NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 439

TOXICOLOGY AND CARCINOGENESIS STUDIES OF METHYLPHENIDATE HYDROCHLORIDE

(CAS NO. 298-59-9)

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

FOREWORD

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

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

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

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

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NTP TECHNICAL REPORT

ON THE

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P.O. Box 12233
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Public Health Service
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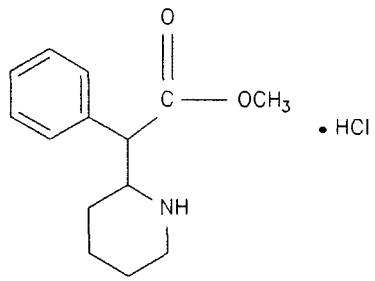
ABSTRACT



METHYLPHENIDATE HYDROCHLORIDE

CAS No. 298-59-9

Chemical Formula: $C_{14}H_{19}NO_2 \cdot HCl$ Molecular Weight: 269.77

Synonyms: α-phenyl-2-piperidineacetic acid methyl ester hydrochloride; methylphenidylacetate hydrochloride; α-phenyl-α-(2-piperidyl)acetic acid methyl ester hydrochloride; methyl α-phenyl-α-(2-piperidyl)acetate hydrochloride
Trade names: Centedrin; Centedrine; Ciba; Meridil; Phenidylate; Ritalin; Ritalin Hydrochloride

Methylphenidate hydrochloride is a drug used in the treatment of narcolepsy and attention deficit hyperactivity disorders. This drug was nominated for study by the Food and Drug Administration and the National Cancer Institute because of its widespread use in human medicine and because of lack of data on its potential carcinogenicity. Oral administration is the most common route of human exposure. Toxicology and carcinogenicity studies were conducted by administering methylphenidate hydrochloride (USP grade) *ad libitum* in feed to groups of male and female F344/N rats and B6C3F$_1$ mice for 14 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and in cultured Chinese hamster ovary cells.

14-Day Study in Rats

Groups of five male and five female F344/N rats were fed diets containing 0, 16, 62, 250, 1,000, or 4,000 ppm methylphenidate hydrochloride for 14 days. All rats survived to the end of the study. The final mean body weights of 4,000 ppm male and female rats were 9% lower than those of the controls. Absolute and relative liver weights of 4,000 ppm males and females were significantly greater than those of the controls. Clinical findings during the first week of the study included hyperactivity in 4,000 ppm males and females, but these animals appeared to be normal during the second week of treatment. No treatment-related gross lesions were observed; however, centrilobular hypertrophy was observed in 4,000 ppm males and females.

14-Day Study in Mice

Groups of five male and five female B6C3F$_1$ mice were fed diets containing 0, 16, 62, 250, 1,000, or 4,000 ppm methylphenidate hydrochloride for 14 days. Three 4,000 ppm males died during the second week of the study; all other mice survived to the end of the study. The final mean body weight of 4,000 ppm females was 11% lower than that of the controls, and the mean body weight gains of 1,000 and 4,000 ppm males and females were also significantly lower than those of the controls. Absolute and relative liver weights of all exposed groups of

males and of 4,000 ppm females were significantly greater than those of the controls. Hyperactivity was observed during the second week of the study in some 4,000 ppm males. Degeneration and necrosis of the renal tubule epithelium were observed in two 4,000 ppm males. Hepatocellular hypertrophy was observed in males and females exposed to 1,000 or 4,000 ppm and in males exposed to 250 ppm.

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were fed diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm methylphenidate hydrochloride for 13 weeks. There were no chemical-related effects on survival. Mean body weight gains of 500, 1,000, and 2,000 ppm males and females and of 250 ppm females were significantly lower than those of the controls. Final mean body weights of exposed males and females were similar to those of the controls. During the first week of the study, feed consumption by 2,000 ppm rats was less than that by controls, but during the remainder of the study feed consumption by exposed and control groups was similar. Rats exposed to 125, 250, 500, 1,000, or 2,000 ppm received approximate doses of 8, 15, 30, 70, or 130 mg methylphenidate hydrochloride per kilogram body weight per day (males) or 9, 18, 30, 70, or 150 mg/kg per day (females). Clinical findings in 1,000 and 2,000 ppm females included slight hypersensitivity to touch, hyperactivity, and increased vocalization during handling periods.

Absolute and relative liver weights of 2,000 ppm males and females were significantly greater than those of the controls, as were the relative liver weights of 1,000 ppm males and females. No chemical-related differences in bone length, bone density, or nose-to-rump lengths were noted in males or females, nor were there treatment-related histopathologic lesions.

13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were fed diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm methylphenidate hydrochloride for 13 weeks. There were no chemical-related effects on survival. Final mean body weights of males exposed to 250, 500, 1,000, or 2,000 ppm and of 2,000 ppm females were significantly lower than those of the controls. The final mean body weights of other exposed male and female groups were similar to those of the controls. During the first week of the study, feed consumption by 2,000 ppm mice was less than that by controls; feed consumption by exposed groups was similar to that by the controls throughout the remainder of the study. Mice exposed to 125, 250, 500, 1,000, or 2,000 ppm received approximate doses of 15, 30, 70, 115, or 230 mg/kg per day (males) or 15, 30, 70, 125, or 260 mg/kg per day (females). No chemical-related clinical findings were observed.

Absolute and relative liver weights of 1,000 and 2,000 ppm males and females were significantly greater than those of the controls, as were the relative liver weights of 125, 250, and 500 ppm males. Centrilobular hypertrophy and hepatocellular degeneration or necrosis were observed in males exposed to 500, 1,000, or 2,000 ppm methylphenidate hydrochloride.

2-Year Study in Rats

Based on the increased liver weights and lower body weight gains in 2,000 ppm rats in the 13-week study, the high dose selected for the 2-year rat study was 1,000 ppm. Groups of 70 male and 70 female F344/N rats were fed diets containing 0, 100, 500, or 1,000 ppm methylphenidate hydrochloride for up to 2 years. As many as 10 male and 10 female rats per exposure group were evaluated at 9 or 15 months.

Survival, Body Weights, Feed and Compound Consumption, and Clinical Findings

Survival of exposed rats was similar to that of the controls at the end of the study. Mean body weights of 500 and 1,000 ppm males were 3% to 10% lower than those of the controls from week 30 to the end of the study; during the same time period, mean body weights of 500 and 1,000 ppm females were 4% to 24% less than those of the controls. Final mean body weights of rats exposed to 100, 500, or 1,000 ppm were 102%, 95%, or 90% (males) and 96%, 89%, or 78% (females) those of the controls. Rats exposed to 100, 500, or 1,000 ppm methylphenidate hydrochloride in feed received approximate doses of 5, 25, or 50 mg/kg per day (males and females). The only chemical-related clinical finding was an increased incidence of fighting among group-housed males exposed to 1,000 ppm.

Hematology and Clinical Chemistry

No biologically significant differences in hematology or clinical chemistry parameters occurred at 9 or 15 months.

Pathology Findings

In female rats exposed to 500 or 1,000 ppm, the incidence of mammary gland fibroadenomas was decreased (0 ppm, 15/49; 100 ppm, 13/50; 500 ppm, 6/48; 1,000 ppm, 5/50), and the decrease was considered to be related to chemical administration. No significant chemical-related increases in neoplasm incidences were observed in male or female rats.

2-YEAR STUDY IN MICE

Based on the liver toxicity and lower body weight gains observed in 1,000 and 2,000 ppm mice in the 13-week study, the high dose selected for the 2-year study was 500 ppm. Groups of 70 male and 70 female B6C3F$_1$ mice were fed diets containing 0, 50, 250, or 500 ppm methylphenidate hydrochloride for 2 years. As many as 10 male and 10 female mice per exposure group were evaluated at 9 or 15 months.

Survival, Body Weights, Feed and Compound Consumption, and Clinical Findings

Survival of exposed mice was similar to that of the controls at the end of the study. Mean body weights of mice exposed to 250 or 500 ppm were 3% to 11% lower than those of the controls throughout much of the study; during the same time period, mean body weights of 250 ppm females were 3% to 7% lower than those of the controls. Final mean body weights of mice exposed to 50, 250, or 500 ppm were 97%, 89%, or 93% (males) and 98%, 93%, or 97% (females) that of the controls. Mice exposed to 50, 250, or 500 ppm methylphenidate hydrochloride in feed were estimated to have received 6, 30, or 60 mg/kg body weight per day (males) or 8, 40, or 80 mg/kg per day (females). There were no chemical-related clinical findings.

Hematology and Clinical Chemistry

No biologically significant differences in hematology or clinical chemistry parameters occurred at 9 or 15 months.

Pathology Findings

The principal lesions associated with the administration of methylphenidate hydrochloride occurred in the liver. A few hepatocellular neoplasms were observed in control and exposed male mice at the 9- and 15-month interim evaluations, but the incidences in exposed groups were not significantly increased. At the end of the 2-year study, incidences of eosinophilic foci were increased in 500 ppm males and females. Increased incidences of hepatoblastoma occurred in 500 ppm males (0 ppm, 0/50; 50 ppm, 1/50; 250 ppm, 1/50; 500 ppm, 5/50). Increased incidences of hepatocellular adenoma also occurred in 500 ppm males (18/50, 18/50, 16/50, 29/50) and females (6/49, 10/48, 10/49, 28/50). The incidences of hepatocellular carcinoma were similar among control and exposed mice.

GENETIC TOXICOLOGY

Methylphenidate hydrochloride was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537, with or without exogenous metabolic activation (S9). Methylphenidate hydrochloride was also tested for induction of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. In the chromosomal aberrations tests, positive results were not consistently dependent upon the presence or absence of S9 activation. Sister chromatid exchanges were not increased in the presence of S9, but one laboratory did obtain a positive response without S9 by testing higher doses than were used in tests with S9.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of methylphenidate hydrochloride in male or female F344/N rats receiving 100, 500, or 1,000 ppm. There was *some evidence of carcinogenic activity* of methylphenidate hydrochloride in male and female B6C3F$_1$ mice based on the occurrence of hepatocellular neoplasms.

Treatment of female rats with methylphenidate hydrochloride was associated with a decrease in the incidence of mammary gland fibroadenomas. Administration of methylphenidate hydrochloride to male and female mice resulted in increased incidences of eosinophilic foci.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Report Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Methylphenidate Hydrochloride

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 100, 500, or 1,000 ppm in feed [approximately 5, 25, or 50 mg/kg/day]	0, 100, 500, or 1,000 ppm in feed [approximately 5, 25, or 50 mg/kg/day]	0, 50, 250, or 500 ppm in feed [approximately 6, 30, or 60 mg/kg/day]	0, 50, 250, or 500 ppm in feed [approximately 8, 40, or 80 mg/kg/day]
Final mean body weights	500 and 1,000 ppm groups slightly lower than controls	500 and 1,000 ppm groups lower than controls	250 ppm group lower than controls	Exposed groups similar to controls
2-Year survival rates	28/50, 33/50, 34/50, 34/51	31/50, 32/50, 36/50, 39/50	45/50, 45/50, 44/50, 41/50	37/50, 35/50, 37/50, 44/50
Nonneoplastic effects	None	None	Eosinophilic foci: 6/50, 8/50, 9/50, 14/50	Eosinophilic foci: 3/49, 3/48, 8/49, 25/50
Neoplastic effects	None	None	Liver: Hepatocellular adenoma: 18/50, 18/50, 16/50, 29/50; hepatoblastoma: 0/50, 1/50, 1/50, 5/50; hepatocellular adenoma, carcinoma, or hepatoblastoma: 24/50, 23/50, 26/50, 34/50	Liver: Hepatocellular adenoma: 6/49, 10/48, 10/49, 28/50; hepatocellular adenoma or carcinoma: 9/49, 11/48, 11/49, 30/50
Decreased incidences	None	Mammary gland: fibroadenomas: 15/49, 13/50, 6/48, 5/50	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	Some evidence	Some evidence

Genetic toxicology

Salmonella typhimurium gene mutation: Negative in strains TA97, TA98, TA100, TA1535, and TA1537 with and without S9

Sister chromatid exchanges

Chinese hamster ovary cells *in vitro*: Positive without S9; negative with S9

Chromosomal aberrations

Chinese hamster ovary cells *in vitro*: Positive without S9 at first lab, positive with S9 at second lab

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on methylphenidate hydrochloride on June 22, 1993, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 22, 1993, the draft Technical Report on the toxicology and carcinogenesis studies of methylphenidate hydrochloride received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of methylphenidate hydrochloride by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplastic and nonneoplastic lesions in mice. The proposed conclusions were: *no evidence of carcinogenic activity* in F344/N rats and *some evidence of carcinogenic activity* in B6C3F_1 mice based on the occurrence of hepatocellular adenomas.

Dr. Taylor, a principal reviewer, agreed with the proposed conclusions. He thought the discussion of metabolism and certain selective aspects of the stereochemistry related to metabolism was quite good. He found the genetic toxicology data hard to interpret.

Dr. Ryan, the second principal reviewer, agreed in principle with the proposed conclusions. She requested more detail on the trends for increased thyroid neoplasms because of the perceived hormonal effects of the chemical. Dr. Dunnick said the numbers didn't support calling this effect chemical related. Dr. Ryan thought there needed to be more discussion on whether the level of evidence in mice based on hepatocellular neoplasms should be raised. Dr. Ryan said that, because this drug is taken by young children, she was concerned that the animals were too old at study start and that bone density measurements might have been useful. Dr. Dunnick responded that the animals were six to seven weeks old at study initiation and that measurements taken during the study showed no effects on bone density. She noted that the purpose of this study was to assess the carcinogenic potential of methylphenidate hydrochloride and that ongoing studies of its other effects are being conducted by the National Institutes of Health.

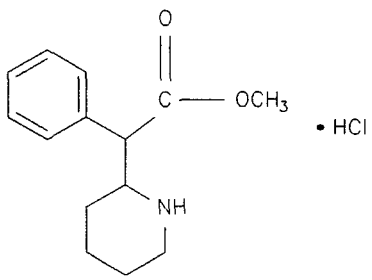
Dr. Davis, the third principal reviewer, did not agree with the proposed conclusions for mice. He said a conclusion of *clear evidence of carcinogenic activity* is supported by dose-related increases in the incidence of hepatocellular adenoma and carcinoma (combined) and in the incidence of hepatoblastoma, a very rare and malignant neoplasm. Dr. Davis commented that the genetic toxicology section was too much a litany of results without a unifying conclusion regarding the genetic toxicology of the chemical. Dr. Dunnick explained that, in this study, the five *Salmonella* strains assayed were all negative, while some other genetic toxicology assays were positive. Dr. E. Zeiger, NIEHS, said that no generally accepted agreement on what defines genotoxicity in a chemical exists. He added that a revised write-up would be included in the report.

