8)	(49)
Hemorrhage			1 (2%)
Angiectasis		5 (63%)	6 (12%)
Hyperplasia, lymphoid	9 (18%)	1 (13%)	5 (10%)
*Bone	(50)	(50)	(50)
Myelofibrosis	2 (4%)		1 (2%)
#Lung	(50)	(13)	(49)
Hyperplasia, lymphoid	2 (4%)		
#Salivary gland	(50)	(3)	(50)
Hyperplasia, lymphoid	7 (14%)		4 (8%)
#Pancreas	(49)	(2)	(50)
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis			1 (2%)
#Peyer's patch	(49)	(3)	(50)
Hyperplasia, lymphoid	1 (2%)		1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Duodenum	(49)	(3)	(50)
Hyperplasia, lymphoid	1 (2%)		2 (4%)
#Jejunum	(49)	(3)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Ileum	(49)	(3)	(50)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
#Cecum	(49)	(3)	(50)
Hyperplasia, lymphoid	4 (8%)		5 (10%)
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
#Urinary bladder	(49)	(6)	(47)
Hyperplasia, lymphoid	1 (2%)		
*Epididymis	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Anterior pituitary	(49)	(3)	(48)
Hyperplasia, basophilic	1 (2%)		
#Thymus	(34)	(3)	(36)
Cyst, NOS	3 (9%)		8 (22%)
Multiple cysts	2 (6%)		1 (3%)
Inflammation, pyogranulomatous	1 (3%)		
Atrophy, NOS	1 (3%)		4 (11%)
Hyperplasia, epithelial	1 (3%)		1 (3%)
Hyperplasia, lymphoid	1 (3%)		
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(49)	(8)	(49)
Lymphangiectasis			1 (2%)
#Heart	(50)	(3)	(50)
Perivasculitis	1 (2%)		
#Myocardium	(50)	(3)	(50)
Degeneration, NOS			2 (4%)
Necrosis, focal	1 (2%)		
*Artery	(50)	(50)	(50)
Periarteritis			1 (2%)
#Kidney	(50)	(50)	(50)
Periarteritis	1 (2%)		
#Prostate	(50)	(3)	(48)
Periarteritis	1 (2%)		
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Hemorrhage		1 (2%)	
*Tooth	(50)	(50)	(50)
Dysplasia, NOS	10 (20%)		2 (4%)
#Salivary gland	(50)	(3)	(50)
Hemorrhage			1 (2%)
Inflammation, acute/chronic	1 (2%)		
Calcification, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Congestion, NOS			2 (4%)
Inflammation, acute focal	1 (2%)		
Necrosis, NOS	1 (2%)		
Necrosis, focal	4 (8%)	4 (8%)	1 (2%)
Necrosis, diffuse			1 (2%)
Metamorphosis, fatty	1 (2%)	1 (2%)	
Cytoplasmic vacuolization		1 (2%)	
Focal cellular change	2 (4%)	6 (12%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver/centrilobular	(50)	(50)	(50)
Metamorphosis, fatty	3 (6%)		
*Gallbladder	(50)	(50)	(50)
Fibrosis	1 (2%)		
*Gallbladder/mucosa	(50)	(50)	(50)
Eosinophilic cyto change	2 (4%)		
Hyperplasia, papillary	1 (2%)		
#Pancreas	(49)	(2)	(50)
Multiple cysts			1 (2%)
Fibrosis			1 (2%)
Atrophy, NOS			2 (4%)
Atrophy, focal			1 (2%)
#Pancreatic acinus	(49)	(2)	(50)
Hypertrophy, focal	1 (2%)		1 (2%)
#Stomach	(49)	(48)	(50)
Eosinophilic cyto change			3 (6%)
#Glandular stomach	(49)	(48)	(50)
Cyst, NOS	3 (6%)	4 (8%)	2 (4%)
Multiple cysts	2 (4%)	3 (6%)	5 (10%)
Inflammation, acute	2 (4%)		1 (2%)
Inflammation, acute/chronic	7 (14%)	3 (6%)	1 (2%)
Inflammation, chronic	2 (4%)	6 (13%)	7 (14%)
Calcification, NOS		9 (19%)	7 (14%)
Eosinophilic cyto change	8 (16%)	7 (15%)	5 (10%)
Hyperplasia, epithelial	11 (22%)	12 (25%)	5 (10%)
Metaplasia, squamous	1 (2%)		
#Forestomach	(49)	(48)	(50)
Acanthosis	1 (2%)		
#Small intestine	(49)	(3)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Duodenal serosa	(49)	(3)	(50)
Cyst, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis	1 (2%)		
Cyst, NOS	8 (16%)	8 (16%)	8 (16%)
Multiple cysts		3 (6%)	2 (4%)
Nephropathy	47 (94%)	46 (92%)	41 (82%)
Infarct, healed	5 (10%)	7 (14%)	3 (6%)
Calcification, NOS	35 (70%)	46 (92%)	43 (86%)
Cytoplasmic vacuolization		1 (2%)	
Hyperplasia, tubular cell		1 (2%)	1 (2%)
Metaplasia, osseous	2 (4%)		
#Perirenal tissue	(50)	(50)	(50)
Inflammation, necrotizing			1 (2%)
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis	1 (2%)		
#Kidney/tubule	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
#Convoluted tubules	(50)	(50)	(50)
Metamorphosis, fatty	1 (2%)		
#Urinary bladder	(49)	(6)	(47)
Calculus, gross observation only			1 (2%)
Hyperplasia, epithelial		1 (17%)	1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary	(49)	(3)	(48)
Congestion, NOS			1 (2%)
#Anterior pituitary	(49)	(3)	(48)
Cyst, NOS	5 (10%)		2 (4%)
Multiple cysts	1 (2%)		
Congestion, NOS			1 (2%)
Hyperplasia, focal	2 (4%)		1 (2%)
#Adrenal/capsule	(50)	(2)	(48)
Cyst, NOS	1 (2%)		
Hyperplasia, stromal	30 (60%)		25 (52%)
#Adrenal cortex	(50)	(2)	(48)
Degeneration, lipoid	3 (6%)		1 (2%)
Hypertrophy, NOS			1 (2%)
Hypertrophy, focal	13 (26%)		2 (4%)
Hyperplasia, focal	1 (2%)		5 (10%)
Angiectasis			1 (2%)
#Adrenal medulla	(50)	(2)	(48)
Hyperplasia, focal			1 (2%)
#Thyroid	(50)	(2)	(50)
Inflammation, acute/chronic	1 (2%)		
Calcification, NOS	1 (2%)		
#Parathyroid	(28)		(34)
Cyst, NOS			1 (3%)
Multiple cysts			1 (3%)
#Pancreatic islets	(49)	(2)	(50)
Hyperplasia, NOS	2 (4%)		2 (4%)
Angiectasis	1 (2%)		
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	3 (6%)	4 (8%)	3 (6%)
Abscess, NOS		1 (2%)	
Inflammation, acute/chronic	3 (6%)		
Inflammation, chronic	1 (2%)		
Inflammation, granulomatous		1 (2%)	
#Prostate	(50)	(3)	(48)
Inflammation, chronic focal			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Inflammation, chronic	1 (2%)		
Fibrosis			1 (2%)
#Testis	(50)	(3)	(49)
Dilatation, NOS	1 (2%)		
Cyst, NOS			1 (2%)
Necrosis, focal	1 (2%)		
Calcification, NOS			2 (4%)
Cytomegaly			1 (2%)
Atrophy, NOS	2 (4%)		1 (2%)
Angiectasis			1 (2%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Fibrosis	1 (2%)		
Calcification, NOS	1 (2%)		3 (6%)
Cytomegaly	1 (2%)		1 (2%)
Angiectasis	1 (2%)		
*Scrotum	(50)	(50)	(50)
Calcification, NOS			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Ependyma third ventricle	(50)	(49)	(50)
Eosinophilic leukocytic infiltrate	1 (2%)		
#Brain	(50)	(49)	(50)
Congestion, NOS			3 (6%)
#Brain/thalamus	(50)	(49)	(50)
Calcification, NOS	42 (84%)	33 (67%)	29 (58%)
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Atrophy, NOS	2 (4%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
*Peritoneum	(50)	(50)	(50)
Hemoperitoneum			1 (2%)
*Mesentery	(50)	(50)	(50)
Fibrosis, focal	1 (2%)		
ALL OTHER SYSTEMS			
Knee			
Dyschondroplasia	1		2
Adipose tissue			
Inflammation with fibrosis			1
Necrosis, fat	5	1	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		1	
Auto/necropsy/histo perf		1	

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *alpha*-METHYLDOPA SESQUIHYDRATE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(49)	(15)	(50)
Alveolar/bronchiolar adenoma	3 (6%)		6 (12%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (7%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)	1 (2%)	
Malignant lymphoma, undifferentiated type	1 (2%)	2 (4%)	1 (2%)
Malignant lymphoma, lymphocytic type	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, mixed type	10 (20%)	5 (10%)	5 (10%)
Granulocytic leukemia		1 (2%)	
#Spleen	(50)	(49)	(49)
Malignant lymphoma, mixed type	1 (2%)	1 (2%)	
#Thymus	(43)	(4)	(41)
Malignant lymphoma, lymphocytic type	1 (2%)		
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangioma			1 (2%)
#Spleen	(50)	(49)	(49)
Hemangioma	1 (2%)		
Hemangiosarcoma		1 (2%)	1 (2%)
#Liver	(50)	(50)	(50)
Hemangioma			1 (2%)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	3 (6%)	1 (2%)	
Hepatocellular carcinoma	1 (2%)		
#Duodenum	(47)	(7)	(47)
Sarcoma, NOS	1 (2%)		
#Jejunum	(47)	(7)	(47)
Carcinoma, NOS		1 (14%)	
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(40)	(50)
Adenoma, NOS			1 (2%)
#Anterior pituitary	(49)	(40)	(50)
Adenoma, NOS	9 (18%)	4 (10%)	2 (4%)
#Adrenal	(49)	(6)	(50)
Pheochromocytoma	1 (2%)		
#Adrenal medulla	(49)	(6)	(50)
Pheochromocytoma	2 (4%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(49)	(5)	(49)
Follicular cell adenoma	2 (4%)		
#Pancreatic islets	(49)	(8)	(47)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenocarcinoma, NOS	3 (6%)		2 (4%)
Fibroadenoma		1 (2%)	
#Uterus	(50)	(49)	(49)
Histiocytic sarcoma	1 (2%)		
Fibrosarcoma	1 (2%)		
Endometrial stromal polyp		1 (2%)	
#Fallopian tube	(50)	(49)	(49)
Papillary adenoma		1 (2%)	
#Ovary	(47)	(15)	(47)
Papillary cystadenoma, NOS			1 (2%)
Teratoma, NOS		1 (7%)	1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	5	5
Moribund sacrifice	3	5	3
Terminal sacrifice	42	40	38
Accidentally killed, nda			4

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	33	22	21
Total primary tumors	46	27	27
Total animals with benign tumors	19	7	13
Total benign tumors	21	8	13
Total animals with malignant tumors	21	16	12
Total malignant tumors	25	18	13
Total animals with tumors uncertain--benign or malignant		1	1
Total uncertain tumors		1	1

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ.

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE: UNTREATED CONTROL

ANIMAL NUMBER	12 29	12 21	11 19	11 15	12 26	14 43	13 36	10 05	10 01	10 02	10 03	10 04	10 06	10 07	10 08	10 09	11 10	11 11	11 12	11 13	11 14	11 16	11 17	11 18	12 20
WEEKS ON STUDY	05 77	07 74	08 00	09 44	09 95	09 99	10 00	10 03	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Malignant lymphoma, mixed type																									X
Lymph nodes	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	A	−	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																						X			
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X															
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	A	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X		X											X	X	
Adrenal	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma					X																				
Thyroid	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
Parathyroid	+	−	A	−	+	−	+	+	−	−	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS						X				X			X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Fibrosarcoma																									
Ovary	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS				X																					
Malignant lymphoma, undifferentiated type		X																							
Malignant lymphoma, lymphocytic type								X																	
Malignant lymphoma, mixed type									X			X	X	X		X									

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	122	123	124	125	127	128	130	131	132	133	134	135	137	138	139	140	141	142	144	145	146	147	148	149	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma									X											X						3
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																			X							1
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Malignant lymphoma, lymphocytic type																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X																			X		3
Hepatocellular carcinoma							X																			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, NOS																							X			1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS				X		X					X					X			X							9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma			X																						X	3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma	X																									2
Parathyroid	+	+	−	−	+	−	+	+	+	+	−	+	+	−	+	+	−	+	−	+	−	+	−	−	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Fibrosarcoma																							X			1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS						X																				1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Malig. lymphoma, undifferentiated type																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type		X				X	X												X						X	10

* Animals necropsied

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

ANIMAL NUMBER	043	001	040	014	047	017	002	050	028	003	004	005	006	007	008	009	010	011	012	013	015	016	018	019	020
WEEKS ON STUDY	022	055	080	082	089	090	092	092	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	−	+	−	−	+	−	−	−	−	−	−	−	−	+	−	−	+	−	−
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Hemangiosarcoma																									
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	+	−	−
Thymus	+	−	+	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X														
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	−	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−
Esophagus	+	+	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	
Small intestine	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Carcinoma, NOS																									
Large intestine	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	+	+	+	+	−	+	+	−	+	+	+	+	−	−	+	+	+	+	−	+	−
Adenoma, NOS													X	X											
Adrenal	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Thyroid	+	+	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Parathyroid	−	−	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS														X											
Fibroadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Papillary adenoma												X													
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	+	−	+	−	−
Teratoma, NOS	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Histiocytic sarcoma							X																		
Malignant lymphoma, NOS									X																
Malignant lymphoma, undifferentiated type			X	X																					
Malignant lymphoma, lymphocytic type								X																	
Malignant lymphoma, mixed type						X					X														
Granulocytic leukemia					X																				

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

ANIMAL NUMBER	0021	0022	0023	0024	0025	0026	0027	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0041	0042	0044	0045	0046	0048	0049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–		15
Alveolar/bronchiolar carcinoma		X																								1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma			X																							1
Malignant lymphoma, mixed type																						X				1
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	10
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	8
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	7
Carcinoma, NOS								X																		1
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	6
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	40
Adenoma, NOS										X													X			4
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Fibroadenoma																		X								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary adenoma																										1
Endometrial stromal polyp										X																1
Ovary	–	+	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	+	–	–	+	–	15
Teratoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																	X									1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Histiocytic sarcoma																										1
Malignant lymphoma, NOS																										1
Malig lymphoma, undifferentiated type																										2
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type											X						X		X							5
Granulocytic leukemia																										1

* Animals necropsied

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

ANIMAL NUMBER	09 8	07 2	09 6	09 7	09 9	07 8	08 0	06 0	05 7	06 1	07 0	06 7	05 1	05 2	05 3	05 4	05 5	05 6	05 8	05 9	06 2	06 3	06 4	06 5	06 6
WEEKS ON STUDY	02 3	02 7	04 1	04 1	04 1	08 1	08 4	08 5	08 7	09 0	09 8	10 0	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X								X					
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma														X											
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS													X						X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	+	+	+	−	−	+	+	+	+	+	+	−	−	−	+	+	−	+	+	−	+	−	+
Pancreatic islets	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS											X														
Uterus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																X									
Teratoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type												X													
Malignant lymphoma, lymphocytic type											X														
Malignant lymphoma, mixed type														X				X							X

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

ANIMAL NUMBER	0068	0069	0071	0073	0074	0075	0076	0077	0079	0081	0082	0083	0084	0085	0086	0087	0088	0089	0090	0091	0092	0093	0094	0095	0100	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangioma	X																									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																X	X				X	6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma										X																1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																			X							3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	+	+	+	−	+	+	+	+	+	−	+	+	+	−	−	+	−	+	+	+	+	−	−	−	33
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
Islet cell adenoma													X													1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS				X																						2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papillary cystadenoma, NOS																										1
Teratoma, NOS																								X		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																			X			X				2
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig lymphoma, undifferentiated type																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type									X															X		5

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control	6,300 ppm	12,500 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/49 (6%)	(b) 0/15 (0%)	6/50 (12%)
Adjusted Rates (c)	7.1%		15.4%
Terminal Rates (d)	3/42 (7%)		5/38 (13%)
Week of First Observation	104		100
Life Table Test (e)			P=0.196
Incidental Tumor Test (e)			P=0.160
Fisher Exact Test (e)			P=0.254
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	(b) 1/15 (7%)	6/50 (12%)
Adjusted Rates (c)	9.3%		15.4%
Terminal Rates (d)	3/42 (7%)		5/38 (13%)
Week of First Observation	100		100
Life Table Test (e)			P=0.308
Incidental Tumor Test (e)			P=0.221
Fisher Exact Test (e)			P=0.383
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	11/50 (22%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (c)	26.2%	14.1%	13.2%
Terminal Rates (d)	11/42 (26%)	5/41 (12%)	5/38 (13%)
Week of First Observation	104	90	104
Life Table Tests (e)	P=0.086N	P=0.156N	P=0.121N
Incidental Tumor Tests (e)	P=0.068N	P=0.110N	P=0.121N
Cochran-Armitage Trend Test (e)	P=0.060N		
Fisher Exact Test (e)		P=0.144N	P=0.086N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	15/50 (30%)	10/50 (20%)	7/50 (14%)
Adjusted Rates (c)	33.1%	21.5%	17.5%
Terminal Rates (d)	12/42 (29%)	5/41 (12%)	5/38 (13%)
Week of First Observation	74	80	98
Life Table Tests (e)	P=0.069N	P=0.218N	P=0.087N
Incidental Tumor Tests (e)	P=0.075N	P=0.144N	P=0.189N
Cochran-Armitage Trend Test (e)	P=0.034N		
Fisher Exact Test (e)		P=0.178N	P=0.045N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	15/50 (30%)	11/50 (22%)	7/50 (14%)
Adjusted Rates (c)	33.1%	23.2%	17.5%
Terminal Rates (d)	12/42 (29%)	5/41 (12%)	5/38 (13%)
Week of First Observation	74	80	98
Life Table Tests (e)	P=0.074N	P=0.291N	P=0.087N
Incidental Tumor Tests (e)	P=0.064N	P=0.160N	P=0.189N
Cochran-Armitage Trend Test (e)	P=0.035N		
Fisher Exact Test (e)		P=0.247N	P=0.045N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (c)	2.4%	2.4%	10.1%
Terminal Rates (d)	1/42 (2%)	1/41 (2%)	3/38 (8%)
Week of First Observation	104	104	87
Life Table Tests (e)	P=0.085	P=0.756	P=0.152
Incidental Tumor Tests (e)	P=0.110	P=0.756	P=0.232
Cochran-Armitage Trend Test (e)	P=0.102		
Fisher Exact Test (e)		P=0.753N	P=0.181

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Control	6,300 ppm	12,500 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (c)	7.1%	2.4%	0.0%
Terminal Rates (d)	3/42 (7%)	1/41 (2%)	0/38 (0%)
Week of First Observation	104	104	
Life Table Tests (e)	P=0.070N	P=0.314N	P=0.139N
Incidental Tumor Tests (e)	P=0.070N	P=0.314N	P=0.139N
Cochran-Armitage Trend Test (e)	P=0.060N		
Fisher Exact Test (e)		P=0.309N	P=0.121N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (c)	9.5%	2.4%	0.0%
Terminal Rates (d)	4/42 (10%)	1/41 (2%)	0/38 (0%)
Week of First Observation	104	104	
Life Table Tests (e)	P=0.031N	P=0.187N	P=0.076N
Incidental Tumor Tests (e)	P=0.031N	P=0.187N	P=0.076N
Cochran-Armitage Trend Test (e)	P=0.026N		
Fisher Exact Test (e)		P=0.181N	P=0.059N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	9/49 (18%)	4/40 (10%)	2/50 (4%)
Adjusted Rates (c)	21.4%	12.1%	5.3%
Terminal Rates (d)	9/42 (21%)	4/33 (12%)	2/38 (5%)
Week of First Observation	104	104	104
Life Table Tests (e)	P=0.025N	P=0.228N	P=0.039N
Incidental Tumor Tests (e)	P=0.025N	P=0.228N	P=0.039N
Cochran-Armitage Trend Test (e)	P=0.016N		
Fisher Exact Test (e)		P=0.210N	P=0.024N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/49 (6%)	(b) 0/6 (0%)	0/50 (0%)
Adjusted Rates (c)	6.8%		0.0%
Terminal Rates (d)	2/42 (5%)		0/38 (0%)
Week of First Observation	95		
Life Table Test (e)			P=0.144N
Incidental Tumor Test (e)			P=0.189N
Fisher Exact Test (e)			P=0.118N
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (c)	6.9%	0.0%	5.1%
Terminal Rates (d)	2/42 (5%)	0/41 (0%)	1/38 (3%)
Week of First Observation	99		98
Life Table Tests (e)	P=0.429N	P=0.130N	P=0.550N
Incidental Tumor Tests (e)	P=0.576N	P=0.205N	P=0.684
Cochran-Armitage Trend Test (e)	P=0.388N		
Fisher Exact Test (e)		P=0.121N	P=0.500N
Mammary Gland: Adenocarcinoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (c)	6.9%	2.4%	5.1%
Terminal Rates (d)	2/42 (5%)	1/41 (2%)	1/38 (3%)
Week of First Observation	99	104	98
Life Table Tests (e)	P=0.443N	P=0.320N	P=0.550N
Incidental Tumor Tests (e)	P=0.577N	P=0.437N	P=0.684
Cochran-Armitage Trend Test (e)	P=0.399N		
Fisher Exact Test (e)		P=0.309N	P=0.500N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Control	6,300 ppm	12,500 ppm
All Sites: Benign Tumors			
Overall Rates (a)	19/50 (38%)	7/50 (14%)	13/50 (26%)
Adjusted Rates (c)	44.1%	17.1%	33.3%
Terminal Rates (d)	18/42 (43%)	7/41 (17%)	12/38 (32%)
Week of First Observation	95	104	100
Life Table Tests (e)	P=0.162N	P=0.007N	P=0.231N
Incidental Tumor Tests (e)	P=0.202N	P=0.009N	P=0.279N
Cochran-Armitage Trend Test (e)	P=0.103N		
Fisher Exact Test (e)		P=0.006N	P=0.142N
All Sites: Malignant Tumors			
Overall Rates (a)	21/50 (42%)	16/50 (32%)	12/50 (24%)
Adjusted Rates (c)	43.7%	33.3%	29.2%
Terminal Rates (d)	15/42 (36%)	9/41 (22%)	9/38 (24%)
Week of First Observation	74	80	87
Life Table Tests (e)	P=0.095N	P=0.268N	P=0.110N
Incidental Tumor Tests (e)	P=0.073N	P=0.198N	P=0.204N
Cochran-Armitage Trend Test (e)	P=0.035N		
Fisher Exact Test (e)		P=0.204N	P=0.044N
All Sites: All Tumors			
Overall Rates (a)	33/50 (66%)	22/50 (44%)	21/50 (42%)
Adjusted Rates (c)	68.7%	44.9%	51.2%
Terminal Rates (d)	27/42 (64%)	14/41 (34%)	18/38 (47%)
Week of First Observation	74	22	87
Life Table Tests (e)	P=0.056N	P=0.060N	P=0.064N
Incidental Tumor Tests (e)	P=0.026N	P=0.014N	P=0.115N
Cochran-Armitage Trend Test (e)	P=0.011N		
Fisher Exact Test (e)		P=0.022N	P=0.014N