In response to the reviewers' concerns about the level of evidence in mice, Dr. J.R. Hailey, NIEHS, led a discussion about the nature of the hepatoblastomas. He said that, although little is known about this neoplasm, a few are being seen in mice from studies that do not yet appear in the NTP historical control database. Hepatoblastomas appear late in mice and are generally observed within other hepatocellular neoplasms, usually carcinomas, and may be considered a more primitive variant. He said the most appropriate treatment for statistical analysis of the hepatoblastomas should be to combine them with adenomas and carcinomas. Dr. Davidson asked that some of this discussion be summarized in the report. Dr. Ward also thought that the high incidence of hepatocellular neoplasms in females and the occurrence of rare neoplasms in males supported raising the conclusion to *clear evidence of carcinogenic activity* in mice. Dr. J.K. Haseman, NIEHS, defended the proposed conclusion, *some evidence*, because most of the increased neoplasms in exposed animals were benign and because all of the hepatoblastomas occurred in animals with other hepatocellular neoplasms, which did not increase the combined incidence.

Dr. Brown moved that the Technical Report on methylphenidate hydrochloride be accepted with the revisions discussed and with the conclusions as written. Dr. Taylor seconded the motion, noting that

the wording at the end of the first paragraph of the conclusions be changed from "adenomas" to "neoplasms." Dr. Zeise offered an amendment that the conclusion for male mice be changed to *clear evidence of carcinogenic activity.* Dr. Ward seconded the amendment, which was defeated by four no votes (Drs. Bailey, Brown, Davidson, and Taylor) to three yes votes (Drs. Davis, Ward, and Zeise) with two abstentions (Drs. Ryan and van Zwieten). The original motion by Dr. Brown, including the wording change, was then accepted by eight yes votes with one abstention (Dr. van Zwieten).

INTRODUCTION



METHYLPHENIDATE HYDROCHLORIDE

CAS No. 298-59-9

Chemical Formula: $C_{14}H_{19}NO_2 \cdot HCl$ Molecular Weight: 269.77

Synonyms: α-phenyl-2-piperidineacetic acid methyl ester hydrochloride; methylphenidylacetate hydrochloride; α-phenyl-α-(2-piperidyl)acetic acid methyl ester hydrochloride; methyl α-phenyl-α-(2-piperidyl)acetate hydrochloride
Trade names: Centedrin; Centedrine; Ciba; Meridil; Phenidylate; Ritalin; Ritalin Hydrochloride

CHEMICAL AND PHYSICAL PROPERTIES

Methylphenidate hydrochloride is a white, odorless, fine crystalline powder with a melting point of 212° to 216° C. It is soluble in water, methanol, and ethanol and slightly soluble in chloroform. The drug is relatively stable in acidic solutions but is degraded extensively in basic solutions (Padmanabhan, 1981). The pK_a of methylphenidate hydrochloride is 8.5 and it is estimated that more than 90% of the drug is in the protonated form at physiological pH (Patrick *et al.*, 1987).

Methylphenidate hydrochloride is a secondary amine containing a methyl ester and possessing two asymmetrical carbon atoms (two chiral centers) which give rise to four optical isomers: *d-threo, l-threo, d-erythro,* and *l-erythro.* Current pharmaceutical products contain only the *threo* racemate. The *threo* enantiomers of methylphenidate hydrochloride are more active pharmacologically than the *erythro* isomers, and *d-threo*-methylphenidate is more active than the *l*-enantiomer (Szporny and Görög, 1961; Srinivas *et al.*, 1987). The *d-threo* enantiomer is believed to be responsible for the therapeutic action of the drug (Maxwell *et al.*, 1970; Patrick *et al.*, 1987).

Methylphenidate hydrochloride is a piperidine derivative structurally related to amphetamine. Methylphenidate hydrochloride is prepared by hydrolyzing α-phenyl-2-pyridineacetonitrile in dilute sulfuric acid to α-phenyl-2-pyridineacetamide; this product is hydrogenated to yield a diastereoisomeric mixture of α-phenyl-2-piperidineacetamide. The diastereoisomeric mixture is converted to a *threo* racemic mixture by heating in sodium hydroxide solution and, in the same reaction, is hydrolyzed to α-phenyl-2-piperidineacetic acid and reacted with methanol to yield the methyl ester free base, which is then converted to methylphenidate hydrochloride (Padmanabhan, 1981).

USE AND HUMAN EXPOSURE

Methylphenidate is used in the treatment of narcolepsy and attention-deficit hyperactivity disorders (ADHD) in children (Barkley *et al.*, 1990) and adults (Gurian and Rosowsky 1990; Heath *et al.*, 1990). Tablets which contain 5, 10, or 20 mg of methylphenidate hydrochloride are available; sustained release preparations are also available. The usual adult dosage is 10 mg given 2 or 3 times daily; the initial dosage recommended for children is 5 mg twice daily and the dosage for children should not exceed 60 mg daily (Hoffman and Lefkowitz, 1990). Doses used in children usually range from 0.3 to 1.0 mg/kg. Methylphenidate (Ritalin) is among the 200 most often dispensed prescription drugs in the United States (American Druggist, 1990).

Barkley *et al.* (1990) estimated that 3% to 6% (1 million) of U.S. elementary school-age children are being treated for ADHD. Methylphenidate hydrochloride is prescribed as the drug of choice in 93% of ADHD cases. During a 10-year survey conducted in Baltimore county schools, the average duration of treatment with methylphenidate hydrochloride was 2 years for elementary school-age children, 4 years for children in middle schools, and 7 years for students starting treatment in high school. ADHD is three to six times more common in boys than in girls (Segal *et al.*, 1976; Srinivas *et al.*, 1987; Safer and Krager, 1988a,b).

Methylphenidate hydrochloride was first used in the mid-1950's (*The NDA Book*, 1990). Because of the potential for abuse, methylphenidate hydrochloride is a Schedule II drug under the Comprehensive Drug Abuse Prevention and Control Act of 1970 (*Goodman and Gilman's*, 1980).

PHARMACOLOGY

While the pharmacologic actions of methylphenidate hydrochloride were first described in 1954 (Brown and Werner, 1954; Meier *et al.*, 1954; Calis *et al.*, 1990), its pharmacologic action in the treatment of attention deficit disorders, a heterogeneous behavioral disorder of unknown etiology, is not fully understood (Zametkin and Rapoport, 1987; Greenhill, 1992). The usefulness of stimulant therapy (amphetamine) in the treatment of children's behavior disorders was first noted by Bradley (1937), where it was reported that this treatment increased compliance and academic performance. Meier *et al.* (1954), looking for analogues of amphetamine, reported that methylphenidate could also be used as a stimulant drug.

Studies to determine the pharmacologic effects of methylphenidate in the treatment of attention-deficit hyperactivity disorder (ADHD) were conducted in rodents and focused on the effects on catecholamine levels in the brain. Selective depletion of brain dopamine with 6-hydroxydopamine in the neonatal rat causes hyperactivity, and this hyperactivity is ameliorated by the administration of methylphenidate or amphetamine (Shaywitz *et al.*, 1976; Luthman *et al.*, 1989).

Methylphenidate increases spontaneous motor activity and stereotyped behavior in normal animals and these effects are correlated with an increase in dopamine levels and decreases in norepinephrine and serotonin in the brain (Bhattacharyya *et al.*, 1980). Studies of methylphenidate in mice, rats, guinea pigs, and rabbits found that oral doses of approximately 10 to 40 mg/kg resulted in increased activities (licking, scratching, eating, chewing, and drinking) and shortened reaction times to environmental stimuli such as light, noise, and touch (Brown and Werner, 1954). Warawa *et. al.* (1975), reported that oral doses of 20 mg/kg in mice and 2.5 mg/kg in squirrel monkeys caused stimulatory effects. Enhanced spontaneous activity was also noted when rats were fed diets containing 2,000 ppm methylphenidate (82 mg/kg per day) for 5 days, but tolerance to this effect may develop (Fregly and Black, 1964). Methylphenidate hydrochloride appears to have a transient anorexic effect (Barone *et al.*, 1979).

The stimulatory effects of methylphenidate in the rodent are thought to be related to their indirect actions on dopaminergic neurons with amphetamine stimulating the release of newly synthesized catecholamines into the synaptic cleft, and methylphenidate stimulating the release of stored or granular pools of catecholamines (Finn *et al.*, 1990). Another difference between amphetamine and methylphenidate is that reserpine antagonizes methylphenidate effects but not those of amphetamine (Patrick *et al.*, 1987).

As a consequence of methylphenidate's effects on dopamine levels in the brain, it may mediate other neuroendocrine functions. Hypothalamic prolactin-inhibiting factor (PIF) is controlled by dopaminergic neurons, and increases in brain dopamine levels, such as are seen with amphetamine and methylphenidate,

may increase the release of PIF, resulting in decreases in serum prolactin (Archer, 1977; Leong *et al.*, 1983).

Recent studies suggest that ADHD may have a familial predisposition and that this disorder is associated with generalized resistance to thyroid hormone in a subset of ADHD patients (Hauser *et al.*, 1993). Not all symptoms of ADHD respond to methylphenidate treatment (Ciarantello, 1993), and the primary defect of ADHD may not lie in the catecholamine system. The pharmacologic effects of methylphenidate may remedy a secondary function found in ADHD (Shenker, 1992).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

The metabolism of methylphenidate hydrochloride has been studied in rats, mice, dogs, and monkeys. In these species, urine is the primary route of excretion. Metabolites of methylphenidate hydrochloride found in rats and dogs are presented in Table 1; the two major pathways of methylphenidate hydrochloride metabolism are summarized in Figure 1. The primary route of metabolism in rats, mice, and dogs is microsomal oxidation of methylphenidate to oxomethylphenidate and *p*-hydroxymethylphenidate (Faraj *et al.*, 1974).

Studies in rats indicate that 19% of an oral dose of 10 mg methylphenidate hydrochloride per kg body weight is absorbed in 1 hour, and that within that hour peak plasma concentrations reach approximately 200 ng/mL. The plasma elimination half-life in monkeys and rats administered oral doses of 3 and 10 mg/kg, respectively, is 2 to 3 hours (Wargin *et al.*, 1983). In tissue distribution studies, rats were administered 1 mg/kg methylphenidate hydrochloride intravenously or orally. Within 1 to 5 minutes, the ratio of methylphenidate in brain tissue to that in serum was 8:1 (Gal *et al.*, 1977; Patrick *et al.*, 1984).

Rats administered 10 to 20 mg/kg ^{14}C-methylphenidate hydrochloride orally or intraperitoneally eliminated 50% to 60% of the radiolabel in urine and 30% to 40% in the feces; a significant amount of radiolabel was also excreted in the bile. Ritalinic acid (α-phenyl-2-piperidineacetic acid) (36%) and *p*-hydroxyritalinic acid (19%) and its glucuronide conjugate (10%) were identified as the major urinary metabolites. Mice and dogs also excreted 50% to 60% of an oral dose in urine within 48 hours. Microsomal oxidation was the predominant metabolic pathway; more than 50% of the metabolites were the products of aromatic hydroxylation (Faraj *et al.*, 1974; Egger *et al.*, 1981).

The pharmacologic actions of methylphenidate hydrochloride appear to result from the parent compound. Studies with ritalinic acid, *p*-hydroxymethylphenidate, and 6-oxomethylphenidate indicate that administration of these metabolites to rats does not produce the pharmacologic activity of methylphenidate (Patrick *et al.*, 1987).

In studies conducted by the National Toxicology Program, [acetic acid-2-^{14}C]-methylphenidate hydrochloride was administered by gavage to male F344/N rats and male and female B6C3F$_1$ mice. The radiolabeled material was used to trace absorption, distribution, metabolism, and excretion of methylphenidate hydrochloride following the administration of single doses of 7, 35, or 70 mg/kg (to rats) or 2.1, 19, or 35 mg/kg (to mice). The overall aim of the study was to determine if sex and species differences observed in connection with liver toxicity in the present studies (toxicity was most severe in the liver of male mice) could be attributed to chemical disposition. The highest methylphenidate tissue concentrations occurred in the liver, kidney, and lung of rats and mice. In all dose groups of rats and mice, approximately 80% of methylphenidate administered was excreted in the urine within 24 hours. No statistically significant differences were observed between species in the rate or route of excretion. Quantitation of radioactive high-performance liquid chromatography peaks from urine suggested that metabolites observed in the urine of male rats were different from those observed in the urine of male mice. However, no such differences were observed between male and female mice. This finding suggests that metabolic differences alone could not account for the sex and species differences observed in the present studies in connection with liver toxicity (Duerson *et al.*, 1988; NTP, 1990).

TABLE 1
Methylphenidate Hydrochloride Metabolites Identified in Rats, Dogs, and Humans[a]

Dose	Route	Time (Hours)	Metabolite (% of Urine)
Rat			
20 mg/kg	Oral	0-24	Methylphenidate (1%); Ritalinic acid (35%-40%); 6-Oxomethylphenidate (1.5%); 6-Oxoritalinic acid (7%-10%); 5-Hydroxy-6-oxomethylphenidate (2%); 5-Hydroxy-6-oxoritalinic acid (15%-17%); Carbamide methylphenidate (1%); *p*-Hydroxyritalinic acid glucuronide (10%); Unknown (20%)
		0-48	Methylphenidate (<1%); Ritalinic acid (36%); 6-Oxomethylphenidate (<1%); 6-Oxoritalinic acid (1.8%); *p*-Hydroxymethylphenidate (3%); *p*-Hydroxyritalinic acid (19%); *p*-Hydroxyritalinic acid glucuronide (10%)
	Intraperitoneal	0-48	Methylphenidate (<1%); Ritalinic acid (27%); 6-Oxomethylphenidate (1.2%); 6-Oxoritalinic acid (3%); *p*-Hydroxymethylphenidate (15%); *p*-Hydroxyritalinic acid (20%); *p*-Hydroxyritalinic acid glucuronide (10%)
Dog			
5 mg/kg	Oral	0-8	Methylphenidate (0.3%); Ritalinic acid (23%); 6-Oxomethylphenidate (1%); 6-Oxoritalinic acid (26.5%); 6-Oxoglucuronide (20%); 5-Hydroxy-6-oxomethylphenidate glucuronide (12%); 4-Hydroxy-6-oxomethylphenidate glucuronide (1%); 5-Hydroxy-6-oxoritalinic acid (4%); Carbamide methylphenidate (1%); *p*-Hydroxy-6-oxoglucuronide (2%-3%); *p*-Hydroxy-6-oxosulfonic acid (1%); Unknown (3%)
10 mg/kg	Intravenous	0-5	Methylphenidate (<1%); Ritalinic acid (44%); *p*-Hydroxymethylphenidate (1.2%); *p*-Hydroxyritalinic acid (2%); 6-Oxomethylphenidate (7%); 6-Oxoritalinic acid (30%); *p*-Hydroxyritalinic acid glucuronide (<1%)
Human			
20 mg/kg	Oral or Intravenous	0-24	Methylphenidate (<1%); Ritalinic acid (80%); *p*-Hydroxymethylphenidate (<1%); *p*-Hydroxyritalinic acid (2%); 6-Oxomethylphenidate (<1%); 6-Oxoritalinic acid (<1%, 1.5% intravenously); *p*-Hydroxyritalinic acid glucuronide (<1%)

[a] Data are presented in Faraj *et al.* (1974) and Egger *et al.* (1981). No quantitative data are available for mice.