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

TABLE D4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	6/50	3/50	9/50
Phenylephrine hydrochloride	3/49	0/49	3/49
Oxytetracycline hydrochloride	5/50	2/50	6/50
TOTAL	14/149 (9.4%)	5/149 (3.4%)	18/149 (12.1%)
SD (b)	2.99%	3.06%	5.94%
Range (c)			
High	6/50	3/50	9/50
Low	3/49	0/49	3/49
Overall Historical Incidence			
TOTAL	97/2,033 (4.8%)	(d) 83/2,033 (4.1%)	177/2,033 (8.7%)
SD (b)	4.14%	2.61%	4.75%
Range (c)			
High	9/49	5/50	10/49
Low	0/50	0/50	0/50

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

TABLE D4b. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE $B6C3F_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma (b)	Carcinoma (c)	Adenoma or Carcinoma (b,c)
Historical Incidence at Physiological Research Laboratories			
Ephedrine sulfate	8/48	2/48	10/48
Phenylephrine hydrochloride	0/48	0/48	0/48
Oxytetracycline hydrochloride	13/50	3/50	16/50
TOTAL	21/146 (14.4%)	5/146 (3.4%)	26/146 (17.8%)
SD (d)	13.17%	3.07%	16.24%
Range (e)			
High	13/50	3/50	16/50
Low	0/48	0/48	0/48
Overall Historical Incidence			
TOTAL	192/1,764 (10.9%)	12/1,764 (0.7%)	204/1,764 (11.6%)
SD (d)	9.47%	1.44%	9.67%
Range (e)			
High	12/40	3/50	16/50
Low	0/48	0/49	0/48

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes adenomas, NOS, and chromophobe adenomas
(c) Includes carcinomas, NOS, adenocarcinomas, NOS, and chromophobe carcinomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Untreated Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ectopia			2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, suppurative	1 (2%)		
*Nasal mucosa	(50)	(50)	(50)
Eosinophilic cyto change	36 (72%)		18 (36%)
Hyperplasia, NOS			1 (2%)
#Lung	(49)	(15)	(50)
Congestion, NOS	5 (10%)	1 (7%)	8 (16%)
Edema, NOS			3 (6%)
Edema, interstitial			1 (2%)
Hemorrhage	2 (4%)		7 (14%)
Inflammation, chronic focal	7 (14%)		3 (6%)
Perivascular cuffing	3 (6%)	1 (7%)	5 (10%)
Alveolar macrophages	2 (4%)	1 (7%)	1 (2%)
Hyperplasia, adenomatous	1 (2%)	1 (7%)	
#Lung/alveoli	(49)	(15)	(50)
Hemorrhage			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	4 (8%)		2 (4%)
*Mammary gland	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Bone marrow	(50)	(7)	(50)
Congestion, NOS	1 (2%)		
Atrophy, NOS			1 (2%)
Hyperplasia, NOS	2 (4%)	1 (14%)	
Hyperplasia, stromal		1 (14%)	
Hyperplasia, hematopoietic			1 (2%)
Hyperplasia, granulocytic	7 (14%)		3 (6%)
#Spleen	(50)	(49)	(49)
Necrosis, NOS			1 (2%)
Amyloidosis		1 (2%)	
Angiectasis	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, reticulum cell	3 (6%)	4 (8%)	
Hyperplasia, lymphoid	23 (46%)	26 (53%)	25 (51%)
Hematopoiesis	3 (6%)	1 (2%)	4 (8%)
#Mandibular lymph node	(49)	(10)	(50)
Hyperplasia, lymphoid	5 (10%)		3 (6%)
#Mesenteric lymph node	(49)	(10)	(50)
Necrosis, NOS			1 (2%)
Angiectasis		2 (20%)	
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Renal lymph node	(49)	(10)	(50)
Inflammation, acute	1 (2%)		
*Bone	(50)	(50)	(50)
Myelofibrosis	26 (52%)		13 (26%)
#Lung	(49)	(15)	(50)
Hyperplasia, lymphoid	1 (2%)		2 (4%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Salivary gland	(50)	(4)	(49)
Hyperplasia, lymphoid	2 (4%)		4(8%)
#Liver	(50)	(50)	(50)
Hyperplasia, lymphoid	5 (10%)	5 (10%)	6 (12%)
Hematopoiesis	1 (2%)		
*Gallbladder	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
#Stomach	(49)	(49)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Cecum	(50)	(6)	(48)
Hyperplasia, lymphoid			1 (2%)
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	7 (14%)	2 (4%)	12 (24%)
#Urinary bladder	(48)	(5)	(47)
Hyperplasia, lymphoid	4 (8%)		6 (13%)
#Thyroid	(49)	(5)	(49)
Hyperplasia, lymphoid		1 (20%)	
#Thymus	(43)	(4)	(41)
Cyst, NOS	5 (12%)	1 (25%)	1 (2%)
Multiple cysts	1 (2%)		1 (2%)
Necrosis, NOS			3 (7%)
Atrophy, NOS		1 (25%)	
Angiectasis	1 (2%)		
Hyperplasia, lymphoid	9 (21%)		10 (24%)
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Perivasculitis			1 (2%)
*Mammary gland	(50)	(50)	(50)
Perivasculitis			1 (2%)
#Mesenteric lymph node	(49)	(10)	(50)
Periarteritis			1 (2%)
#Heart	(50)	(7)	(50)
Inflammation, granulomatous			1 (2%)
Periarteritis			1 (2%)
#Myocardium	(50)	(7)	(50)
Necrosis, focal		1 (14%)	1 (2%)
*Artery	(50)	(50)	(50)
Perivasculitis			1 (2%)
#Salivary gland	(50)	(4)	(49)
Perivasculitis			1 (2%)
#Liver	(50)	(50)	(50)
Periarteritis			1 (2%)
#Pancreas	(49)	(8)	(47)
Periarteritis			1 (2%)
Perivasculitis	1 (2%)		
#Stomach	(49)	(49)	(49)
Periarteritis			1 (2%)
*Mesentery	(50)	(50)	(50)
Periarteritis			1 (2%)
#Jejunum	(47)	(7)	(47)
Periarteritis			1 (2%)
#Colon	(50)	(6)	(48)
Periarteritis			1 (2%)
*Rectum	(50)	(50)	(50)
Perivasculitis			1 (2%)
#Kidney	(50)	(50)	(50)
Perivasculitis			1 (2%)
#Urinary bladder	(48)	(5)	(47)
Periarteritis			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Uterus	(50)	(49)	(49)
Lymphangiectasis	1 (2%)		
#Uterine serosa	(50)	(49)	(49)
Lymphangiectasis	1 (2%)		
#Ovary	(47)	(15)	(47)
Thrombosis, NOS	2 (4%)		
#Thyroid	(49)	(5)	(49)
Periarteritis			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Dysplasia, NOS			1 (2%)
#Liver	(50)	(50)	(50)
Multiple cysts			1 (2%)
Congestion, NOS			1 (2%)
Hemorrhage			2 (4%)
Necrosis, NOS			1 (2%)
Necrosis, focal	7 (14%)	12 (24%)	14 (28%)
Necrosis, coagulative		1 (2%)	
Metamorphosis, fatty	2 (4%)	1 (2%)	1 (2%)
Pigmentation, NOS	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change	3 (6%)	2 (4%)	
Cytologic alteration, NOS		1 (2%)	
Angiectasis		2 (4%)	1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, coagulative	1 (2%)		
*Gallbladder	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Multiple cysts	1 (2%)		
#Pancreas	(49)	(8)	(47)
Cyst, NOS	1 (2%)	1 (13%)	
Multiple cysts		2 (25%)	
Atrophy, NOS	1 (2%)	1 (13%)	
#Pancreatic acinus	(49)	(8)	(47)
Cytoplasmic vacuolization			1 (2%)
Atrophy, NOS	1 (2%)		
#Glandular stomach	(49)	(49)	(49)
Cyst, NOS	3 (6%)	1 (2%)	2 (4%)
Multiple cysts	5 (10%)	13 (27%)	7 (14%)
Inflammation, acute/chronic	3 (6%)	11 (22%)	7 (14%)
Inflammation, chronic	8 (16%)	9 (18%)	4 (8%)
Inflammation, chronic focal	1 (2%)		
Degeneration, hydropic			1 (2%)
Calcification, NOS	4 (8%)		1 (2%)
Crystals, NOS		4 (8%)	1 (2%)
Eosinophilic cyto change	11 (22%)	24 (49%)	16 (33%)
Hyperplasia, epithelial	3 (6%)	22 (45%)	6 (12%)
#Forestomach	(49)	(49)	(49)
Ulcer, NOS			1 (2%)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, epithelial			1 (2%)
Hyperkeratosis			1 (2%)
Acanthosis		1 (2%)	
#Duodenum	(47)	(7)	(47)
Diverticulosis			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS	2 (4%)	3 (6%)	3 (6%)
Multiple cysts		7 (14%)	7 (14%)
Congestion, NOS	1 (2%)		3 (6%)
Glomerulonephritis, acute	1 (2%)		
Nephropathy	3 (6%)	21 (42%)	32 (64%)
Infarct, healed	4 (8%)		4 (8%)
Calcification, NOS	4 (8%)	1 (2%)	
Nuclear enlargement		46 (92%)	44 (88%)
Hyperplasia, tubular cell	1 (2%)		
Metaplasia, osseous	1 (2%)		1 (2%)
#Renal papilla	(50)	(50)	(50)
Calcification, NOS	1 (2%)		
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis	1 (2%)		
#Convoluted tubules	(50)	(50)	(50)
Degeneration, hyaline		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary	(49)	(40)	(50)
Hemorrhage			1 (2%)
#Anterior pituitary	(49)	(40)	(50)
Cyst, NOS	1 (2%)	1 (3%)	3 (6%)
Hyperplasia, focal	11 (22%)	2 (5%)	9 (18%)
Angiectasis		3 (8%)	
#Adrenal/capsule	(49)	(6)	(50)
Hyperplasia, stromal	46 (94%)	5 (83%)	47 (94%)
#Adrenal cortex	(49)	(6)	(50)
Ectopia			1 (2%)
Degeneration, lipoid	1 (2%)		
Focal cellular change	1 (2%)		
Hypertrophy, focal	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Adrenal medulla	(49)	(6)	(50)
Hyperplasia, focal	2 (4%)		1 (2%)
#Thyroid	(49)	(5)	(49)
Multiple cysts			1 (2%)
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic			3 (6%)
Inflammation, chronic focal			1 (2%)
Inflammation, granulomatous	2 (4%)		1 (2%)
Inflammation with fibrosis			1 (2%)
Hyperplasia, papillary	1 (2%)		
Hyperplasia, follicular cell			1 (2%)
#Thyroid follicle	(49)	(5)	(49)
Dilatation, NOS	1 (2%)		
Multiple cysts		1 (20%)	
Inflammation, acute/chronic			1 (2%)
Calcification, NOS			1 (2%)
Hyperplasia, papillary	1 (2%)		1 (2%)
#Pancreatic islets	(49)	(8)	(47)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	3 (6%)		5 (10%)
Edema, NOS			1 (2%)
Hyperplasia, NOS			1 (2%)
*Clitoral gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Uterus	(50)	(49)	(49)
Dilatation, NOS	5 (10%)	16 (33%)	9 (18%)
Pyometra		1 (2%)	
Angiectasis			3 (6%)
#Uterus/endometrium	(50)	(49)	(49)
Multiple cysts		1 (2%)	2 (4%)
Hematoma, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
Hyperplasia, cystic	44 (88%)	21 (43%)	20 (41%)
Angiectasis	5 (10%)	1 (2%)	2 (4%)
#Fallopian tube	(50)	(49)	(49)
Calcification, NOS	1 (2%)		
#Ovary	(47)	(15)	(47)
Cyst, NOS	15 (32%)	7 (47%)	3 (6%)
Multiple cysts	2 (4%)		
Hematoma, NOS		1 (7%)	
Hematoma, organized	1 (2%)		
Hemorrhagic cyst	4 (9%)		3 (6%)
Calcification, NOS	2 (4%)		
Angiectasis	2 (4%)	2 (13%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(49)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Third ventricle	(50)	(49)	(50)
Calcification, NOS	1 (2%)		
#Brain	(50)	(49)	(50)
Hemorrhage			1 (2%)
#Brain/thalamus	(50)	(49)	(50)
Calcification, NOS	33 (66%)	23 (47%)	21 (42%)
#Midbrain	(50)	(49)	(50)
Epidermal inclusion cyst		1 (2%)	
#Cerebellum	(50)	(49)	(50)
Perivascular cuffing			1 (2%)
*Spinal cord	(50)	(50)	(50)
Demyelinization			1 (2%)
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, suppurative	1 (2%)		
*Harderian gland	(50)	(50)	(50)
Pigmentation, NOS	1 (2%)		2 (4%)
MUSCULOSKELETAL SYSTEM			
*Maxilla	(50)	(50)	(50)
Hyperplasia, focal			1 (2%)
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Knee			
Dyschondroplasia	3		3