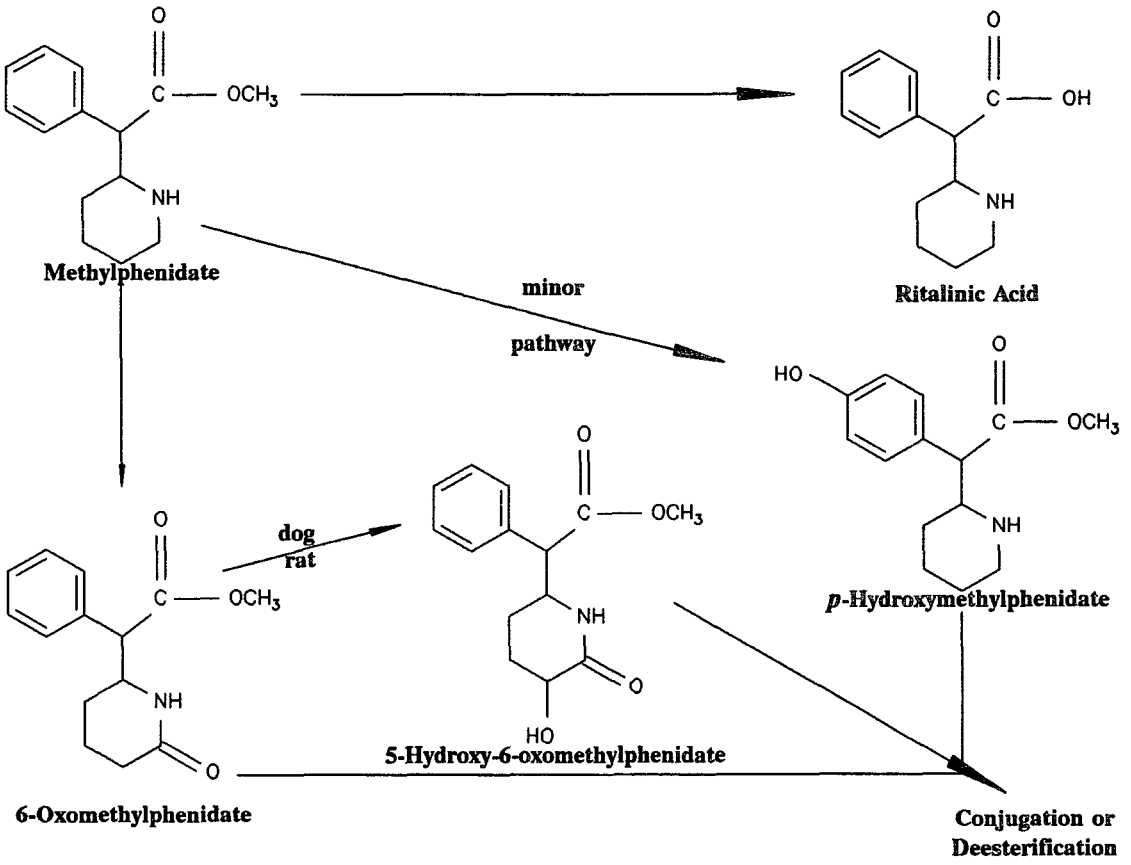


FIGURE 1
Metabolic Pathways of Methylphenidate
(Patrick *et al.*, 1987)

Humans

Methylphenidate hydrochloride is absorbed from the gastrointestinal tract and attains peak plasma level concentrations in approximately 2 hours. The oral bioavailability of methylphenidate is estimated to be 11% to 53% (Chan *et al.*, 1983). The plasma elimination half-life of a 10 to 20 mg dose of methylphenidate administered intravenously or orally is approximately 2 hours (Chan *et al.*, 1980, 1983).

In humans, methylphenidate's predominant metabolic pathway is deesterification to form the corresponding carboxylic acid metabolite commonly known as ritalinic acid. Other minor metabolic pathways involve aromatic hydroxylation to form *p*-hydroxymethylphenidate (4%) and microsomal oxidation to form oxomethylphenidate (2% to 5%). These compounds are then excreted in the urine in the form of esters, free acids, and conjugates (Table 1; Chan *et al.*, 1980; Srinivas *et al.*, 1987). Ritalinic acid, the most common metabolite in man, is pharmacologically inactive (Faraj *et al.*, 1974; Patrick *et al.*, 1987; Calis *et al.*, 1990).

By measuring plasma concentrations of individual enantiomers, Lim *et al.* (1986) found that levels of *d-threo*-methylphenidate were consistently higher than those of the *l*-enantiomer after a single oral dose of 20 to 40 mg. Peak plasma concentrations of the *d*-enantiomer are approximately 8 times greater than those of the *l*-enantiomer after an oral dose of 10 mg methylphenidate hydrochloride (Srinivas *et al.*, 1987).

TOXICITY

Experimental Animals

The oral LD_{50} of methylphenidate has been reported to range from 180 to 350 mg/kg in rats (Brown and Werner, 1954; Padmanabhan, 1981) and from 60 to 450 mg/kg in mice (Karczmar and Howard, 1959; Warawa *et al.*, 1975). The probable cause of death at these dose levels is excessive central adrenergic stimulation (Segal *et al.*, 1976).

Methylphenidate treatment lowers serum and brain cholesterol levels in experimental animals (Kabara, 1965; Kabara *et al.*, 1972) and weakly inhibits hepatic microsomal drug metabolism *in vitro* (Dayton *et al.*, 1975). Methylphenidate hydrochloride administered subcutaneously for 21 days to 5- to 7-day old rats at doses of 35 or 100 mg/kg resulted in significant reduction of serum thyroxine and triiodothyronine (Greeley *et al.*, 1980).

Humans

Side effects from methylphenidate hydrochloride treatment for attention-deficit disorders include decreased appetite, insomnia, stomach ache, headache, weight loss, and transient growth suppression. Fewer than half of the children treated with methylphenidate experience side effects, which are usually considered mild (Barkley *et al.*, 1990; Calis *et al.*, 1990).

Clinical studies have provided conflicting information concerning retardation of growth in children administered methylphenidate (Safer *et al.*, 1972, 1975; Roche *et al.*, 1979; Mattes and Gittelman, 1983). When methylphenidate hydrochloride therapy is discontinued, children seem to experience rapid growth that completely reverses any anti-growth effect of transient therapy (Safer *et al.*, 1975; Gross, 1976; Satterfield *et al.*, 1979). Prolonged treatment may cause an increase or a decrease in serum growth hormone (Brown and Williams, 1976; Aarskog *et al.*, 1977). Barter and Kammer (1978) have speculated that methylphenidate hydrochloride may interfere with the normal diurnal variation of growth hormone release.

Hepatotoxicity and cardiotoxicity have been reported after methylphenidate treatment, but these effects are rare and have not conclusively been shown to be caused by methylphenidate (Goodman, 1972).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The effects of methylphenidate hydrochloride on fertility and reproduction in Swiss CD-1® mice were studied using a continuous breeding protocol (NTP, 1989). Methylphenidate hydrochloride was administered in feed at concentrations of 120, 500, and 1,000 ppm to male and female mice for 7 days prior to cohabitation and for 98 days following cohabitation. The F_1 generation was weaned and administered the same concentrations of methylphenidate hydrochloride in feed; they were cohabitated for 1 week at sexual maturity. The following parameters were evaluated for both generations: fertility, litters per pair, live pups per litter, proportion of pups born alive, sex of live pups, and pup body weight. Methylphenidate hydrochloride had no apparent effect on

fertility or reproduction in either the parental or F_1 generation. Some increases in liver weights were noted in 1,000 ppm parental and F_1 males and females. Methylphenidate hydrochloride had no effect on parental or F_1 epididymal sperm density, motility, morphology, or on female estrous cycle. In an evaluation of the effects of 25 chemicals on rodent sperm morphology and vaginal cytology, Morrissey *et al.* (1988) found that methylphenidate (125, 500, or 2,000 ppm in feed for 13 weeks) did not cause significant toxicity to the reproductive system of male or female rats or mice, although sperm motility was reduced in 2,000 ppm mice.

CARCINOGENICITY

Experimental Animals

There are no carcinogenicity studies of methylphenidate hydrochloride reported in the literature. *N*-Nitrosomethylphenidate administered orally to 15 male and 15 female rats twice weekly for 50 weeks at a dose of 12 mg/rat did not increase the incidence of neoplasms (Lijinsky and Taylor, 1975). In another study, mice were administered drinking water containing 100 mg/L *N*-nitrosomethylphenidate (12.5 mg/kg/day) 4 days per week from the time they were 1 week old until they were 18 months old; the animals exhibited no increased incidences of neoplasms or nonneoplastic lesions when evaluated at 25 to 26 months (Giner-Sorolla *et al.*, 1980).

Humans

A review of pharmacy records from 1969 to 1973 for a cohort of 143,574 patients in a medical care program showed that in 529 patients receiving methylphenidate the number of cancers observed was less than expected (Selby *et al.*, 1989).

GENETIC TOXICITY

The limited mutagenicity data that are available for either methylphenidate or its hydrochloride salt indicate that the chemical is not a gene mutagen in bacteria or mammalian cells, but that it might have some potential for inducing clastogenic damage in mammalian cells. Methylphenidate hydrochloride was not mutagenic in any of several strains of *Salmonella typhimurium* when tested with and without S9 metabolic activation enzymes (Mortelmans *et al.*, 1986). However, sister chromatid exchanges were induced in cultured Chinese hamster ovary cells treated with methylphenidate hydrochloride both in the presence and absence of S9 (Galloway *et al.*, 1987); chromosomal aberrations were also induced in the presence of S9. Although methylphenidate hydrochloride gave statistically positive responses in both of these cytogenetic assays, the increases in sister chromatid exchanges occurred at doses which produced severe toxicity, and the increases in chromosomal aberrations were not well correlated with dose.

Results of genotoxicity tests that were performed with methylphenidate (nonsalt) are limited to three brief abstracts which include little or no supporting data. Walker and Dumars (1977) reported that sister chromatid exchange frequencies were elevated in human lymphocytes obtained from pediatric patients treated with methylphenidate. However, Rudd *et al.* (1983) reported that no induction of chromosomal damage or gene mutations occurred in L5178Y mouse lymphoma cells treated with methylphenidate *in vitro*. Methylphenidate did not induce unscheduled DNA synthesis in hepatocytes of Fischer 344 rats treated *in vivo* (Mirsalis *et al.*, 1983).

STUDY RATIONALE

The National Cancer Institute and the Food and Drug Administration nominated methylphenidate hydrochloride for study because it is a widely used drug in the treatment of attention-deficit disorders and because there were no adequate toxicity and carcinogenicity studies for this chemical. The oral route of administration was selected because it is the primary route of human exposure.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF METHYLPHENIDATE HYDROCHLORIDE

Methylphenidate hydrochloride, United States Pharmacopeia grade, was supplied gratis by Ciba-Geigy Corporation (Summit, NJ) in two lots. Lot M1088 was used throughout the 14-day and 13-week studies. Lot CMS86-166-001 was used throughout the 2-year studies. The USP designation implies that the chemical is a racemate of two optical isomers: *d-threo* and *l-threo*. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the methylphenidate hydrochloride studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

Both lots of the chemical, a white, fine crystalline solid, were identified as methylphenidate hydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of each lot was determined to be greater than 99% by elemental analyses, Karl Fischer water analysis, titration of the amine group, thin-layer chromatography, and high-performance liquid chromatography.

Confirmation that the test chemical was a racemate was obtained based on the lack of optical activity. Results of a USP XX thin layer chromatographic analysis confirmed that the *erythro* (*d, l*) isomer was not present at the 1% USP limit. Therefore, it was concluded that both lots contained the *threo* racemate of methylphenidate hydrochloride. A second USP XX thin-layer chromatographic method was used to determine if the impurity α-phenyl-2-piperidineacetic acid hydrochloride was present in either lot. No α-phenyl-2-piperidineacetic acid hydrochloride was detected above the USP specified limit of 0.6%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory. High-performance liquid chromatography was performed and these studies indicated that methylphenidate hydrochloride was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. At the study laboratory, the chemical was stored at 20° to 24° C. Stability of the bulk chemical was confirmed during the 2-year studies using high performance liquid chromatography and titration of the amine group.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared weekly by mixing methylphenidate hydrochloride with feed (Table I1). Homogeneity and stability studies of the 200 ppm dose formulation was performed by the analytical chemistry laboratory using high-performance liquid chromatography. Homogeneity was confirmed and the stability of the dose formulation was confirmed for at least 3 weeks at 5° C and for up to 7 days when exposed to air and light under simulated animal cage conditions. During the toxicity studies, dose formulations were stored at 4° C for up to 2 weeks.

Periodic analyses of the dose formulations of methylphenidate hydrochloride were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. During the 14-day studies, only the initial formulation was analyzed (Table I2). For the 13-week studies, dose formulations were analyzed at the beginning, midpoint, and end of the studies (Table I3). During the 2-year studies, the dose formulations were analyzed initially and then every 6 to 10 weeks (Table I4). Of the dose formulations analyzed, 88% (146/167) were within 10% of the target concentration, with no value greater than 21% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I5).