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE (Continued)

	Untreated Control	Low Dose	High Dose
ALL OTHER SYSTEMS (Continued)			
Adipose tissue			
Inflammation, granulomatous			1
Necrosis, fat	5	1	1
Omentum			
Inflammation, chronic	1		
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/histo perf	1		

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

APPENDIX E

GENETIC TOXICOLOGY OF

alpha-METHYLDOPA SESQUIHYDRATE

TABLE E1. MUTAGENICITY OF α-METHYLDOPA SESQUIHYDRATE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (μg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+10% S9 (hamster) Trial 1	+10% S9 (hamster) Trial 2	+10% S9 (rat) Trial 1	+10% S9 (rat) Trial 2
TA100	0	101 ± 5.5	103 ± 3.7	103 ± 7.3	96 ± 1.8	121 ± 8.8	118 ± 6.7
	33	--	104 ± 3.5	--	103 ± 3.0	--	123 ± 5.1
	100	110 ± 4.3	104 ± 7.3	93 ± 5.0	97 ± 2.1	122 ± 8.0	111 ± 3.5
	333	116 ± 1.8	100 ± 11.9	98 ± 3.0	101 ± 5.2	104 ± 8.2	122 ± 2.6
	1,000	117 ± 8.7	98 ± 2.3	111 ± 11.2	110 ± 1.5	110 ± 1.5	116 ± 6.2
	3,333	99 ± 8.9	96 ± 2.0	90 ± 5.2	95 ± 2.2	114 ± 1.8	110 ± 8.1
	10,000	5 ± 2.3	--	42 ± 3.5	--	29 ± 1.7	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	1,022 ± 17.5	1,157 ± 34.5	977 ± 32.2	1,532 ± 48.2	1,905 ± 66.4	996 ± 5.7
TA1535	0	30 ± 1.2	27 ± 3.6	18 ± 2.7	11 ± 4.4	16 ± 2.9	8 ± 2.3
	33	--	23 ± 0.6	--	10 ± 0.6	--	15 ± 0.7
	100	27 ± 0.9	26 ± 3.2	18 ± 0.3	9 ± 0.7	14 ± 2.6	10 ± 1.5
	333	32 ± 2.6	24 ± 4.0	19 ± 2.9	11 ± 0.7	19 ± 3.5	11 ± 1.0
	1,000	28 ± 4.5	27 ± 0.3	20 ± 6.8	10 ± 1.5	21 ± 1.8	13 ± 2.3
	3,333	10 ± 1.7	19 ± 2.6	12 ± 0.9	11 ± 2.3	13 ± 2.3	8 ± 1.5
	10,000	0 ± 0.0	--	2 ± 1.5	--	3 ± 1.5	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	842 ± 11.3	951 ± 31.7	64 ± 3.4	283 ± 0.9	77 ± 8.7	181 ± 10.7
TA98	0	24 ± 2.5	17 ± 2.9	33 ± 0.9	23 ± 0.6	34 ± 3.3	23 ± 0.3
	33	--	21 ± 1.5	--	24 ± 3.7	--	26 ± 3.1
	100	16 ± 1.7	18 ± 3.5	25 ± 1.2	24 ± 3.8	33 ± 3.2	29 ± 0.9
	333	23 ± 3.2	18 ± 0.3	30 ± 2.1	31 ± 1.0	33 ± 4.3	25 ± 0.3
	1,000	22 ± 0.6	16 ± 1.5	34 ± 8.0	23 ± 3.6	30 ± 2.2	24 ± 1.3
	3,333	26 ± 2.9	17 ± 2.0	37 ± 3.1	18 ± 4.7	27 ± 1.2	24 ± 4.4
	10,000	2 ± 0.3	--	26 ± 1.8	--	14 ± 3.6	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	1,515 ± 46.5	1,763 ± 35.4	846 ± 41.9	896 ±103.1	1,334 ± 40.4	438 ± 3.6

	−S9 Trial 1	−S9 Trial 2	+ S9 (hamster) 10%	+ S9 (hamster) 10%	+ S9 (hamster) 30%	+ S9 (rat) 10%	+ S9 (rat) 10%	+ S9 (rat) 30%
TA97								
0	100 ± 9.4	93 ± 4.7	138 ± 4.6	152 ± 2.8	168 ± 8.7	87 ± 13.9	157 ± 17.3	216 ± 15.2
33	85 ± 4.3	90 ± 1.5	--	150 ± 4.1	145 ± 9.8	--	163 ± 7.5	225 ± 11.5
100	94 ± 6.4	87 ± 1.9	116 ± 6.0	154 ± 5.8	155 ± 6.5	85 ± 11.1	141 ± 6.0	204 ± 12.1
333	108 ± 5.7	97 ± 5.8	134 ± 8.4	153 ± 1.3	169 ± 5.6	114 ± 8.3	159 ± 3.5	216 ± 5.4
1,000	98 ± 2.7	88 ± 5.6	118 ± 3.5	127 ± 4.6	159 ± 2.3	120 ± 4.6	148 ± 1.8	201 ± 4.6
3,333	92 ± 2.0	93 ± 2.8	116 ± 7.8	123 ± 14.8	140 ± 8.4	117 ± 4.7	153 ± 4.6	171 ± 3.4
10,000	--	--	58 ± 7.8	--	--	34 ± 11.9	--	--
Trial summary	Negative	Negative	Negative	Negative	Negative	Equivocal	Negative	Negative
Positive control (c)	1,408 ± 39	1,041 ± 89	408 ± 18	1,074 ± 27	1,188 ± 38	617 ± 13	1,455 ± 10	1,000 ± 63

(a) Study performed at Microbiological Associates. The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 μg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA97

TABLE E2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY α-METHYLDOPA SESQUIHYDRATE (a)

Compound	Dose (μg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)--Summary: Negative								
Dimethyl sulfoxide		50	1,022	423	0.41	8.5	25.5	--
α-Methyldopa sesquihydrate	3.5	50	1,039	425	0.41	8.5	25.5	100.0
	11.7	50	1,042	482	0.46	9.6	25.5	112.9
	35	50	1,034	459	0.44	9.2	25.5	108.2
	116.7	0	--	--	--	--	25.5	--
Mitomycin C	0.001	50	1,039	537	0.52	10.7	25.5	125.9
	0.01	5	105	230	2.19	46.0	25.5	541.2
+S9 (d)--Summary: Negative								
Dimethyl sulfoxide		50	1,042	421	0.40	8.4	25.5	--
α-Methyldopa sesquihydrate	350	50	1,047	394	0.38	7.9	25.5	94.0
	1,200	50	1,044	417	0.40	8.3	25.5	98.8
	3,500	50	1,047	434	0.41	8.7	25.5	103.6
Cyclophosphamide	0.4	50	1,042	664	0.64	13.3	25.5	158.3
	2	5	104	184	1.77	36.8	25.5	438.1

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

TABLE E3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY α-METHYLDOPA SESQUIHYDRATE (a)

−S9 (b)					+S9 (c)				
Dose (μg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time 10.5 h					Harvest time 12.5 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	3	0.03	3		100	4	0.04	4
α-Methyldopa sesquihydrate					α-Methyldopa sesquihydrate				
49.6	100	2	0.02	2	2,500	100	1	0.01	1
75.2	100	6	0.06	5	3,000	100	3	0.03	2
99	100	2	0.02	2	3,500	100	1	0.01	1
300	0								
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.150	100	16	0.16	12	7.5	100	10	0.10	9
0.500	25	15	0.60	40	37.5	25	19	0.76	44

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

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

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

II. Results

Results are presented in Table F1.

TABLE F1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF α-METHYLDOPA SESQUIHYDRATE (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	10/10	Sendai
12	10/10	Sendai
18	9/9	Sendai
24	7/10	RCV
	6/10	Sendai
MICE		
6	10/10	Sendai
12	10/10	Sendai
18	8/9	Sendai
24	5/10	Sendai

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX G

FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF *alpha*-METHYLDOPA SESQUIHYDRATE

TABLE G1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control		Low Dose				High Dose			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
6	16	290	14	258	0.9	168	13	243	0.8	337
10	17	330	16	301	0.9	165	15	290	0.9	326
15	16	371	16	346	1.0	143	15	336	0.9	281
18	15	386	14	355	0.9	122	15	344	1.0	275
24	16	403	15	366	0.9	127	16	362	1.0	278
28	17	414	13	379	0.8	106	14	373	0.8	236
31	12	420	10	375	0.8	83	11	372	0.9	186
36	14	420	13	373	0.9	108	13	371	0.9	221
40	15	429	14	381	0.9	114	15	379	1.0	249
44	15	432	16	387	1.1	128	15	381	1.0	248
48	15	440	14	390	0.9	111	15	384	1.0	246
53	15	444	15	399	1.0	117	15	394	1.0	240
57	15	446	14	407	0.9	107	14	396	0.9	223
62	14	451	14	410	1.0	106	14	401	1.0	220
66	14	450	14	412	1.0	105	13	400	0.9	205
70	14	451	13	405	0.9	100	13	404	0.9	203
74	13	442	13	408	1.0	99	13	405	1.0	202
79	13	440	11	405	0.8	84	12	409	0.9	185
83	13	435	12	401	0.9	93	12	396	0.9	191
87	13	423	13	403	1.0	100	12	396	0.9	191
92	13	427	12	402	0.9	93	11	388	0.8	179
96	13	423	11	396	0.8	86	11	388	0.8	179
101	14	424	12	388	0.9	96	12	377	0.9	201
Mean	14.4	417	13.4	380	0.9	111	13.4	373	0.9	230
SD (d)	1.4		1.6		0.1	23	1.5		0.1	45
CV(e)	9.7		11.9		11.1	20.7	11.2		11.1	19.6

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of α-methyldopa sesquihydrate consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE G2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control		Low Dose				High Dose			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
6	10	180	9	168	0.9	166	8	161	0.8	313
10	11	193	8	182	0.7	136	8	174	0.7	290
15	11	219	10	206	0.9	150	12	194	1.1	390
18	10	221	9	213	0.9	131	9	202	0.9	281
24	11	224	9	218	0.8	128	10	213	0.9	296
28	9	234	11	226	1.2	151	10	224	1.1	281
31	10	239	7	226	0.7	96	8	233	0.8	216
36	11	239	10	234	0.9	132	9	236	0.8	240
40	10	244	9	234	0.9	119	10	247	1.0	255
44	11	253	10	240	0.9	129	9	252	0.8	225
48	11	262	9	244	0.8	114	9	259	0.8	219
53	11	278	10	259	0.9	120	10	267	0.9	236
57	11	287	10	263	0.9	118	9	271	0.8	209
62	12	301	10	272	0.8	114	10	279	0.8	226
66	11	307	10	274	0.9	113	10	282	0.9	223
70	11	316	9	278	0.8	100	9	286	0.8	198
74	11	315	10	281	0.9	110	10	291	0.9	216
79	11	331	10	291	0.9	107	9	295	0.8	192
83	11	319	10	290	0.9	107	9	292	0.8	194
87	12	329	10	295	0.8	105	11	301	0.9	230
92	11	332	10	296	0.9	105	10	307	0.9	205
96	11	331	11	299	1.0	114	10	308	0.9	205
101	11	340	11	304	1.0	112	10	308	0.9	205
Mean	10.8	274	9.7	252	0.9	121	9.5	256	0.9	241
SD (d)	0.7		0.9		0.1	18	0.9		0.1	48
CV (e)	6.5		9.3		11.1	14.9	9.5		11.1	19.9

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of α-methyldopa sesquihydrate consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE G3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control		Low Dose				High Dose			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
4	4	26.2	5	24.6	1.3	1,280	5	23.4	1.3	2,671
8	4	28.4	5	27.0	1.3	1,167	6	25.6	1.5	2,930
13	6	31.6	6	30.6	1.0	1,235	4	28.7	0.7	1,742
16	5	32.3	5	31.5	1.0	1,000	4	30.0	0.8	1,667
21	6	33.0	6	32.0	1.0	1,181	5	30.3	0.8	2,063
25	6	34.3	5	32.7	0.8	963	5	31.1	0.8	2,010
30	5	34.9	4	33.9	0.8	743	4	32.2	0.8	1,553
32-33	5	36.9	4	33.7	0.8	748	5	32.4	1.0	1,929
38	4	36.6	5	35.2	1.3	895	5	34.9	1.3	1,791
43	5	37.8	5	36.1	1.0	873	5	34.5	1.0	1,812
46	5	38.7	5	36.1	1.0	873	5	34.4	1.0	1,817
51	4	38.4	5	37.3	1.3	845	5	35.7	1.3	1,751
55	4	39.3	5	37.9	1.3	831	5	36.2	1.3	1,727
59	5	40.4	5	37.8	1.0	833	5	36.9	1.0	1,694
64	4	41.6	5	38.8	1.3	812	5	36.9	1.3	1,694
68	5	42.2	5	39.6	1.0	795	5	36.8	1.0	1,698
72	3	42.8	5	39.1	1.7	806	5	35.9	1.7	1,741
77	4	43.2	5	40.1	1.3	786	4	38.1	1.0	1,312
81	4	43.3	4	39.7	1.0	635	4	38.0	1.0	1,316
85	5	44.3	5	41.7	1.0	755	5	38.7	1.0	1,615
90	4	44.5	5	40.6	1.3	776	5	39.1	1.3	1,598
94	5	43.0	5	39.8	1.0	791	5	38.4	1.0	1,628
99	4	43.3	5	39.8	1.3	791	5	38.3	1.3	1,632
Mean	4.6	38.1	5.0	35.9	1.1	888	4.8	34.2	1.1	1,800
SD (d)	0.8		0.5		0.2	172	0.5		0.2	363
CV (e)	17.4		10.0		18.2	19.4	10.4		18.2	20.2

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of α-methyldopa sesquihydrate consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE G4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF α-METHYLDOPA SESQUIHYDRATE

	Control		Low Dose				High Dose			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
4	3	20.6	3	18.6	1.0	1,016	4	19.0	1.3	2,632
8	3	23.4	4	22.6	1.3	1,115	4	22.3	1.3	2,242
13	3	24.3	4	23.9	1.3	1,054	4	23.6	1.3	2,119
16	3	26.2	4	25.0	1.3	1,008	4	24.7	1.3	2,024
21	4	26.7	4	26.1	1.0	966	4	25.3	1.0	1,976
25	4	28.2	4	26.5	1.0	951	4	24.8	1.0	2,016
30	4	28.9	4	26.6	1.0	947	4	26.0	1.0	1,923
33	4	29.6	4	26.8	1.0	940	5	26.1	1.3	2,395
38	3	31.8	3	28.1	1.0	673	3	27.6	1.0	1,359
43	4	32.7	4	29.1	1.0	866	4	28.2	1.0	1,773
46	4	33.7	4	29.3	1.0	860	4	28.2	1.0	1,773
51	4	35.1	4	30.6	1.0	824	4	29.7	1.0	1,684
55	3	35.0	4	30.9	1.3	816	4	29.2	1.3	1,712
59	4	37.2	4	32.4	1.0	778	4	29.9	1.0	1,672
64	4	39.7	4	32.9	1.0	766	4	32.0	1.0	1,563
68	4	40.3	4	33.3	1.0	757	4	31.4	1.0	1,592
72	4	40.7	4	33.2	1.0	759	4	32.0	1.0	1,563
77	3	40.6	4	34.4	1.3	733	4	33.3	1.3	1,502
81	4	42.4	4	34.9	1.0	722	4	33.3	1.0	1,502
85	4	43.0	3	36.6	0.8	516	3	34.0	0.8	1,103
90	3	43.0	4	37.3	1.3	676	4	35.0	1.3	1,429
94	4	43.4	4	36.5	1.0	690	4	35.2	1.0	1,420
99	4	43.8	4	37.1	1.0	679	4	35.3	1.0	1,416
Mean	3.7	34.4	3.9	30.1	1.1	831	4.0	29.0	1.1	1,756
SD (d)	0.5		0.3		0.2	149	0.4		0.2	365
CV (e)	13.5		7.7		18.2	17.9	10.0		18.2	20.8

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of α-methyldopa sesquihydrate consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX H

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

Meal Diet: June 1981 to July 1983

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

TABLE H1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE H2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE H3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.97 ± 1.16	21.7-26.3	27
Crude fat (percent by weight)	5.0 ± 0.46	4.2-6.0	27
Crude fiber (percent by weight)	3.38 ± 0.36	2.4-4.2	27
Ash (percent by weight)	6.56 ± 0.27	5.97-7.11	27
Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	12,163 ± 3,045	7,800-22,000	27
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm) (b)	18.2 ± 3.4	12-26	26
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.24 ± 0.10	1.10-1.45	27
Phosphorus (percent)	0.97 ± 0.05	0.84-1.10	27
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