14-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). At receipt, the rats and mice were an average of 5 weeks old. Rats were quarantined for 15 days and mice for 16 days before exposure began. Before the beginning of the studies, two male

and two female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease.

An initial 14-day study was conducted in which rats and mice received 0, 62.5, 125, 250, 500, or 1,000 ppm methylphenidate hydrochloride. There were no treatment-related effects on body weight or survival, and no target organ lesions attributed to chemical administration. Rats and mice exposed to 1,000 ppm methylphenidate hydrochloride were estimated to receive daily doses of 80 mg/kg body weight (rats) or 160 mg/kg (mice). Because of the lack of toxicity in the initial 14-day studies, these studies were repeated with exposure levels of 0, 16, 62, 250, 1,000, and 4,000 ppm. The 4,000 ppm concentration was estimated to deliver 370 mg/kg body weight in rats and approximated the oral LD_{50} value reported for rats in the literature (Padmanabhan, 1981).

Groups of five male and five female rats and mice were fed diets containing 0, 16, 62, 250, 1,000, or 4,000 ppm methylphenidate hydrochloride. Feed and water were available *ad libitum*. Rats and mice were housed five per cage. Clinical findings for rats and mice were recorded twice daily. Feed consumption by cage was recorded twice weekly. The animals were weighed at the beginning of the studies, twice weekly, and 16 hours prior to necropsy. Details of the study design and animal maintenance are summarized in Table 2.

At the end of the 14-day studies, blood was collected from the orbital sinus of all animals for clinical chemistry parameters. The parameters measured are listed in Table 2. A gross necropsy was performed on all rats and mice. The brain, heart, liver, lungs, right kidney, right testis, and thymus were weighed. Histopathologic examinations were performed on the livers and kidneys of all rats and mice.

13-Week Studies

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to methylphenidate hydrochloride and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). On receipt, rats and mice were an average of 4 weeks old; animals were quarantined for 13 days before exposure began. Prior to the beginning of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At terminal sacrifice, serologic analyses were performed on five male and five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice were fed diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm methylphenidate hydrochloride. Feed and water were available *ad libitum*. Rats and female mice were housed five per cage throughout the studies. Male mice were housed five per cage for the first 7 weeks of the study and individually for the remainder of the study because of fighting among group-housed animals. Clinical findings were recorded twice daily. Feed consumption was recorded weekly by cage. The animals were weighed prior to the beginning of the studies, once weekly during the studies, and at necropsy. Further details of study design and animal maintenance are summarized in Table 2.

Nose-to-rump length measurements were taken on all rats before the beginning of the study and on surviving rats at 4, 8, and 13 weeks into the study. Bone density analyses were performed on all rats surviving to the end of the study. Nose-to-rump length and bone density measurements were performed using the protocols outlined in Appendix H.

A gross necropsy was performed on all animals. The brain, heart, liver, lungs, right kidney, left testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on control and 2,000 ppm rats and mice and on animals that died during the study. The liver and kidneys of all other animals were also examined. Table 2 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 70 male and 70 female rats were fed diets containing 0, 100, 500, or 1,000 ppm methylphenidate hydrochloride and 70 male and 70 female mice were fed diets containing 0, 50, 250, or 500 ppm

methylphenidate hydrochloride. After 9 and 15 months of exposure, groups of up to 10 male and 10 female rats and mice per group were evaluated for absolute and relative organ weights, hematology and clinical chemistry parameters, and histopathology.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA) for use in the 2-year studies. Male rats were quarantined for 13 days; female rats were quarantined for 14 days. Mice were received in two shipments on two consecutive days and were quarantined for 14 to 15 days. Five male and five female rats and mice were killed and examined for parasites; these animals were also observed grossly for disease. Rats and mice were approximately 6 weeks old at the beginning of the studies. Additionally, as many as five male and five female rats and mice were evaluated at 6, 12, and 18 months and at the end of the studies using the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats were housed five per cage and mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was measured once every 4 weeks (Appendix J). Cages and racks were rotated once every 2 weeks. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded once every 4 weeks; body weights were recorded weekly for the first 13 weeks and monthly thereafter.

A gross necropsy was performed on all rats and mice. The brain, right kidney, liver, and right testis of rats and mice evaluated at 9 and 15 months were weighed. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all major tissues and samples of grossly visible lesions. Tissues examined are listed in Table 2.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscope slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated.

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

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test

to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, see Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test, a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical chemistry and hematology data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe,

1973). Nose-to-rump lengths were analyzed using Williams' or Dunnett's test.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of methylphenidate hydrochloride was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and chromosomal damage in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix E.

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

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* alone. The predictivity of carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Methylphenidate Hydrochloride

14-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Hazleton Laboratories America, Inc. (Madison, WI)	Hazleton Laboratories America, Inc. (Madison, WI)	TSI Mason Research Institute (Worcester, MA)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies		
Rats: 15 days Mice: 16 days	13 days	Rats: 13 days (males) or 14 days (females) Mice: 14 or 15 days
Average Age When Studies Began		
7 weeks	6 weeks	6 weeks
Date of First Dose		
Rats: 16 June 1983 Mice: 17 June 1983	11 October 1983	Rats: 27 August 1986 (males) or 28 August 1986 (females) Mice: 1 August 1986
Duration of Dosing		
14 days	Rats: 90 days Mice: 92 days	104 weeks (males) 105 weeks (females)
Date of Last Dose		
Rats: 29 June 1983 Mice: 30 June 1983	Rats: 9, 10 January 1984 Mice: 11, 12 January 1984	Rats: 9-Month interim evaluation: 28 May 1987 (males); 4 June 1987 (females) 15-Month interim evaluation: 1 December 1987 (males); 3 December 1987 (females) Terminal: 17 August 1988 (males); 25 August 1988 (females) Mice: 9-Month interim evaluation: 30 April 1987 (males); 7 May 1987 (females) 15-Month interim evaluation 27 October 1987 (males); 29 October 1987 (females) Terminal: 21 July 1988 (males); 29 July 1988 (females)

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Methylphenidate Hydrochloride
(continued)

14-Day Studies	13-Week Studies	2-Year Studies
Necropsy Dates		
Rats: 30 June 1983 Mice: 1 July 1983	Rats: 9, 10 January 1984 Mice: 11, 12 January 1984	Rats: 9-Month interim evaluation: week of 25 May 1987 (males); week of 1 June 1987 (females) 15-Month interim evaluation: week of 30 November 1987 Terminal: 24-31 August 1988 (males); 2-13 September 1988 (females) Mice: 9-Month interim evaluation: week of 27 April 1987 (males); week of 4 May 1987 (females) 15-Month interim evaluation: week of 26 October 1987 Terminal: 29 July-9 August 1988 (males); 8-16 August 1988 (females)
Average Age at Necropsy		
9 weeks	19 weeks	9-Month interim evaluation: 47 weeks 15-Month interim evaluation: 71 weeks Terminal: 111 weeks (males); 112 weeks (females)
Size of Study Groups		
5 males and 5 females	10 males and 10 females	70 males and 70 females
Method of Distribution		
Animals assigned at random and proportionately by weight class	Same as 14-day studies	The required number of animals were placed into pre-numbered cages using a table of random numbers. A second table of random numbers was used to assign cages to dose groups. Cages were placed on racks in dose columns using a third random number table.
Animals per Cage		
5	Rats: 5 Mice: 5 per cage until 22 November 1983, when males were housed separately	Rats: 5 Mice: 1
Method of Animal Identification		
Rats: metal ear tag Mice: metal neck tag and ear punch	Rats: metal ear tag Mice: ear notches and toe clips	Rats: toe clip and tail tattoo Mice: toe clip

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Methylphenidate Hydrochloride
(continued)

14-Day Studies	13-Week Studies	2-Year Studies
Diet		
NIH-7 open formula rat and mouse ration (Teklad Test Diets, Winfield, IA), available *ad libitum* until 16 hours prior to serum collection; changed twice weekly	Same as 14-day studies, but available *ad libitum* until terminal sacrifice	NIH-07 open formula mash (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*; changed once weekly
Maximum Storage Time for Feed		
3 weeks	Same as 14-day studies	Same as 14-day studies
Water Distribution		
Water supplied by Systems Engineering (Palo Alto, CA) via automatic watering system, available *ad libitum*	Same as 14-day studies	Tap water (City of Worcester water supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*
Cages		
Clear polycarbonate (Hazleton Systems, Inc., Aberdeen, MD), changed twice weekly	Same as 14-day studies, but changed once weekly for males caged separately	Polycarbonate (Lab Products, Inc., Rochelle Park, NJ), changed twice weekly
Bedding		
Heat-treated hardwood chips (Northeastern Products, Corp., Warrensburg, NY), changed twice weekly	Same as 14-day studies, but changed once weekly for males caged separately	BetaChip® hardwood chips (Northeastern Products, Inc., Warrensburg, NY), changed twice weekly (rats) or weekly (mice)
Cage Filters		
Not available	Non-woven polyester fiber	Non-woven polyester fiber (Snow Filtration Co., Cincinnati, OH), changed once each 2 weeks
Racks		
Stainless steel (Hazleton Systems, Inc., Aberdeen, MD), changed once each 2 weeks	Same as 14-day studies	Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed once each 2 weeks
Animal Room Environment		
Average temperature: 22.2° C Relative humidity: 50% ± 20% Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour	Same as 14-day studies	Temperature: 19.4° C to 25° C Relative humidity: 40% to 55% Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour
Doses		
0, 16, 62, 250, 1,000, or 4,000 ppm in feed, available *ad libitum*	0, 125, 250, 500, 1,000, or 2,000 ppm in feed, available *ad libitum*	Rats: 0, 100, 500, or 1,000 ppm in feed, available *ad libitum* Mice: 0, 50, 250, or 500 ppm in feed, available *ad libitum*

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Methylphenidate Hydrochloride
(continued)

14-Day Studies	13-Week Studies	2-Year Studies
Type and Frequency of Observation		
Observed twice daily for clinical signs, moribundity, and death; clinical observations recorded twice daily. Animals were weighed at the beginning of the study, twice weekly, and approximately 16 hours before terminal sacrifice. Feed and water consumption was recorded twice weekly by cage.	Observed twice daily for clinical signs, moribundity, and death; clinical observations recorded twice daily. Animals were weighed at the beginning of the study, weekly, and at the end of the studies. Feed consumption was recorded weekly by cage.	Observed twice daily for moribundity and mortality; clinical observations recorded once every 4 weeks. Animals weighed at the beginning of the studies, once weekly for the first 13 weeks, and once every 4 weeks thereafter. Feed consumption measured once every 4 weeks.
Method of Sacrifice		
CO_2 asphyxiation	CO_2 asphyxiation	CO_2 asphyxiation
Necropsy		
Necropsy performed on all animals. The heart, right kidney, liver, lung, right testis, and thymus of all animals were weighed.	Necropsy performed on all animals. The heart, right kidney, liver, lung, left testis, and thymus of animals surviving to the end of the studies were weighed.	Necropsy performed on all animals. Organs weighed at the 9- and 15-month interim evaluations were brain, right kidney, liver, and right testis.
Clinical Pathology		
Blood was collected from the orbital sinuses of all animals. ***Clinical Chemistry:*** Blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase	None	The following parameters were measured from blood collected from the retro-orbital sinus of all 9- and 15-month interim evaluation animals. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, reticulocytes, leukocytes, segmented neutrophils, lymphocytes, monocytes, eosinophils, and nucleated erythrocytes. ***Clinical Chemistry:*** γ-glutamyltransferase, blood urea nitrogen, creatinine, alanine aminotransferase, and aspartate aminotransferase.
Special Studies		
None	Nose-to-rump length measurements taken on all rats prior to the beginning of the study and on surviving rats at 4, 8, and 13 weeks after study initiation. Bone density measured on all surviving rats at the end of the study.	None

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Methylphenidate Hydrochloride
(continued)

14-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
Histopathology was performed on the kidneys and livers of all animals.	Complete histopathology was performed on all control and 2,000 ppm rats and mice and on all animals that died before the end of the study. In addition to gross lesions, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland (rats only), esophagus, heart, kidney, liver, lung, mammary gland, large intestine (cecum, colon, rectum), mandibular or mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats only), prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), thymus, testis with epididymis and seminal vesicle, thyroid gland, trachea, urinary bladder and uterus. The kidney and liver of 125, 250, 500, and 1,000 ppm animals were also examined microscopically.	Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland (rats only), esophagus, gallbladder (mice only), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mammary gland, mandibular or mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats only), prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

14-DAY STUDY

All animals survived to the end of the study (Table 3). Final mean body weights and mean body weight gains of 4,000 ppm males and females were significantly lower than those of the controls. The mean body weight gain of 1,000 ppm males was slightly lower than that of the controls.

During the first 5 days of the study, feed consumption by 4,000 ppm males and females was lower than that by controls, but was similar to or greater than that by controls throughout the rest of the study. These findings are consistent with literature reports of a transient anorexic effect of methylphenidate hydrochloride. Rats exposed to 16, 62, 250, 1,000, or 4,000 ppm received approximate doses of 1, 5, 20, 90, or 380 mg/kg body weight per day (males) or 1, 5, 20, 90, or 360 mg/kg per day (females).

Clinical findings during the first week of the study included hyperactivity in 4,000 ppm males and females and in females exposed to 250 or 1,000 ppm methylphenidate hydrochloride; these animals appeared normal throughout the remainder of the study.