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

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

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.48 ± 0.13	0.21-0.74	27
Cadmium (ppm)	<0.01	<0.01-0.01	27
Lead (ppm)	0.91 ± 0.75	0.27-2.93	27
Mercury (ppm) (a)	< 0.05		27
Selenium (ppm)	0.28 ± 0.06	0.16-0.40	27
Aflatoxins (ppb) (a,b)	<5	<5.0-<10.0	27
Nitrate nitrogen (ppm) (c)	9.97 ± 4.64	0.6-19.0	27
Nitrite nitrogen (ppm) (c)	1.99 ± 1.23	0.4-5.3	27
BHA (ppm) (d)	5.42 ± 4.94	<2.0-20.0	27
BHT (ppm) (d)	3.19 ± 2.52	<1.0-13.0	27
Aerobic plate count (CFU/g) (e,f)	110,956 ± 82,794	7,000-310,000	25
Aerobic plate count (CFU/g) (e,g)	133,848 ± 114,587	7,000-420,000	27
Coliform (MPN/g) (h)	931.1 ± 973.4	<3->2,400	27
E. coli (MPN/g) (h,i)	6.89 ± 7.46	<3-23	26
E. coli (MPN/g) (h,j)	12.15 ± 28.51	<3-150	27
Total nitrosamines (ppb) (k)	3.73 ± 3.26	0.9-12.9	27
N-Nitrosodimethylamine (ppb) (k)	2.93 ± 2.89	0.7-12.9	27
N-Nitrosopyrrolidine (ppb) (l)	1.24 ± 0.60	<0.9-3.2	24
Pesticides (ppm)			
α-BHC (a,m)	<0.01		27
β-BHC (a)	<0.02		27
γ-BHC-Lindane (a)	<0.01		27
δ-BHC (a)	<0.01		27
Heptachlor (a)	<0.01		27
Aldrin (a)	<0.01		27
Heptachlor epoxide (a)	<0.01		27
DDE (a)	<0.01		27
DDD (n)	<0.01	0.05 (7/14/81)	27
DDT (a)	<0.01		27
HCB (a)	<0.01		27
Mirex (a)	<0.01		27
Methoxychlor (o)	<0.05	0.13 (8/25/81); 0.6 (6/24/82)	27
Dieldrin (n)	<0.01	0.02 (7/27/82)	27
Endrin (a)	<0.01		27
Telodrin (a)	<0.01		27
Chlordane (a)	<0.05		27
Toxaphene (a)	<0.1		27
Estimated PCBs (a)	<0.2		27
Ronnel (a)	<0.01		27
Ethion (a)	<0.02		27
Trithion (a)	<0.05		27
Diazinon (a)	<0.1		27
Methyl parathion (a)	<0.02		27
Ethyl parathion (a)	<0.02		27
Malathion (p)	0.10 ± 0.07	<0.05-0.34	27
Endosulfan I (a,q)	<0.01		21
Endosulfan II (a,q)	<0.01		21
Endosulfan sulfate (a,q)	<0.03		21

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

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Sources of contamination: alfalfa, grains, and fish meal
(d) Sources of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) Mean, standard deviation, and range exclude one very high value of 420,000 obtained for the batches produced on 3/23/83 and 7/12/83.
(g) Mean, standard deviation, and range include the very high value given in footnote (f).
(h) MPN = most probable number
(i) Mean, standard deviation, and range exclude one very high value of 150 obtained for the batch produced on 8/26/82.
(j) Mean, standard deviation, and range include the very high value given in footnote (i).
(k) All values were corrected for percent recovery.
(l) Values were not detected on 6/26/83, 6/22/83, or 7/12/83.
(m) BHC = hexachlorocyclohexane or benzene hexachloride
(n) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(o) Two observations were above the detection limit. The values and the dates they were obtained are listed under the range.
(p) Twelve batches contained more than 0.05 ppm.
(q) Six batches were not analyzed for endosulfan I, endosulfan II, or endosulfan sulfate.

APPENDIX I

REPRODUCTIVE TOXICOLOGY OF METHYLDOPA IN MALE F344/N RATS

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REPRODUCTIVE TOXICOLOGY OF METHYLDOPA IN MALE F344/N RATS

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SUMMARY

Methyldopa, a widely used antihypertensive drug, was administered to male Fischer 344/N rats by gavage 5 days/week for 65 days at dosages of 0, 50, 100, 200, or 400 mg/kg. Decreased body weight was seen in treated animals. After mating to untreated female Fischer 344/N rats on days 57—61, the male rats were necropsied (days 65—67) and reproductive toxicity was measured by sperm count, sperm motility, organ weights, hormone levels and histologic evaluation of the testis. Decreased fertility was seen in males dosed with 200 or 400 mg/kg methyldopa. Decreases were also seen in sperm count, sperm motility, apparent number of late spermatids, and plasma testosterone levels in males in the 200 and 400 mg/kg groups. This alteration of reproductive function in male rats was found to be reversible after a 13-week recovery period without dosing. The marked decrease in circulating testosterone levels following methyldopa treatment at 200 or 400 mg/kg may have contributed to the reproductive toxicity of this drug.

Key words: Methyldopa; Reproductive toxicity; Fischer 344/N rat

INTRODUCTION

Methyldopa (L-α-methyl-3,4-dihydroxyphenylalanine) is widely used for the treatment of hypertension and is one of the most frequently prescribed drugs in the United States [1,2]. Clinical studies have indicated that men receiving methyldopa treatment may experience sexual dysfunction [3,4,5].

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Studies in rodents have also indicated that methyldopa may cause reproductive toxicity in the male [6,7]. This study was designed to measure the reproductive toxicity of methyldopa in the male Fischer 344/N rats, and was initiated because a previous subchronic toxicity study in rats had shown lesions of the testis after methyldopa treatment [8].

MATERIALS AND METHODS

Animals

Male Fischer 344/N rats were obtained from Charles River Breeding Laboratories, Portage, Michigan and were 68 days of age on the first day of dosing (referred to as day 1). Female Fischer 344/N rats were also obtained from Charles River Breeding Laboratories and were 70 days of age when mated. Open formula NIH 31 laboratory feed and tap water were available ad libitum. Room temperature was maintained at 21.1 ± 1.1°C and the relative humidity at 50 ± 10%. A 12-h fluorescent light/dark cycle was provided. Animals were acclimated for 14 days prior to treatment or breeding. Male rats were housed 3 per cage except during the mating trial when the males were separated and housed with 2 female rats. Body weights and cage food consumption were recorded weekly.

Chemical

Methyldopa [L-α-methyl-3,4-dihydroxyphenylalanine (lot M122782) 99% pure] was supplied by Merck, Sharpe and Dohme Research Laboratories (Rahway, NJ). The chemical was administered orally to mimic human exposure; corn oil was used as a vehicle for daily gavaging because the chemical was insoluble in water at concentrations used in these experiments. Methyldopa suspensions were prepared fresh each week in Mazola® corn oil at concentrations of 0, 15.4, 30.8, 61.5 and 123.0 mg/ml. Animals were administered methyldopa mixtures by gavage at a volume of 3.25 ml/kg body weight to deliver methyldopa doses of 0, 50, 100, 200 or 400 mg/kg. The dose preparations were within ± 10% of the theoretical concentration as determined by absorbance of each solution using a Cary 219 Spectrophotometer set at 281 nm.

Treatment groups

Male Fischer 344/N rats were randomly assigned to 1 of 3 treatment regimens; (1) exposure to methyldopa for interim sacrifice on days 5, 12 and 19; (2) exposure to methyldopa for 65 days; and (3) exposure to methyldopa for 65 days followed by a recovery period (Table I). The dose levels were chosen to include human exposure levels (Table II).

Mating trials

On days 57—61 of treatment 21 male rats in each of the treatment groups 1—5 were mated to untreated virgin female Fischer 344/N rats (mating trial one). Fifteen animals in groups 1, 3, 4 and 5 were kept for an additional

TABLE I

METHYLDOPA STUDY DESIGN IN MALE FISCHER/344N RATS

Dose groups (mg/kg)	No. Animals		
	Interim Sacrifice[a]	Dosed for 65 days	Dosed for 65 days and then kept for a 17-week recovery period
1. 0	15[b]	21	15
2. 50		21	—
3. 100	15	21	15
4. 200	15	21	15
5. 400		21	15[b]

[a]Five animals sacrificed on day 5, 12 and 19 and testis removed for histopathologic analysis.
[b]One accidental death during first week of dosing.

17-week recovery period without dosing and 13 weeks into this recovery period were mated to untreated female rats (mating trial 2). After analysis of the second mating trial results, males were killed at 17 weeks for analysis of testicular and sperm function. The mating trials consisted of housing 2 female rats with each male rat for 4 days or until evidence of mating as determined by presence of sperm in vaginal lavage fluid, whichever came first. Females were asphyxiated with CO_2 15 days after the middle of the mating trial and their uteri examined for number of live fetuses, number of dead fetuses, and number of resorptions. Number of corpora lutea were similar in all dosed groups (an average of 10 per female).

TABLE II

COMPARISON OF METHYLDOPA DOSAGES IN MALE FISCHER 344/N RATS AND HUMANS

	Body wt (mg/kg)	Body surface area[a] (mg/m^2)
Rats	50	260
	100	520
	200	1040
	400	2080
Humans		
Estimated dose of 3 g/day for a 70-kg man[b]	42	1554

[a]Calculations based on estimates by Freireich et al. [22].
[b]Physicians Desk Ref. [23].

Evaluation of sperm count, motility and morphology

Sperm samples from the right caudal epididymis were collected at necropsy and were used for evaluation of sperm count, sperm motility, and sperm morphology. The right epididymis was separated from the testis and weighed; a small sample of sperm from the caudal epididymis was teased into egg yoke medium [9] at 37°C. A sample of this sperm preparation was placed on a slide, and the motility was calculated by counting all sperm in 20 fields (magnification of 40×) and categorizing them as either motile or nonmotile (any movement vs. no movement). Sperm motility was determined within 5 min after the animal was killed.

A 20—35-mg piece of the right caudal epididymis was minced and evenly distributed with a Pasteur pipet in phosphate-buffered saline. Approximately 1 ml of this sperm suspension was stained with 1% eosin Y for 45 min, and then one drop was spread on a microscope slide, air-dried, and coverslipped. These slides were used to evaluate sperm morphology at 400×. Sperm were classified as normal or abnormal according to the descriptions of Wyrobek and Bruce [10]. The remaining sperm were inactivated in a diluted glutaraldehyde solution, and counted using an Elzone cell counter (Renwar Technologies, Inc. Gaithersburg, MD).

Hormone levels

Testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were determined on plasma samples collected 1, 2 and 3 days after the 65-day dosing period. Radioimmunoassay kits for FSH and LH were provided by the National Hormone and Pituitary Program, NIAMDD, Bethesda, MD and included FSH standard (FSH-RP-1) and LH standard (LH-RP-1). Radioimmunoassay kits for testosterone were obtained from Diagnostic Products Corp., Los Angeles, CA and included a testosterone standard derived from human serum.

Pathology

After 5, 12, 19 and 65 days of dosing and after the recovery period of 17 weeks, male rats were asphyxiated by CO_2, necropsied and examined for gross abnormalities. Blood was collected by cardiac puncture after the 65-day dosing period. The left testis was fixed in 10% neutral buffered formalin, dehydrated in ethanol, embedded in glycol methacrylate, sectioned at 2 μm and stained with periodic acid-Schiff and hematoxylin [11]. Kidneys, ventral prostrate gland, testis, seminal vesicles and epididymis were weighed and organ to body weight ratios calculated.

A cross section of the left testis was examined in detail from 6 animals (randomly selected) in the control and 200 mg/kg groups after 65 days of dosing. The cross-section of seminiferous tubules with an axial ratio < 2 were categorized by stages of spermatogenesis [12]. At each of the following stages of spermatogenesis, nuclei of specific listed cell types were counted; stage III — Sertoli cells, intermediate spermatogonia, and pachytene spermatocytes; stage VI — Sertoli cells, B-spermatogonia, and pachytene spermato-

cytes; stage VIII — Sertoli cells, preleptotene and pachytene spermatocytes; and stage XII — Sertoli cells, zygotene and pachytene spermatocytes. Only definable nuclei were counted; indistinct forms of questionable identity were excluded. For each germ cell type a ratio was calculated comparing the number of germ cell nuclei to the number of Sertoli cell nuclei in each tubule. Statistics were performed on these ratios to determine if cell death had occurred at any specific stage of spermatocyte maturation. Stages IX–XI tubules were examined for increased numbers of step 19 spermatid heads embedded in the epithelium, and those tubules with more than 4 of these spermatid heads were considered abnormal.