Absolute and relative liver weights of 4,000 ppm males and females were significantly greater than those of the controls, and the relative kidney weight of 4,000 ppm males was greater than that of the

TABLE 3
Survival, Mean Body Weights, and Feed Consumption of Rats in the 14-Day Feed Study of Methylphenidate Hydrochloride

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 2
Male							
0	5/5	155 ± 2	216 ± 4	61 ± 2		16.3	17.0
16	5/5	161 ± 1	215 ± 4	53 ± 3	99	16.0	16.4
62	5/5	159 ± 1	216 ± 4	57 ± 4	100	16.0	17.0
250	5/5	156 ± 2	212 ± 2	56 ± 2	98	15.5	16.6
1,000	5/5	159 ± 2	211 ± 3	52 ± 2*	98	15.1	16.4
4,000	5/5	159 ± 2	196 ± 4**	37 ± 3**	91	13.6	20.4
Female							
0	5/5	116 ± 1	143 ± 2	27 ± 2		11.3	11.1
16	5/5	119 ± 1	144 ± 2	25 ± 2	100	11.9	10.7
62	5/5	118 ± 1	143 ± 1	24 ± 2	99	11.7	10.7
250	5/5	116 ± 2	136 ± 3	20 ± 1	95	11.1	10.1
1,000	5/5	119 ± 2	142 ± 2	23 ± 2	99	10.2	12.3
4,000	5/5	118 ± 1	131 ± 3**	13 ± 3**	91	8.4	14.3

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
a Number of animals surviving at 14 days/number initially in group
b Weights are given as mean ± standard error.
c Feed consumption is expressed as grams per animal per day.

controls (Table F1). Serum alanine aminotransferase and aspartate aminotransferase activity levels of exposed rats were generally similar to those of the controls except in 4,000 ppm males where aspartate aminotransferase activity was lower than that of the controls (Table G1). Serum urea nitrogen levels of males exposed to 1,000 or 4,000 ppm and of all exposed groups of females except the 16 ppm group were significantly greater than those of the controls. Serum creatinine levels were significantly decreased in all male exposure groups.

There were no treatment-related gross lesions. Centrilobular hepatocellular hypertrophy was observed in four 4,000 ppm males and in all five 4,000 ppm females. These changes were not observed in animals exposed to lower concentrations of methylphenidate hydrochloride or in controls.

Because of the lower mean body weights and liver effects observed in 4,000 ppm males and females in the 14-day study, the high dose selected for the 13-week study was 2,000 ppm.

13-WEEK STUDY

One male and three females exposed to 125 ppm and one 250 ppm male died; these deaths were not considered related to chemical administration (Table 4). Final mean body weights of exposed males and females were similar to those of the controls. Mean body weight gains of males and females exposed to 500, 1,000, or 2,000 ppm and of females exposed to 250 ppm were significantly lower than those of the controls. During the first week of the study, feed consumption by 2,000 ppm rats was less than that by controls; there were no other consistent differences in feed consumption between control and exposed groups. Rats exposed to 125, 250, 500, 1,000, or 2,000 ppm received approximate doses of 7, 15, 30, 70, or 130 mg/kg per day (males) or 9, 18, 30, 70, or 150 mg/kg per day (females).

Clinical findings in 1,000 and 2,000 ppm females included slight hypersensitivity to touch, hyperactivity, and increased vocalization for weeks 1 or 2 of the study, and 2,000 ppm females were hyperactive during weeks 9 through 13. These clinical findings were not reported in males. Methylphenidate and other similar drugs have been shown to increase locomotive activity and to enhance stereotypical behavior in rats, but systematic measurements for these clinical findings were not conducted during this study.

Absolute and relative liver weights of male and female 2,000 ppm rats were significantly greater than those of the controls, as were relative liver weights of 1,000 ppm rats (Table F2). Relative kidney and brain weights of 1,000 and 2,000 ppm male and female rats were greater than those of the controls. Absolute brain weight of 1,000 ppm males and absolute and relative brain weights of 500 ppm males were greater than those of the controls. No chemical-related histopathologic lesions were observed.

No statistically significant differences were noted in nose-to-rump lengths measured prior to study initiation and at 4, 8, and 13 weeks into the study (Table H1). No treatment-related changes in bone length or bone density were noted at the end of the 13-week exposure period.

Dose selection rationale: Because of the lower mean body weight gains and the significant increase in absolute and relative liver weights in 2,000 ppm male and female rats, the high dose selected for the 2-year studies was 1,000 ppm.

TABLE 4
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of Methylphenidate Hydrochloride

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	131 ± 3	366 ± 7	236 ± 5		13.6	18.2
125	9/10[d]	131 ± 3	361 ± 8	229 ± 6	98	14.1	16.5
250	9/10[e]	132 ± 4	367 ± 9	233 ± 7	100	14.1	17.1
500	10/10	136 ± 2	348 ± 7	212 ± 6*	95	13.6	17.6
1,000	10/10	130 ± 3	351 ± 6	221 ± 5*	96	13.1	20.9[f]
2,000	10/10	133 ± 2	347 ± 6	214 ± 5**	95	12.6	17.7[f]
Female							
0	10/10	102 ± 1	215 ± 4	114 ± 3		10.5	12.0
125	7/10[e]	99 ± 2	204 ± 2	106 ± 2	95	10.3	11.5
250	10/10	100 ± 1	204 ± 4	104 ± 3*	95	10.2	11.2
500	10/10	104 ± 2	209 ± 3	105 ± 3*	97	9.4[f]	12.1
1,000	10/10	103 ± 2	204 ± 4	101 ± 4**	95	9.2[f]	12.2
2,000	10/10	102 ± 1	207 ± 3	104 ± 3**	96	9.6[f]	14.2

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.
[d] Week of death: 5 (death attributed to anesthetic administered during interim bleeding for studies not reported here)
[e] Week of death: All died during week 9 (deaths attributed to anesthetic administered during bleeding)
[f] Bedding in feed jars

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female rats receiving methylphenidate hydrochloride in feed for 2 years are presented in Table 5 and in Kaplan-Meier survival curves (Figure 2). Survival of exposed rats was similar to that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of exposed and control rats were similar until week 30 of the study (Figure 3 and Tables 6 and 7). Mean body weights of males exposed to 500 or 1,000 ppm were 3% to 10% lower than those of controls from week 30 to the end of the study. Mean body weights of females exposed to 500 or 1,000 ppm were 4% to 24% lower than that of controls from week 30 to the end of the study. Final mean body weights of males exposed to 100, 500, or 1,000 ppm were 102%, 95%, and 90% of control values. Final mean body weights of exposed females were 96%, 89%, and 78% of the controls. Feed consumption by exposed animals was similar to that by the controls (Tables J1 and J2). Exposures of 100, 500, or 1,000 ppm were estimated to deliver 5, 25, and 50 mg methylphenidate hydrochloride per kilogram body weight per day for males and females.

TABLE 5
Survival of Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

	0 ppm	100 ppm	500 ppm	1,000 ppm
Male				
Animals initially in study	70	70	70	70
9-Month interim evaluation[a]	10	10	10	9
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]		1		
Moribund	14	9	7	9
Natural deaths	8	7	9	8
Animals surviving to study termination	28	33	34	34[e]
Percent probability of survival at end of study[b]	57	68	69	69
Mean survival (days)[c]	587	585	598	582
Survival analysis[d]	P=0.529N	P=0.344N	P=0.257N	P=0.426N
Female				
Animals initially in study	70	70	70	70
9-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	10	10	10
Moribund	13	12	10	7
Natural deaths	6	6	4	4
Animals surviving to study termination	31[f]	32[f]	36	39[e]
Percent probability of survival at end of study[b]	63	64	73	79
Mean survival (days)[c]	601	611	603	610
Survival analysis[d]	P=0.096N	P=0.818N	P=0.426N	P=0.154N

a Censored from survival analyses
b Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
c Mean of all deaths (uncensored, censored, and terminal sacrifice)
d The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or lower mortality in an exposure group is indicated by N.
e Includes one animal that died during the last week of the study
f Includes two animals that died during the last week of the study

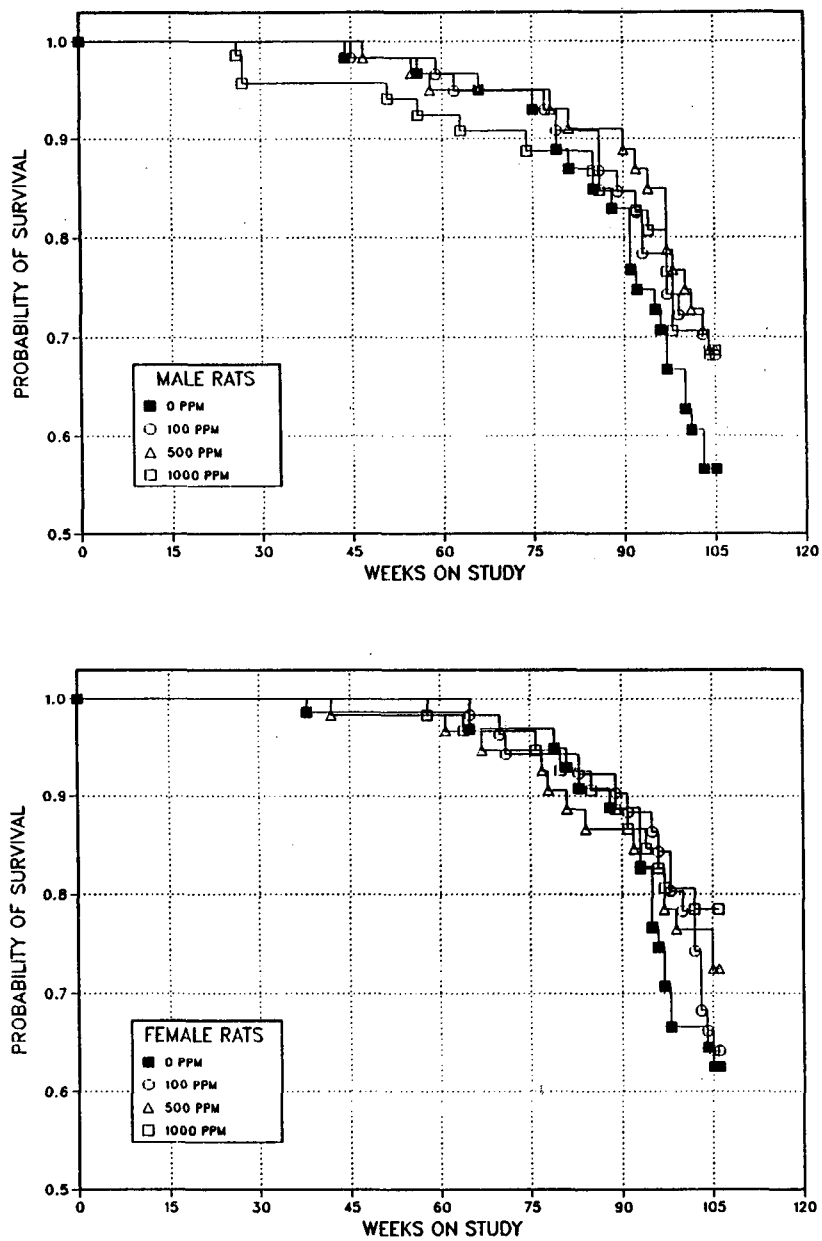


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Methylphenidate Hydrochloride in Feed for 2 Years

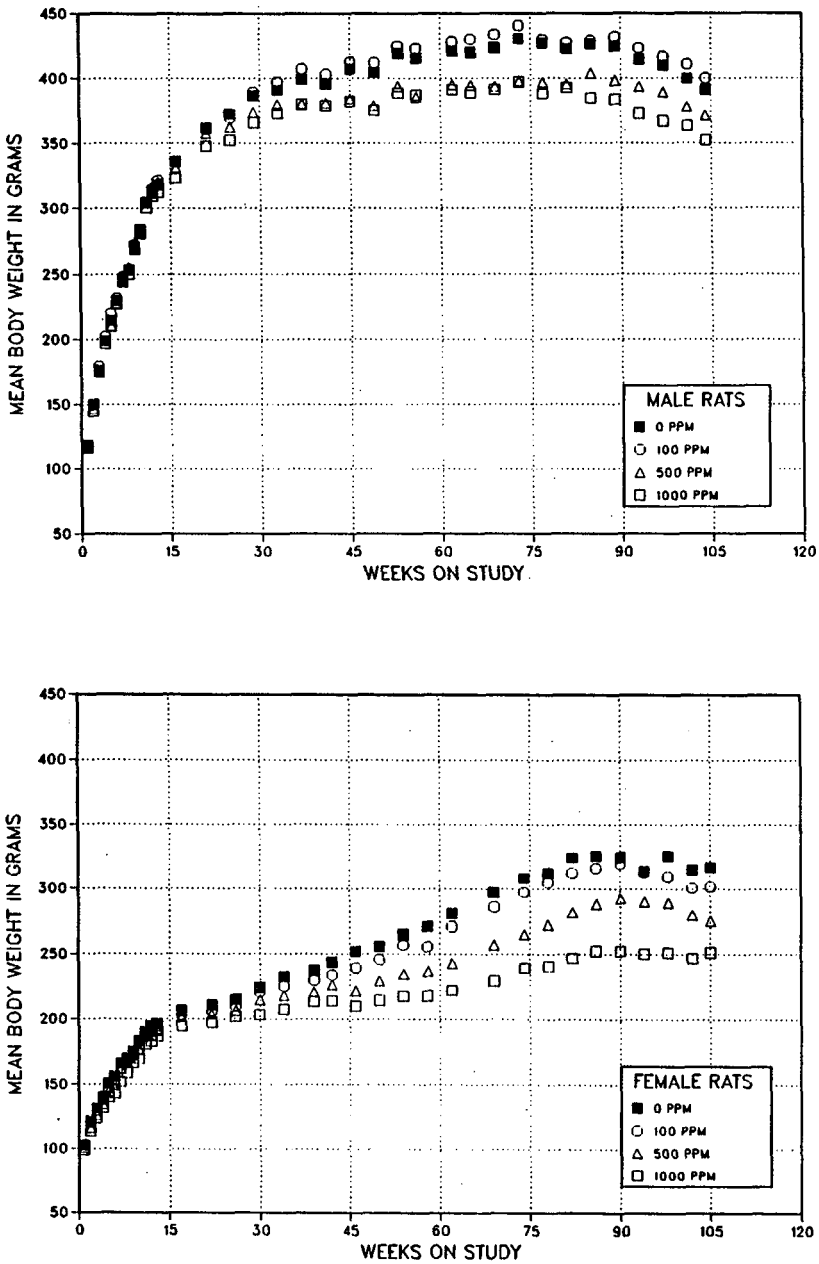


FIGURE 3
Growth Curves for Male and Female Rats Administered Methylphenidate Hydrochloride in Feed for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm No. of Survivors	500 ppm Av. Wt. (g)	500 ppm Wt. (% of controls)	500 ppm No. of Survivors	1,000 ppm Av. Wt. (g)	1,000 ppm Wt. (% of controls)	1,000 ppm No. of Survivors
1	118	70	118	99	70	118	100	70	117	99	70
2	150	70	150	100	70	147	98	70	145	96	70
3	176	70	179	102	70	175	100	70	176	100	70
4	199	70	202	102	70	199	100	70	197	99	70
5	215	70	220	102	70	211	98	70	211	98	70
6	230	70	232	101	70	228	99	70	228	99	70
7	246	70	248	101	70	249	101	70	245	99	70
8	254	70	254	100	69	256	101	70	250	99	70
9	271	70	273	101	69	274	101	70	269	99	70
10	284	70	284	100	69	282	99	70	281	99	70
11	299	70	301	101	69	300	100	70	297	99	70
12	314	70	315	100	69	314	100	70	310	99	70
13	318	70	321	101	69	320	101	70	312	98	70
16	336	70	337	100	69	332	99	70	323	96	70
21	362	70	362	100	69	358	99	70	348	96	70
25	372	70	370	99	69	362	97	70	352	95	70
29	387	70	389	101	69	374	97	70	366	95	67
33	391	70	397	102	69	380	97	70	373	96	67
37	399	70	407	102	69	380	95	70	380	95	67
41[a]	396	60	403	102	59	381	96	60	379	96	58
45	407	59	413	101	59	384	94	60	382	94	58
49	405	59	412	102	58	379	94	59	376	93	58
53	419	59	425	101	58	394	94	59	388	93	57
56	415	58	423	102	58	385	93	58	387	93	56
62	421	58	428	102	57	395	94	57	391	93	56
65	420	58	430	102	56	395	94	57	389	93	55
69[a]	424	47	433	102	46	393	93	47	391	92	45
73	431	47	441	102	46	398	93	47	397	92	45
77	427	46	430	101	46	397	93	47	388	91	44
81	423	44	427	101	44	395	94	46	393	93	44
85	426	43	429	101	44	404	95	45	385	90	44
89	425	41	432	102	42	398	94	45	384	90	42
93	414	37	423	102	40	393	95	42	373	90	40
97	410	35	417	102	38	389	95	42	367	90	40
101	400	30	411	103	36	378	95	36	364	91	35
104	391	28	400	102	34	372	95	35	353	90	34
Mean for weeks											
1-13	236		238	101		236	100		234	99	
14-52	384		388	101		370	96		364	95	
53-104	418		425	102		392	94		382	91	

[a] Interim evaluations occurred during weeks 40 and 66.

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm No. of Survivors	500 ppm Av. Wt. (g)	500 ppm Wt. (% of controls)	500 ppm No. of Survivors	1,000 ppm Av. Wt. (g)	1,000 ppm Wt. (% of controls)	1,000 ppm No. of Survivors
1	103	70	103	101	70	101	98	70	99	96	70
2	122	70	121	99	70	117	96	70	114	93	70
3	132	70	130	99	70	126	96	70	124	94	70
4	141	70	138	98	70	134	96	70	132	94	70
5	151	70	147	97	70	144	96	70	140	93	70
6	156	70	150	96	70	154	98	70	143	92	70
7	167	70	162	97	70	162	98	70	152	91	70
8	171	70	168	99	70	168	98	70	159	93	70
9	176	70	173	98	70	173	98	70	167	95	70
10	184	70	178	97	70	177	97	70	170	93	70
11	188	70	186	99	70	185	98	70	179	95	70
12	195	70	191	98	70	189	97	70	184	94	70
13	197	70	193	98	70	192	98	70	188	95	70
17	207	70	203	98	70	202	97	70	195	94	70
22	211	70	206	98	70	204	97	70	198	94	70
26	215	70	210	98	70	207	96	70	202	94	70
30	225	70	221	98	70	215	96	70	204	91	70
34	233	70	226	97	70	218	94	70	208	89	70
39	238	69	230	97	70	221	93	70	214	90	70
42[a]	244	59	234	96	60	227	93	60	214	88	60
46	252	59	240	95	60	222	88	59	210	83	60
50	256	59	246	96	60	230	90	59	215	84	60
54	265	59	257	97	60	235	89	59	218	82	60
58	271	59	256	94	60	237	87	59	218	80	60
62	281	59	271	97	60	243	87	58	222	79	59
69[a]	297	48	286	96	49	257	87	47	230	77	48
74	308	48	298	97	47	266	86	47	240	78	48
78	312	48	305	98	47	273	87	46	241	77	47
82	324	46	313	96	47	282	87	44	247	76	46
86	326	45	316	97	46	288	89	43	253	78	45
90	325	44	320	98	45	293	90	43	252	78	44
94	314	41	314	100	44	290	92	41	251	80	43
98	326	35	310	95	42	290	89	39	251	77	40
102	315	33	301	96	38	280	89	38	247	78	40
Mean for weeks											
1-13	160		157	98		156	98		150	94	
14-52	231		224	97		216	94		207	90	
53-102	305		296	97		270	89		239	78	

[a] Interim evaluations occurred during weeks 40 and 66.

Absolute and relative brain weights of 1,000 ppm females were greater than those of the controls, as was the relative brain weight of 500 ppm females (Tables F3 and F4).

The only treatment-related clinical finding was an increased incidence in fighting among the group-housed 1,000 ppm males.

Hematology and Clinical Chemistry

At the 9-month interim evaluation, levels of serum alanine aminotransferase activity were slightly decreased in 500 and 1,000 ppm males and at 15 months were decreased in all exposed groups of males. Serum alanine aminotransferase levels in exposed females were generally similar to those of the controls (Tables G2 and G3). Leukocyte and lymphocyte counts were generally increased in males and females at the 9-month interim evaluation; the increases were statistically significant in 1,000 ppm males and females.

Pathology and Statistical Evaluation

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

Adrenal Gland: The combined incidences of benign and malignant adrenal medulla pheochromocytomas in exposed groups of male rats were significantly lower than that in the controls (Tables 8 and A3), and the incidence in 500 ppm males was slightly below the range in historical controls (Table A4). The incidence of adrenal medulla hyperplasia in exposed males was similar to that of the controls.

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Gland of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

Dose (ppm)	0	100	500	1,000
9-Month Interim Evaluation				
Adrenal Medulla[a]	10	10	10	9
Hyperplasia[b]	0	0	0	0
Benign Pheochromocytoma	0	0	0	0
Malignant Pheochromocytoma	0	0	0	0
15-Month Interim Evaluation				
Adrenal Medulla	10	10	10	10
Hyperplasia	0	0	1	0
Benign Pheochromocytoma	0	0	0	1
Malignant Pheochromocytoma	0	0	0	0
2-Year Study				
Adrenal Medulla	49	48	49	50
Hyperplasia	16	12	16	22
Benign Pheochromocytoma				
Overall rates[c]	17/49 (35%)	6/48 (13%)	5/49 (10%)	10/50 (20%)
Adjusted rates[d]	50.8%	17.9%	13.8%	30.3%
Terminal rates[e]	12/28 (43%)	5/32 (16%)	4/34 (12%)	10/33 (30%)
First incidence (days)	639	676	653	729 (T)
Logistic regression tests[f]	P=0.151N	P=0.005N	P=0.001N	P=0.049N
Malignant Pheochromocytoma				
Overall rates	1/49 (2%)	1/48 (2%)	1/49 (2%)	0/50 (0%)
Adjusted rates	3.6%	3.1%	2.9%	0.0%
Terminal rates	1/28 (4%)	1/32 (3%)	1/34 (3%)	0/33 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	–[g]
Logistic regression tests	P=0.273N	P=0.732N	P=0.718N	P=0.467N
Benign or Malignant Pheochromocytoma[h]				
Overall rates	18/49 (37%)	7/48 (15%)	5/49 (10%)	10/50 (20%)
Adjusted rates	53.9%	20.9%	13.8%	30.3%
Terminal rates	13/28 (46%)	6/32 (19%)	4/34 (12%)	10/33 (30%)
First incidence (days)	639	676	653	729 (T)
Logistic regression tests	P=0.087N	P=0.006N	P<0.001N	P=0.029N

(T)Terminal sacrifice
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Number of animals with neoplasm per number of animals with organ examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[g] Not applicable; no neoplasms in animal group
[h] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 445/1,234 (36.1% ± 11.0%); range 14%-63%

Mammary Gland: In female rats, the incidence of mammary gland fibroadenomas occurred with a significant negative trend and the incidences in the 500 and 1,000 ppm groups were significantly lower than in controls (Tables 9 and B3). The historical control incidence in recent NTP feed studies for fibroadenomas of the mammary gland in female rats is 484/1,251 (39%) with a range of 8% to 58% (Table B4). The incidences of mammary gland fibroadenomas in 500 and 1,000 ppm females were 12% and 10%, respectively, and these incidences are less than the incidences in all but one of 25 studies in the current historical database. Additionally, there were decreases in the incidences of galactoceles and lactation in exposed females (Tables 9 and B5).

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

Dose (ppm)	0	100	500	1,000
9-Month Interim Evaluation				
Mammary Gland[a]	10	9	8	10
Lactation[b]	0	0	0	0
Galactocele	0	0	0	0
Fibroadenoma	0	0	0	0
15-Month Interim Evaluation				
Mammary Gland	10	10	10	10
Lactation	0	0	0	0
Galactocele	0	0	0	0
Fibroadenoma	0	0	0	0
2-Year Study				
Mammary Gland	49	50	48	50
Lactation	35	36	27	25**
Galactocele	10	6	2**	1**
Fibroadenoma[c]				
Overall rates[d]	15/49 (30%)	13/50 (26%)	6/48 (12%)	5/50 (10%)
Adjusted rates[e]	45.3%	38.0%	15.9%	11.7%
Terminal rates[f]	13/31 (42%)	11/32 (34%)	5/36 (14%)	3/39 (8%)
First incidence (days)	680	720	638	559
Logistic regression tests[g]	P=0.002N	P=0.280N	P=0.014N	P=0.008N

** Significantly different (P≤0.01) from the control group by the logistic regression test
a Number of animals with organ examined microscopically
b Number of animals with lesion
c Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 484/1,251 (38.7% ± 13.5%); range 8%-58%
d Number of animals with neoplasm per number of animals necropsied (100 and 1,000 ppm groups) or examined microscopically (0 and 500 ppm groups)
e Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
f Observed incidence at terminal kill
g Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.

MICE

14-DAY STUDY

Three 4,000 ppm males died during the last week of the study, one on the last day. All other mice survived until the end of the study (Table 10). The final mean body weight of 4,000 ppm females was significantly less than that of the controls and the mean body weight gains of 1,000 and 4,000 ppm males and females were significantly less than those of the controls. Feed consumption by 1,000 and 4,000 ppm males and females was less than that by controls during the first week of the study. Mice exposed to 16, 62, 250, 1,000, or 4,000 ppm received approximate doses of 2, 10, 40, 120, or 460 mg methylphenidate hydrochloride/kg body weight per day (males) or 2, 10, 40, 140, or 410 mg/kg per day (females). Hyperactivity was observed during the second week of the study in some 4,000 ppm males, but not in other exposed groups of mice.

Absolute and relative liver weights of all exposed groups of males and of 4,000 ppm females were significantly greater than those of the controls (Table F5). Absolute and relative thymus weights of 4,000 ppm females were less than those of the controls. There were no significant clinical chemistry findings to indicate damage to the liver or other organ systems (Table G4).

Chemical-related lesions were found in the kidney and liver. Slight, multifocal tubule epithelial cell degeneration and necrosis were found in the kidneys of two 4,000 ppm males that died before the end of the study. However, renal tubule degeneration and necrosis were not found in mice that lived to the end of the study.

Centrilobular hepatocellular hypertrophy was observed in all mice exposed to 1,000 or 4,000 ppm and in males exposed to 250 ppm. In general, the severity was dose related and the hypertrophy was more severe in males than in females.

Because of decreased survival in 4,000 ppm males, 2,000 ppm was the high dose selected for the 13-week study.

TABLE 10
Survival, Mean Body Weights, and Feed Consumption of Mice in the 14-Day Feed Study of Methylphenidate Hydrochloride

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 2
Male							
0	5/5	20.5 ± 0.5	24.1 ± 0.5	3.6 ± 0.2		3.3	3.3
16	5/5	22.1 ± 0.6	25.2 ± 0.9	3.1 ± 0.3	104	3.2	3.7
62	5/5	22.0 ± 0.5	24.6 ± 0.5	2.6 ± 0.0	102	3.0	3.9
250	5/5	20.2 ± 0.4	23.7 ± 0.4	3.6 ± 0.3	98	2.9	4.4
1,000	5/5	20.7 ± 0.4	22.9 ± 0.5	2.2 ± 0.3**	95	2.4	2.7
4,000	2/5[d]	22.2 ± 0.5	22.7 ± 1.5	0.6 ± 0.6**	94	2.0	3.2
Female							
0	5/5	16.3 ± 0.4	19.4 ± 0.2	3.1 ± 0.3		2.0	2.4
16	5/5	16.1 ± 0.3	19.2 ± 0.5	3.1 ± 0.2	99	1.9	3.3
62	5/5	16.8 ± 0.3	18.9 ± 0.4	2.1 ± 0.3	97	2.0	3.2
250	5/5	15.9 ± 0.3	19.4 ± 0.5	3.5 ± 0.4	100	1.9	3.6
1,000	5/5	16.7 ± 0.2	18.7 ± 0.3	2.0 ± 0.3*	96	1.6	3.2
4,000	5/5	16.5 ± 0.2	17.3 ± 0.2**	0.9 ± 0.2**	89	1.4	2.1

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
a Number of animals surviving at 14 days/number initially in group
b Weights are given as mean ± standard error.
c Feed consumption is expressed as grams per animal per day.
d Day of death: 11, 11, 14

13-WEEK STUDY

One control male and one 1,000 ppm male died before the end of the study, but the deaths were attributed to fighting among group-housed males. The remaining animals survived to the end of the study (Table 11). Final mean body weights of all exposed groups of males, with the exception of 125 ppm males, were significantly lower than those of the controls; all exposed groups had significantly lower mean body weight gains. The final mean body weight of males exposed to 250, 500, or 1,000 ppm was 90%, 87%, or 88% of the controls, respectively. The final mean body weight of 2,000 ppm males was 81% of the controls. The final mean body weight of 2,000 ppm females was 87% that of the controls, and reduced body weight gains were observed in females exposed to 250 ppm or greater methylphenidate hydrochloride.

Mice exposed to 125, 250, 500, 1,000, or 2,000 ppm methylphenidate hydrochloride were estimated to receive approximately 15, 30, 70, 115, or 230 mg/kg body weight per day (males) or 15, 30, 70, 125, or 260 mg/kg per day (females).