Statistics

For the dichotomous response data (sperm-positive and pregnancy rates), the Cochran-Armitage test was used to assess the significance of dose-response trends, and Fischer's exact test was used to make pairwise comparison [13,14]. For the remaining variables multiple comparison procedures [15–17] were utilized to assess the effects of methyldopa. For those variables showing heterogeneity of variance, thus making parametric analyses questionable, non-parametric techniques [18] were employed to compare treated and control groups. A result was considered statistically significant if the *P*-value was less than 0.05.

RESULTS

Survival, clinical signs, organ and body weights

All animals survived the 65-day treatment period except for 2 animals (one in the control group and one at 400 mg/kg). During the 65-day dosing period, several animals in the high dose group were inactive or presented with crusting around the nose, but this observation was sporadic and symptoms cleared within 1–2 days. No other dose-related clinical signs were noted.

Body weights were depressed in all dosed groups, and after 65 days of dosing the organ/body weight ratios of the testis, epididymis, seminal vesicles, and prostate were lower in the 200 and 400 mg/kg groups compared to controls (Table III). The treated animals showed an absolute decreased food consumption, but when food consumption was measured as food consumed/kg body weight the consumption was similar among all groups of animals. During the recovery period, animals from all treatment groups rapidly gained weight, though the final body weight was still below that of the control group. After the recovery period, organ/body weight ratios were comparable among groups.

Plasma hormone levels

A dose-related reduction of plasma testosterone levels was seen 1 day after the 65-day dosing period, but 2 days after dosing the hormone levels

TABLE III

BODY WEIGHTS AND ORGAN/BODY WEIGHT RATIOS FOR MALE FISCHER 344/N RATS RECEIVING METHYLDOPA

Dose (mg/kg)	Body weight (g)[a]			Organ to body weight ratio[b]									
	Initial	End of dosing[d]	End of recovery period[e]	Testis		Epididymis		Seminal vesicles		Prostate		Kidney	
				A[f]	B[g]	A	B	A	B	A	B	A	B
0	183±1	325±4	421±6	4.4±0.1	3.8±0.1	1.5±0.1	1.2±0.1	3.4±0.1	3.4±0.1	1.3±0.1	1.6±0.04	6.0±0.1	6.7±0.1
50	181±1	310±4**	—[c]	4.5±0.1	—[c]	1.5±0.4	—[c]	3.5±0.1	—[c]	1.4±0.1	—[c]	6.9±0.1	—[c]
100	183±1	283±4**	401±4**	4.9±0.1	3.7±0.2	1.5±0.1	1.2±0.1	3.0±0.1	3.1±0.1	1.3±0.1	1.6±0.1	7.1±0.1	6.7±0.1
200	184±1	244±5**	387±5**	3.5±0.2**	3.8±0.2	0.9±0.1**	1.3±0.1	1.2±0.2**	3.4±0.1	0.8±0.1**	1.8±0.1	7.1±0.1	6.7±0.1
400	183±1	237±3**	388±5**	3.8±0.2**	4.1±0.1	0.9±0.1**	1.4±0.1*	1.3±0.1**	3.4±0.1	1.0±0.1**	1.7±0.1	7.0±0.1	7.0±0.1

[a]Mean ± S.E.M.
[b](Mean ± S.E.M.) × 10^3.
[c]No group in recovery phase.
[d]65 days.
[e]184 days (65 days dosing + 119 day recovery period).
[f]After 65 day dosing.
[g]After recovery period.
*Significantly different from control group, $P < 0.05$.
**Significantly different from control group, $P < 0.01$.

TABLE IV

PLASMA HORMONE LEVELS IN MALE FISCHER 344/N RATS AFTER EXPOSURE TO METHYLDOPA FOR 65 DAYS

Dose (mg/kg)	Hormone levels (ng/ml plasma mean ± S.E.M.)		
	Days after last exposure		
	1	2	3
Testosterone			
0	2.7 ± 1.0	1.6 ± 0.7	0.7 ± 0.4
50	2.0 ± 0.6	0.6 ± 0.3	1.4 ± 0.5
100	0.8 ± 0.3	0.6 ± 0.1	1.0 ± 0.2
200	0.2 ± 0.1*	2.6 ± 0.7	1.0 ± 0.4
400	0.2 ± 0.1*	2.8 ± 0.7	1.1 ± 0.4

*Significantly different from control group, $P < 0.05$.

had rebounded, and by 3 days after the dosing were at levels comparable to controls (Table IV). No significant dose-related effects were seen on FSH or LH levels.

Testicular abnormalities

Treatment-related testicular abnormalities were not seen after 5, 12, or 19 days of dosing or after the recovery period. Dose-related testicular toxicity was seen after 65 days of dosing, characterized by increased numbers of basally located spermatid heads in stage IX–XI tubules, decrease in numbers

TABLE V

TESTICULAR HISTOPATHOLOGIC ABNORMALITIES IN MALE FISCHER 344/N RATS RECEIVING METHYLDOPA FOR 65 DAYS

Dose (mg/kg)	Not affected	Mildly affected[a]	Affected[b]	Severely affected[c]
0	6/7	1/7	0	0
50	7/7	0	0	0
100	4/6	2/6	0	0
200	2/7	2/7	2/7	1/7
400	0	1/7	3/7	3/7

[a]At least 4 basally located heads of step 19 spermatids in more than 50% of tubules in stages IX, X, or XI.
[b]At least 6 basally located spermatid heads in more than 75% of stage IX, X, XI tubules.
[c]Decrease in number of late-stage spermatids in epithelium; apparent reduction in germ cell number in addition to the above mentioned effects.

of late stage spermatids, and reduction in germ cell number (Table V). Testes from control and 400 mg/kg groups are seen in Figs. 1—4. The treated group showed disorganization of seminiferous tubules and loss of late spermatids.

Epididymal sperm analysis

After 65 days of dosing, a decrease in percent motile sperm and sperm count was observed in the 200 and 400 mg/kg groups. The percent abnormal sperm increased with increasing dose of methyldopa (Table VI).

Mating trial

The results of the mating trial at 57—61 days paralleled the sperm analysis data and histopathologic findings in the testis, with reproductive toxicity seen at 200 and 400 mg/kg (Table VII). Male fertility index in the control group was 62% vs. a fertility index of 14% and 5% in the 200 and 400 mg/kg groups, respectively.

Recovery period

Analysis of the second mating trial which was performed after a 13-week recovery period, indicated that reproductive function of methyldopa treated male rats had returned to levels comparable to those in the concurrent

Fig. 1. Testicular section from animal receiving 0 mg/kg methyldopa for 65 days. Note well-ordered epithelia and presence of all cell types. *Tubule in stage V.

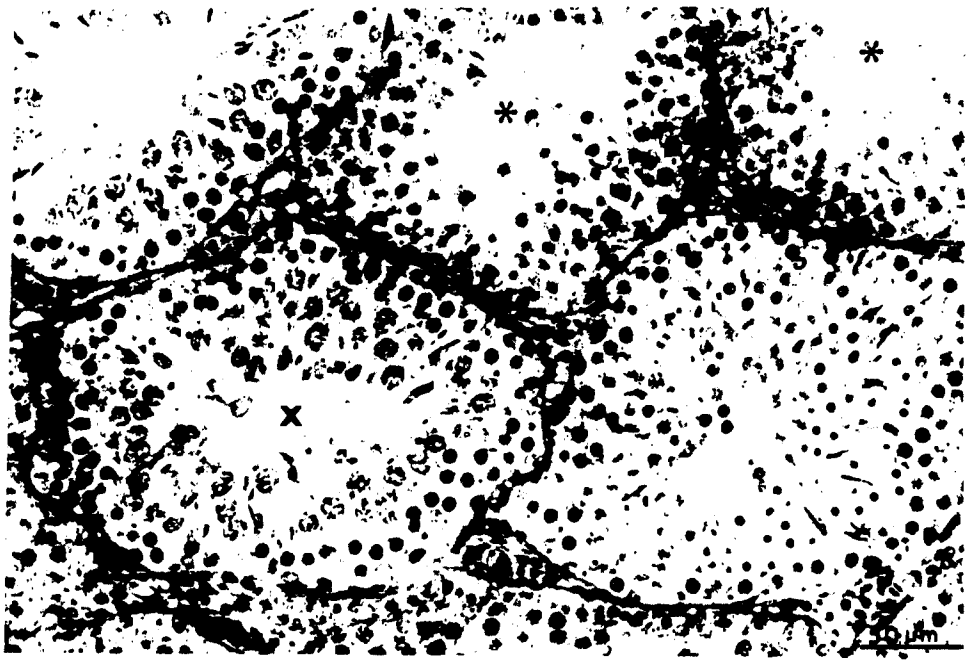
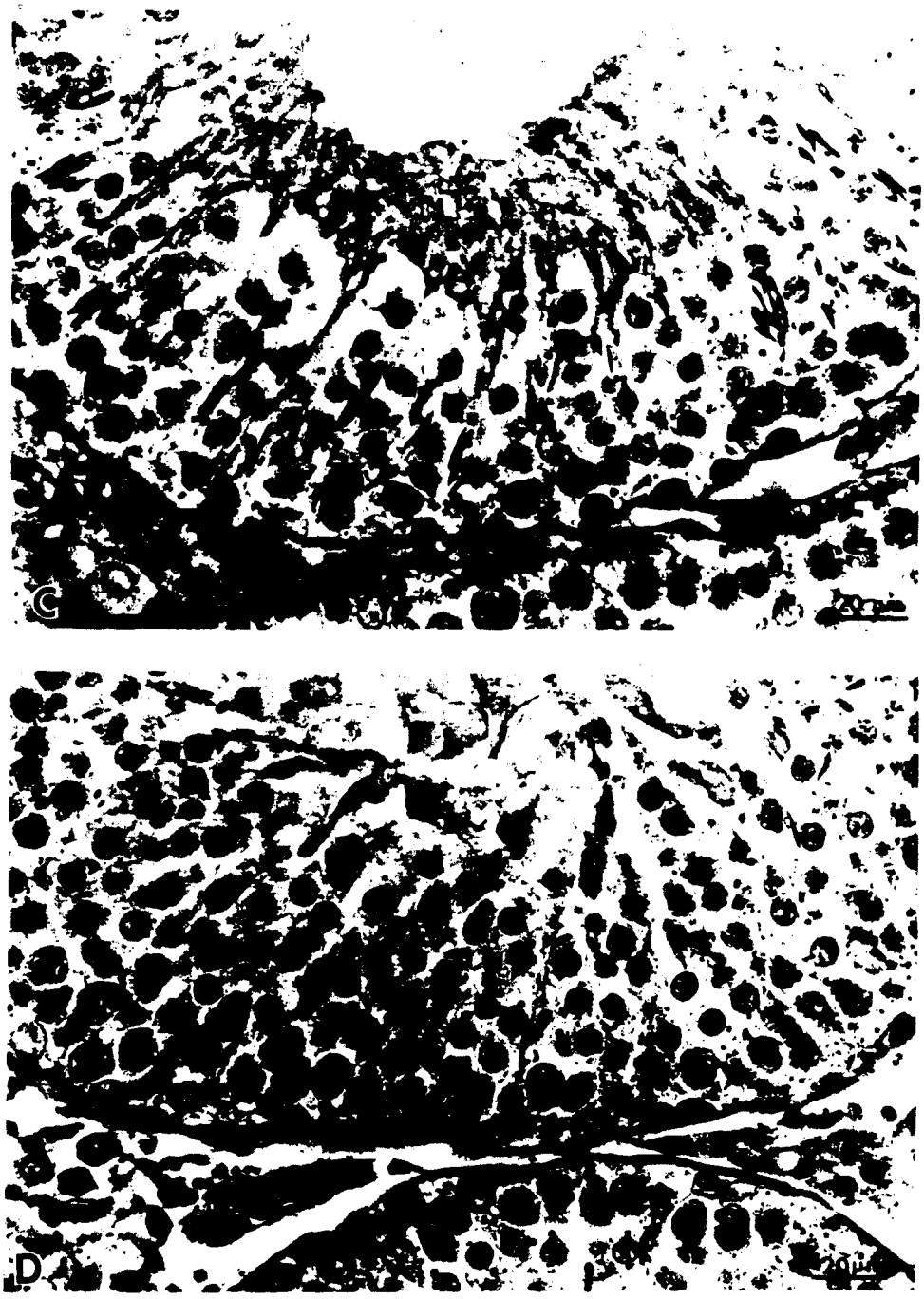