The absolute and relative liver weights of 1,000 and 2,000 ppm mice were significantly greater than those of the controls, as were the relative liver weights of male mice in lower exposure groups (Table F6). Other increases in relative organ weights were attributed to decreases in body weights; in most cases, the absolute organ weight was not increased.

TABLE 11
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of Methylphenidate Hydrochloride

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1[d]	Week 13
Male							
0	9/10[e]	22.8 ± 0.4	35.9 ± 0.5	13.2 ± 0.6		2.9	4.1
125	10/10	23.1 ± 0.2	33.6 ± 0.5	10.5 ± 0.4*	94	3.0	3.7
250	10/10	22.8 ± 0.4	32.4 ± 1.1**	9.6 ± 1.1**	90	3.1	3.7
500	10/10	22.5 ± 0.6	31.1 ± 1.1**	8.6 ± 1.0**	87	3.7	3.7
1,000	9/10[f]	23.5 ± 0.3	31.7 ± 0.5**	8.2 ± 0.5**	88	2.7	3.6
2,000	10/10	22.9 ± 0.3	28.9 ± 0.7**	6.0 ± 0.7**	81	2.2	3.7
Female							
0	10/10	17.4 ± 0.3	28.5 ± 1.5	11.2 ± 1.3		4.3	2.7
125	10/10	17.7 ± 0.3	27.1 ± 0.5	9.4 ± 0.5	95	2.7	2.5
250	10/10	17.4 ± 0.3	26.6 ± 0.7	9.2 ± 0.6*	93	3.1	2.6
500	10/10	17.6 ± 0.2	26.6 ± 0.6	9.0 ± 0.4*	93	3.6	2.7
1,000	10/10	17.7 ± 0.2	26.6 ± 0.6	8.9 ± 0.5*	93	2.9	2.7
2,000	10/10	17.3 ± 0.2	24.8 ± 0.3**	7.5 ± 0.2**	87	2.7	2.8

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
a Number of animals surviving/number initially in group
b Weights and weight changes are given as mean ± standard error.
c Feed consumption is expressed as grams per animal per day.
d Due to feed spillage during week one, mouse jars were placed inside rat jars for the remainder of the study.
e Week of death: 3 (death was attributed to fighting)
f Week of death: 6 (death was attributed to fighting)

Centrilobular hypertrophy and degeneration or necrosis of individual hepatocytes were observed in males exposed to 500, 1,000, or 2,000 ppm (Table 12). Degeneration and minimal necrosis were seen in 250 and 125 ppm males, but hypertrophy was not. Similar histopathologic lesions were not observed in females.

Dose selection rationale: Because of lower final mean body weights in males and females and liver lesions observed in 1,000 and 2,000 ppm male mice in the 13-week study, a high dose of 500 ppm was selected for the 2-year mouse study.

TABLE 12
Incidences of Nonneoplastic Lesions of the Liver of Male Mice in the 13-Week Feed Study of Methylphenidate Hydrochloride

Dose (ppm)	0	125	250	500	1,000	2,000
Liver[a]	9	10	10	10	9	10
Centrilobular hypertrophy[b]	0	0	0	1 (1.0)[c]	8** (1.1)	10** (2.0)
Degeneration	0	1 (1.0)	1 (2.0)	7** (1.1)	7** (1.1)	7** (2.0)
Necrosis	1 (1.0)	0	1 (1.0)	2 (1.0)	1 (1.0)	7** (1.7)

** Significantly different (P≤0.01) from the control group by the Fisher exact test.
[a] Number of animals with liver examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals (1=minimal; 2=mild; 3=moderate; 4=marked)

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female mice receiving methylphenidate hydrochloride in feed for 2 years are presented in Table 13 and in Kaplan-Meier survival curves (Figure 4). Survival of all exposed groups of male and female mice was similar to that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Throughout much of the study, mean body weights of 250 and 500 ppm males were approximately 3% to 11% lower than those of the controls and mean body weights of 250 ppm females were 3% to 7% lower than those of the controls (Figure 5 and Tables 14 and 15). Final mean body weights of mice exposed to 50, 250, or 500 ppm methylphenidate hydrochloride were 97%, 89%, or 93% (males) and 98%, 93%, or 97% (females) that of the controls. Feed consumption by exposed mice was similar to that by controls (Tables J3 and J4). Exposures of 50, 250, and 500 ppm were estimated to provide 6, 30, and 60 mg methylphenidate hydrochloride per kilogram body weight per day for males and 8, 40, and 80 mg per kilogram body weight per day for females. There were no chemical-related clinical findings.

Hematology and Clinical Chemistry

There were no biologically significant differences in hematology or clinical chemistry parameters at the 9- or 15-month interim evaluations (Tables G5 and G6).

TABLE 13
Survival of Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride

	0 ppm	50 ppm	250 ppm	500 ppm
Male				
Animals initially in study	70	70	70	70
9-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	10	10	10
Moribund	2	2	4	4
Natural deaths	3	3	2	5
Animals surviving to study termination	45	45	44[e]	41
Percent probability of survival at end of study[b]	90	90	88	82
Mean survival (days)[c]	618	623	615	616
Survival analysis[d]	P=0.219	P=1.000N	P=0.967	P=0.414
Female				
Animals initially in study	69	69	70	70
9-Month interim evaluation[a]	10	9	10	10
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	1			
Missing[a]		1		
Moribund	6	7	7	6
Natural deaths	5	7	6	
Animals surviving to study termination	37[e]	35[e]	37	44
Percent probability of survival at end of study[b]	78	73	75	88
Mean survival (days)[c]	604	582	603	627
Survival analysis[d]	P=0.102N	P=0.597	P=0.888	P=0.235N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or lower mortality in an exposure group is indicated by N.
[e] Includes one animal that died during the last week of the study

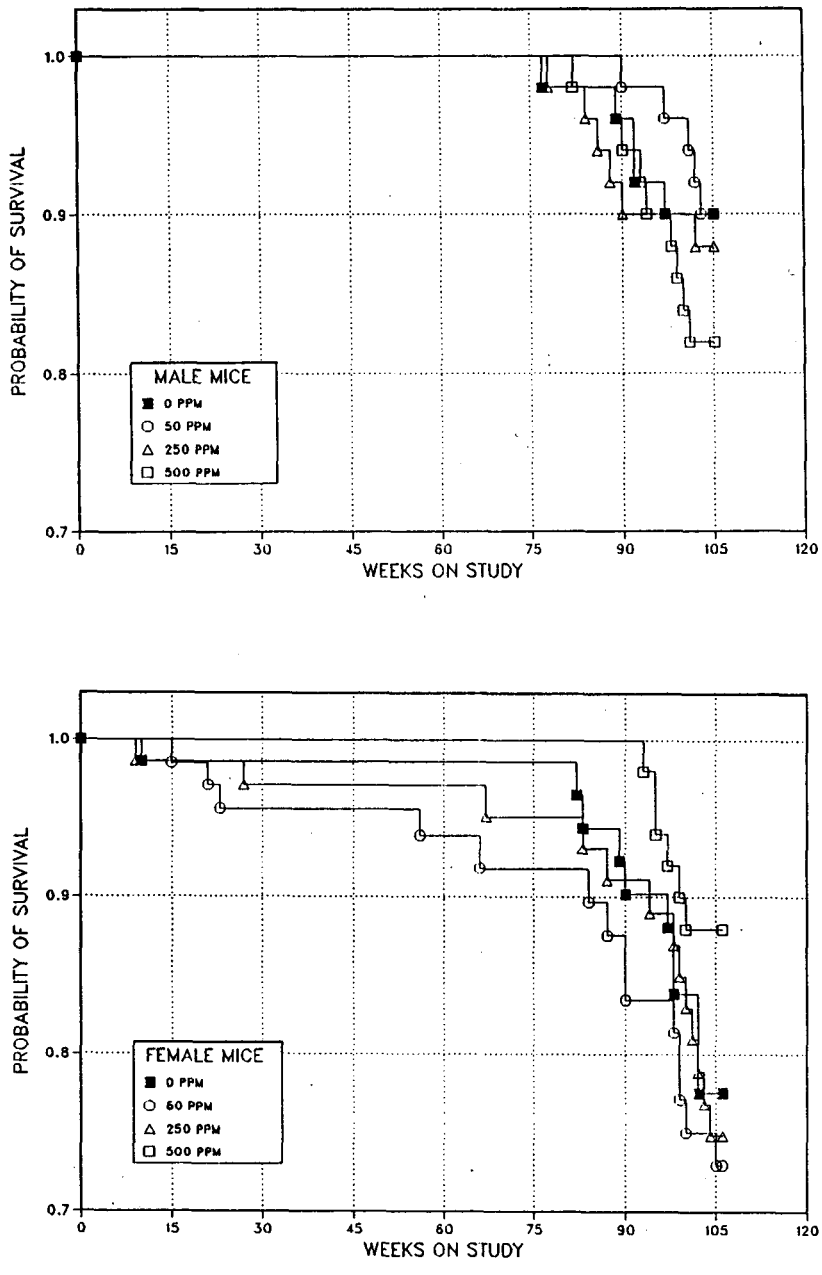


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered Methylphenidate Hydrochloride in Feed for 2 Years

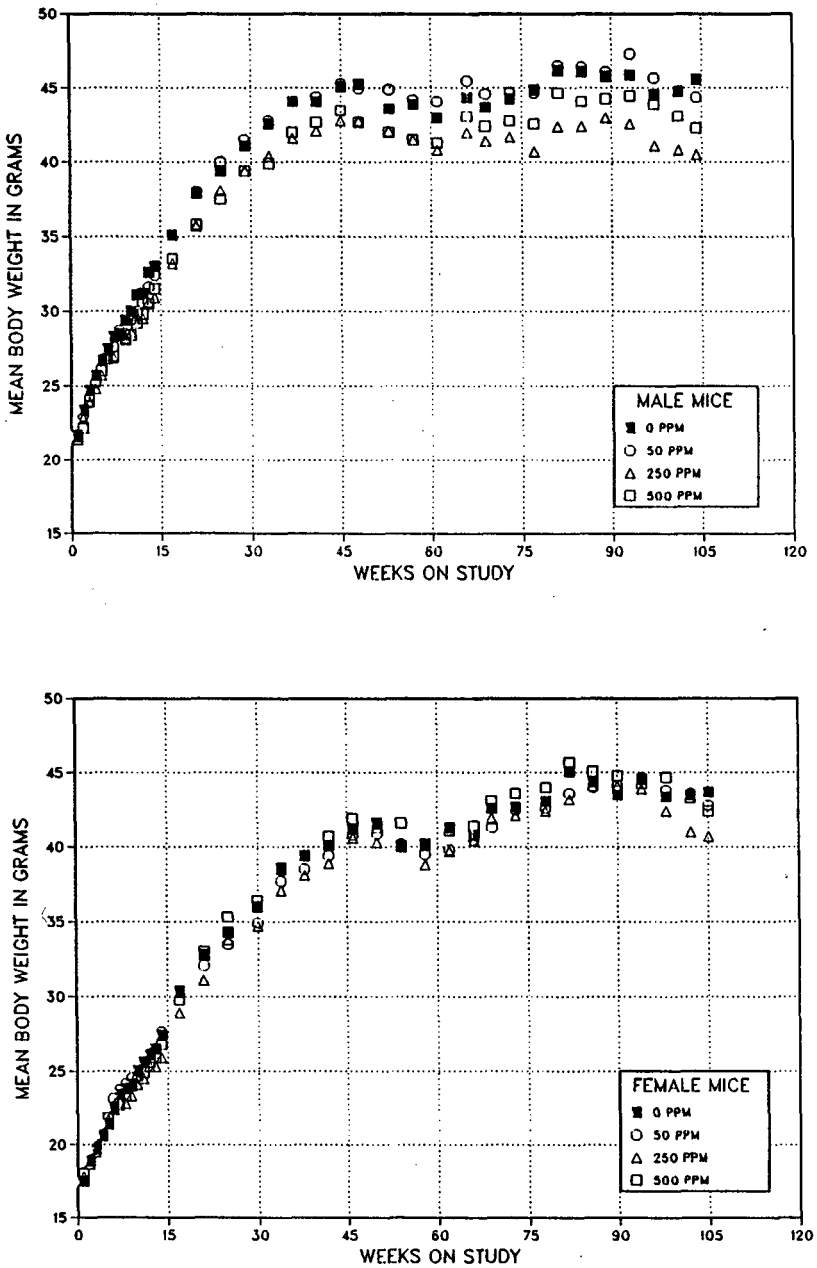


FIGURE 5
Growth Curves for Male and Female Mice Administered Methylphenidate Hydrochloride in Feed for 2 Years

TABLE 14
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride

Weeks on Study	0 ppm		50 ppm			250 ppm			500 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	21.7	70	21.6	100	70	21.4	99	70	21.4	99	70
2	23.4	70	23.0	98	70	22.8	97	70	22.2	95	70
3	24.7	70	24.3	98	70	23.9	97	70	24.0	97	70
4	25.7	70	25.2	98	70	24.8	97	70	25.3	98	70
5	26.7	70	26.8	100	70	25.7	96	70	26.0	97	70
6	27.5	70	27.4	100	70	27.0	98	70	26.9	98	70
7	28.3	70	27.6	98	70	26.9	95	70	27.0	95	70
8	28.5	70	28.7	101	70	28.4	100	70	28.5	100	70
9	29.4	70	28.5	97	70	28.2	96	70	28.1	96	70
10	30.0	70	29.4	98	70	28.6	93	70	28.4	95	70
11	31.1	70	30.0	97	70	29.7	96	70	29.2	94	70
12	31.2	70	30.6	98	70	29.5	95	70	29.8	96	70
13	32.6	70	31.6	97	70	30.6	94	70	30.5	94	70
14	33.0	70	32.4	98	70	30.9	94	70	31.5	96	70
17	35.1	70	35.1	100	70	33.2	95	70	33.5	95	70
21	37.9	70	38.0	100	70	35.7	94	70	35.8	95	70
25	39.4	70	40.0	102	70	38.1	97	70	37.5	95	70
29	41.1	70	41.5	101	70	39.4	96	70	39.4	96	70
33	42.6	70	42.8	101	70	40.4	95	70	39.9	94	70
37	44.1	70	44.1	100	70	41.6	94	70	42.0	95	70
41[a]	44.1	60	44.4	101	60	42.1	96	60	42.7	97	60
45	45.1	60	45.3	100	60	42.8	95	60	43.5	97	60
48	45.3	60	45.0	99	60	42.8	95	60	42.7	94	60
53	43.6	60	44.9	103	60	42.1	97	60	42.0	96	60
57	43.9	60	44.2	101	60	41.5	95	60	41.5	95	60
61	43.0	60	44.1	103	60	40.8	95	60	41.3	96	60
66[a]	44.4	50	45.5	103	50	42.0	95	50	43.1	97	50
69	43.7	50	44.6	102	50	41.4	95	50	42.4	97	50
73	44.3	50	44.7	101	50	41.7	94	50	42.8	97	50
77	44.9	50	44.7	100	50	40.7	91	50	42.6	95	50
81	46.2	49	46.5	101	50	42.4	92	49	44.7	97	50
85	46.1	49	46.4	101	50	42.4	92	48	44.1	96	49
89	45.8	49	46.1	101	50	43.0	94	46	44.3	97	49
93	45.9	46	47.3	103	49	42.6	93	45	44.5	97	45
97	44.6	46	45.7	103	49	41.1	92	45	43.9	98	45
101	44.8	45	44.8	100	48	40.8	91	45	43.1	96	42
104	45.6	45	44.4	97	45	40.5	89	44	42.3	93	41
Mean for weeks											
1-13	27.8		27.3	98		26.7	96		26.7	96	
14-52	40.8		40.9	100		38.7	95		38.9	95	
53-104	44.8		45.3	101		41.6	93		43.0	96	

[a] Interim evaluations occurred during weeks 39 and 65.