Fig. 2. Testicular section from animal receiving 400 mg/kg methyldopa for 65 days. Note disorganization and some cell loss in tubules marked x and *. *Stage V tubules.

control male rats (Table VII). Based on these results, recovery group animals were sacrificed (after a 17-week recovery period) and sperm and testis analyzed. Sperm motility, sperm count and percent abnormal sperm were comparable among groups, and no dose-related histopathologic abnormalities of the testis were found.

DISCUSSION

Methyldopa was toxic to the reproductive system of the male rat at 200 and 400 mg/kg, dosages that are similar to human dosages when compared on the basis of dose/body surface area (mg/m^2). Body weight gains were also depressed in rats at these dosages. Reproductive toxicity was measured by decreased fertility, decreased sperm count and percent motile sperm, increased percent abnormal sperm, and decreased reproductive and accessory sex organ weights. No treatment-related differences were seen in these measures of reproductive toxicity after the recovery period. In a previous subchronic study in the male Fischer 344/N rat, where methyldopa was administered in the feed at levels up to 5%, histopathologic abnormalities were not seen in other organ systems (e.g. liver, spleen, gastrointestinal tract, urinary bladder, kidney, etc.) [8].



Figs. 3 and 4. Stage III tubules from control (C) and 400 mg/kg methyldopa-treated (D) rats, respectively. Note loss of late spermatids from the treated tubule.

TABLE VI

ANALYSIS OF SPERM FROM MALE FISCHER 344/N RATS RECEIVING METHYLDOPA

Dose mg/kg	% motile sperm (mean ± S.E.M.)		Sperm count/mg caudal epididymis (mean ± S.E.M. x 10^3)		% sperm head abnormalities (mean ± S.E.M.)	
	A[a]	B[b]	A	B	A	B
0	75.1 ± 7.3	53.6 ± 9.7	695.2 ± 30.3	784.0 ± 20.8	0.3 ± 0.1	0.2 ± 0.1
50	72.9 ± 6.5	—[c]	700.6 ± 35.2	—[c]	0.5 ± 0.1	—[c]
100	77.7 ± 5.1	56.3 ± 9.6	729.4 ± 17.4	762.9 ± 48.5	0.6 ± 0.3	0.1 ± 0.1
200	12.2 ± 5.8**	72.8 ± 7.6	476.8 ± 126.3*	773.1 ± 40.2	35.5 ± 7.0**	0.1 ± 0.1
400	19.9 ± 7.9**	58.8 ± 8.0	325.8 ± 51.3**	820.1 ± 24.5	24.7 ± 6.1**	0.1 ± 0.1

[a] After 65 days of treatment.
[b] After 65 days of treatment + recovery period 17 weeks.
[c] No rats at this dose level in recovery group.
*Significantly different from control group, $P < 0.05$.
**Significantly different from control group, $P < 0.01$.

TABLE VII

MEASUREMENT OF REPRODUCTIVE EFFECTS IN MALE FISCHER 344/N MALE RATS TREATED WITH METHYLDOPA, AND MATED TO UNTREATED FEMALE FISCHER 344/N RATS

	Methyldopa dose(mg/kg/day)				
	0	50	100	200	400
Mating after 65 days of treatment					
Male with sperm positive females	62% (13/21)	76% (16/21)	67% (14/21)	10% (2/21)**	0% (0/21)**
Male Fertility Index	62% (13/21)	81% (17/21)	67% (14/21)	14% (3/21)**	5% (1/21)**
% Fertility (in females)	40% (17/42)	52% (22/42)	40% (17/42)	7% (3/42)**	2% (1/42)**
Live implants/female ($\bar{x}$ ± S.E.M.)	8.8 ± 0.5	9.5 ± 0.3	9.4 ± 0.3	6.0 ± 2.1	6.0
% Resorptions	3.8% (6/156)	2.8% (6/211)	3.6% (6/166)	5.2% (1/19)	0% (0/6)
Mating after a 13-week recovery period					
Males with sperm positive females	40% (6/15)	—	40% (6/15)	40% (6/15)	29% (4/14)
Male Fertility Index	40% (6/15)	—	33% (5/15)	40% (6/15)	29% (4/14)
% Fertility (in females)	23% (7/30)	—	17% (5/30)	27% (8/30)	21% (6/28)
Live implant/female ($\bar{x}$ ± S.E.M.)	10.0 ± 0.6	—	8.8 ± 0.4	10.0 ± 0.2	10.5 ± 0.8
% Resorptions	1.4% (1/70)	—	4.3% (2/44)	1.2% (1/80)	0% (0/63)

Fertility Index = [(No. of males with 1 or 2 pregnant females)/(No. of males mated)] x 100.
% Fertility = [(No. of fertilized females)/(No. of females mated)] x 100.
% Resorptions = [(No. of resorptions)/(total No. fetuses + total no. resorptions)].
**Significantly different from concurrent control group, $P < 0.01$.

Methyldopa has been shown to decrease testosterone levels in male rats [7]. In the current study, methyldopa altered plasma testosterone levels when measured within 1 day of treatment, but testosterone levels rebounded within 2–3 days after cessation of treatment. These hormonal alterations may have contributed to the reproductive toxic effects of methyldopa. No dose-related alterations in plasma FSH and LH levels were seen.

Dose-related histopathologic abnormalities of the testis were seen after 65 days of dosing, characterized by increased numbers of basally located spermatid heads, an apparent, but unquantified, decrease in number of late-stage spermatids, and reduction in germ cell number. Russell et al. [19] suggested that when hormonal stimulation of the testis is interrupted there is a characteristic pattern of testicular histopathology, where there is an increase in, inter alia, stage VII degenerating pachytene spermatocytes. This characteristic morphologic pattern was not observed in methyldopa treated rats, even though testosterone levels were decreased in treated animals. The germ cell count data indicate that much of the germ cell loss occurred after late pachytene. Basally located heads of spermatids were seen after methyldopa treatment, an effect which has been seen with other toxicants (dimethyl methyl phosphonate and ethylene glycol monomethyl ether) [20,21].

A decrease in body weight gain was observed in methyldopa treated male rats, despite unlimited access to food. The decrease in weight gain observed in the methyldopa male rats may have contributed to the reproductive toxicity in the male rat, but probably was not the sole cause of this toxicity, because, for example, the testosterone levels were decreased during methyldopa treatment, but rebounded when treatment ended. After the recovery period, body weights of male rats that had been treated with methyldopa were still significantly lower than the body weight of control animals, but the toxicity to the reproductive system had been reversed.

In these methyldopa studies reproductive toxicity in the male F344/N rat was seen at dose levels that are comparable to those used in man when compared on a mg/m^2 basis. Decreased testosterone levels after methyldopa treatment may have contributed to the reproductive toxicity of this drug.

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APPENDIX J

AUDIT SUMMARY

APPENDIX J. AUDIT SUMMARY

The experimental data, documents, and pathology specimens for the 2-year toxicology and carcinogenesis studies of α-methyldopa sesquihydrate in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (fully implemented by the NTP beginning October 1, 1981). The laboratory experiments were conducted for the NTP by Physiological Research Laboratories (Minneapolis, Minnesota) under a subcontract with Tracor Jitco, Inc., until February 28, 1983, and then under contract with the National Institute of Environmental Health Sciences (NIEHS). The exposure to the chemical (in feed) began on August 11, 1981, for rats and August 26, 1981, for mice. The retrospective audit was conducted at the NTP Archives in June 1987 by Argus Research Laboratories, Inc., Paul A. Wennerberg, D.V.M., M.S., Principal Investigator. Other individuals involved in the audit are listed in the full audit report that is on file at the NIEHS. The audit included a review of:

(1) All inlife records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife observations recorded during the last 3 months of life, all body weights, and feed consumption measurements for a random 10% sample of the study animals.
(3) All inlife records concerning environmental conditions, palpable masses, mortality, animal identification, and correlation of final inlife observation of masses, date of death, and disposition with necropsy records.
(4) All chemistry records including Midwest Research Institute's reports, shipping receipts, chemical use and dose preparation records, analytical records, and correspondence.
(5) Pathology tables and all postmortem records for individual animals concerning identification, disposition codes, condition codes, and correlation between gross observations and microscopic diagnoses.
(6) Inventory and labeling for all wet tissue bags.
(7) Wet tissues from a random 20% sample of the study animals plus those from animals that had an inlife or a gross observation without a corresponding microscopic diagnosis in order to verify animal identification and to examine for untrimmed potential lesions.
(8) Slides and blocks of tissues from the random 20% sample of the study animals to examine for proper match and inventory.

For the audit of the inlife portion of the studies, all necessary study records were present except for the standard operating procedures referred to in the Protocol and complete information on the number of animals received, the disposition of those animals, and the randomization procedure.

For the audit of the chemistry portion of the studies, all analytical chemistry records necessary were available. The audit revealed no points that affected the evaluation of these studies.

For the audit of the pathology portion of the studies, all necessary documents and specimens were present; the audit revealed five potential gross to microscopic noncorrelations, and these were determined to have no impact on the interpretation of the pathology data.

A random sample of wet tissues was examined for animal identification, and there was no finding that animals were exchanged within groups or among groups.

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

* U. S. GOVERNMENT PRINTING OFFICE: 1989-241-221:80396