TABLE 15
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	50 ppm Av. Wt. (g)	50 ppm Wt. (% of controls)	50 ppm No. of Survivors	250 ppm Av. Wt. (g)	250 ppm Wt. (% of controls)	250 ppm No. of Survivors	500 ppm Av. Wt. (g)	500 ppm Wt. (% of controls)	500 ppm No. of Survivors
1	17.5	69	18.1	103	69	17.8	102	70	18.0	103	70
2	18.9	69	19.0	101	69	18.7	99	70	18.9	100	70
3	19.8	69	19.9	101	68	19.5	99	70	19.7	100	70
4	20.6	69	20.7	101	68	20.7	101	70	20.6	100	70
5	21.4	69	21.8	102	68	21.7	101	70	21.8	102	70
6	22.5	69	23.1	103	68	22.7	101	70	22.4	100	70
7	23.4	69	23.7	101	68	22.9	98	70	22.7	97	70
8	23.8	69	24.1	101	68	22.8	96	70	23.3	98	70
9	24.0	69	24.5	102	68	23.3	97	69	24.1	100	70
10	25.0	69	25.0	100	68	24.1	96	69	24.7	99	70
11	25.6	68	25.6	100	68	24.5	96	69	24.9	97	70
12	26.1	68	26.2	100	68	25.3	97	69	25.6	98	70
13	26.5	68	26.2	99	68	25.3	96	69	25.9	98	70
14	27.4	68	27.6	101	68	25.9	95	69	26.8	98	70
17	30.4	68	30.3	100	67	28.9	95	69	29.8	98	70
21	32.8	68	32.1	98	66	31.1	95	69	33.0	101	70
25	34.3	68	33.5	98	65	33.8	99	69	35.3	103	70
30	36.0	68	34.9	97	65	34.7	96	68	36.4	101	70
34	38.5	68	37.7	98	65	37.1	96	68	38.6	100	70
38	39.4	68	38.5	98	65	38.1	97	68	39.4	100	70
42[a]	40.1	58	39.4	98	56	38.9	97	58	40.7	102	60
46	41.2	58	40.8	99	56	40.6	99	58	41.9	102	60
50	41.6	58	40.9	98	56	40.3	97	58	41.3	99	60
54	40.1	57	40.2	100	56	40.0	100	58	41.6	104	60
58	40.2	57	39.5	98	55	38.8	97	58	40.1	100	60
62	41.3	57	39.8	96	55	39.7	96	58	41.1	100	60
66[a]	40.8	47	40.5	99	45	40.4	99	48	41.4	102	50
69	42.6	47	41.3	97	44	41.9	98	47	43.1	101	50
73	42.7	47	42.5	100	44	42.1	99	47	43.6	102	50
78	43.1	47	42.6	99	44	42.4	98	47	44.0	102	50
82	45.1	47	43.6	97	44	43.2	96	47	45.7	101	50
86	44.4	45	44.0	99	43	44.1	99	46	45.1	102	50
90	43.5	44	44.1	101	42	44.1	101	45	44.8	103	50
94	44.6	43	44.7	100	40	43.9	98	45	44.3	99	49
98	43.4	42	43.8	101	40	42.4	98	44	44.7	103	46
102	43.5	40	43.6	100	36	41.0	94	40	43.3	100	44
105	43.7	37	42.8	98	36	40.7	93	37	42.4	97	44
Mean for weeks											
1-13	22.7		22.9	101		22.3	98		22.5	99	
14-52	36.2		35.6	98		34.9	96		36.3	100	
53-105	42.8		42.2	99		41.8	98		43.2	101	

[a] Interim evaluations occurred during weeks 40 and 65.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions in the liver and lung. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: At the 9- and 15-month interim evaluations, the relative liver weights of all groups of exposed males except those exposed to 50 ppm at 9 months were greater than those of the controls, as were the absolute liver weights of all exposed groups of females (Tables F7 and F8). Relative liver weights were also increased in exposed female groups. Other absolute and relative organ weights of exposed mice were generally similar to those of the controls.

The incidences of hepatocellular adenoma and hepatoblastoma and the combined incidence of hepatocellular neoplasms were significantly increased in 500 ppm male mice (Tables 16 and C3). The incidences of adenoma and adenoma or carcinoma (combined) were also significantly increased in 500 ppm females (Tables 16 and D3). The rate in 500 ppm males in this study exceeds the rate observed in all but one of the studies included in the current historical database, and the rate in 500 ppm females is far above the control rate of any of the studies. There was also an increase in the number of exposed animals with multiple adenomas. Additionally, there was a significantly increased incidence of hepatoblastoma in 500 ppm males. Hepatoblastoma is a rare neoplasm, occurring in 0/1,366 male and 1/1,363 female historical control mice. The incidence of eosinophilic foci was increased in 500 ppm males and females (Tables 16, C5, and D5). Foci of hepatocellular alteration, hepatocellular adenoma, and hepatocellular carcinoma are thought to represent a spectrum that constitutes the progression of proliferative liver lesions. The increased incidences of adenomas and eosinophilic foci in 500 ppm male and female mice and in hepatoblastomas in 500 ppm males were considered related to methylphenidate hydrochloride administration.

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride

Dose (ppm)	0	50	250	500
Male				
9-Month Interim Evaluation				
Liver[a]	10	10	10	10
Eosinophilic Foci[b]	0	0	0	0
Hepatocellular Adenoma	0	0	1	0
Hepatocellular Adenoma, Multiple	0	0	0	0
Hepatocellular Carcinoma	0	0	0	0
Hepatoblastoma	0	0	0	0
15-Month Interim Evaluation				
Liver	10	10	10	10
Basophilic Foci	0	0	1	1
Clear Cell Foci	1	0	1	0
Eosinophilic Foci	0	1	0	0
All Foci	1	1	2	1
Hepatocellular Adenoma	2	0	1	1
Hepatocellular Adenoma, Multiple	0	0	0	1
Hepatocellular Carcinoma	0	0	0	1
Hepatoblastoma	0	0	0	0
2-Year Study				
Liver	50	50	50	50
Basophilic Foci	1	2	4	0
Clear Cell Foci	4	3	2	6
Eosinophilic Foci	6	8	9	14*
All Foci	9	12	14	18*
Hepatocellular Adenoma, Multiple	5	10	6	14*
Hepatocellular Adenoma (single or multiple)				
Overall rates[c]	18/50 (36%)	18/50 (36%)	16/50 (32%)	29/50 (58%)
Adjusted rates[d]	39.1%	39.1%	35.5%	64.2%
Terminal rates[e]	17/45 (38%)	17/45 (38%)	15/44 (34%)	25/41 (61%)
First incidence (days)	679	720	610	618
Logistic regression tests[f]	P=0.009	P=0.524N	P=0.437N	P=0.020
Hepatocellular Carcinoma				
Overall rates	10/50 (20%)	9/50 (18%)	17/50 (34%)	11/50 (22%)
Adjusted rates	20.7%	19.5%	34.7%	23.4%
Terminal rates	7/45 (16%)	8/45 (18%)	12/44 (27%)	6/41 (15%)
First incidence (days)	537	707	541	574
Logistic regression tests	P=0.396	P=0.598N	P=0.101	P=0.564

(continued)

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

Dose (ppm)	0	50	250	500
Male (continued)				
2-Year Study (continued)				
Hepatoblastoma[g]				
Overall rates	0/50 (0%)	1/50 (2%)	1/50 (2%)	5/50 (10%)
Adjusted rates	0.0%	2.2%	2.3%	12.2%
Terminal rates	0/45 (0%)	1/45 (2%)	1/44 (2%)	5/41 (12%)
First incidence (days)	–[h]	730 (T)	730 (T)	730 (T)
Logistic regression tests	P=0.004	P=0.500	P=0.496	P=0.026
Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma[i]				
Overall rates	24/50 (48%)	23/50 (46%)	26/50 (52%)	34/50 (68%)
Adjusted rates	49.9%	48.9%	53.0%	70.7%
Terminal rates	21/45 (47%)	21/45 (47%)	21/44 (48%)	27/41 (66%)
First incidence (days)	537	707	541	574
Logistic regression tests	P=0.016	P=0.505N	P=0.444	P=0.037
Female				
9-Month Interim Evaluation				
Liver	10	9	10	10
Eosinophilic Foci	0	0	0	1
All Foci	0	0	0	1
Hepatocellular Adenoma	0	0	0	0
Hepatocellular Adenoma, Multiple	0	0	0	0
Hepatocellular Carcinoma	0	0	0	0
15-Month Interim Evaluation				
Liver	10	10	10	10
Basophilic Foci	0	0	1	0
Eosinophilic Foci	0	0	2	1
All Foci	0	0	3	1
Hepatocellular Adenoma	1	1	1	1
Hepatocellular Adenoma, Multiple	0	0	0	0
Hepatocellular Carcinoma	0	0	0	0

(continued)

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

Dose (ppm)	0	50	250	500
Female (continued)				
2-Year Study				
Liver	49	48	49	50
Basophilic Foci	2	4	2	1
Clear Cell Foci	0	2	2	0
Eosinophilic Foci	3	3	8	25**
All Foci	5	8	11	26**
Hepatocellular Adenoma, Multiple	2	0	3	15**
Hepatocellular Adenoma (single or multiple)				
Overall rates	6/49 (12%)	10/48 (21%)	10/49 (20%)	28/50 (56%)
Adjusted rates	16.2%	26.6%	26.1%	62.2%
Terminal rates	6/37 (16%)	8/35 (23%)	9/37 (24%)	27/44 (61%)
First incidence (days)	739 (T)	588	689	690
Logistic regression tests	P<0.001	P=0.164	P=0.220	P<0.001
Hepatocellular Carcinoma				
Overall rates	5/49 (10%)	3/48 (6%)	2/49 (4%)	6/50 (12%)
Adjusted rates	13.5%	8.3%	5.4%	13.2%
Terminal rates	5/37 (14%)	2/35 (6%)	2/37 (5%)	5/44 (11%)
First incidence (days)	739 (T)	730	739 (T)	660
Logistic regression tests	P=0.430	P=0.383N	P=0.215N	P=0.575
Hepatocellular Adenoma or Carcinoma[j]				
Overall rates	9/49 (18%)	11/48 (23%)	11/49 (22%)	30/50 (60%)
Adjusted rates	24.3%	28.7%	28.7%	65.2%
Terminal rates	9/37 (24%)	8/35 (23%)	10/37 (27%)	28/44 (64%)
First incidence (days)	739 (T)	588	689	660
Logistic regression tests	P<0.001	P=0.335	P=0.427	P<0.001

* Significantly different (P≤0.05) from the control group by the logistic regression test.
** P≤0.01
(T) Terminal sacrifice
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Number of animals with neoplasm per number of animals necropsied
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by N.
[g] Historical incidence: 0/1,366
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 485/1,366 (35.5% ± 14.3%); range 10%-68%
[j] Historical incidence: 223/1,363 (16.4% ± 10.7%); range 3%-42%

Lung: There was a marginally significant decrease in the number of alveolar/bronchiolar adenomas or carcinomas (combined) in males (16/50, 10/50, 9/50, 6/50), and a positive trend in the number in females (1/48, 1/49, 6/50, 7/50) (Tables C3 and D3). The historical control rate in recent NTP feed studies for alveolar/bronchiolar adenomas or carcinomas (combined) for male mice is 242/1,369 (18%) with a range of 4% to 30%, and for female mice is 106/1,371 (8%) with a range of 2% to 26%. In the present study, rates in control groups vary greatly from average historical rates, while the incidences in exposed groups are more consistent with historical control rates. Neither the decreased incidence in males nor the positive trend in females were considered related to methylphenidate hydrochloride administration.

GENETIC TOXICOLOGY

Methylphenidate hydrochloride was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, TA1535, or TA1537 when tested at two laboratories with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Mortelmans *et al.*, 1986). A slight degree of toxicity was noted in the tests performed at Microbiological Associates, limiting the highest dose tested to 5,000 μg/plate, compared to the 10,000 μg/plate tested at SRI, International.

In cytogenetic tests with cultured Chinese hamster ovary cells, apparently inconsistent results were obtained for induction of sister chromatid exchanges (Table E2) and chromosomal aberrations (Table E3) between two laboratories. However, closer examination of the data shows that the positive responses were recorded in tests that employed higher doses of methylphenidate hydrochloride. In the sister chromatid exchange test performed at Environmental Health Research and Testing (EHRT), negative results were obtained with and without S9. At Litton Bionetics, Inc. (LBI), a positive response was obtained at all three scorable doses in the test performed without S9 (data presented in Galloway *et al.*, 1987). The cells in this trial were harvested 10 hours later than the normal harvest time of 26 hours to offset the severe cell cycle delay induced by treatment with methylphenidate hydrochloride. The doses that produced the positive response ranged from 702 to 900 μg/mL, much higher doses than those tested at EHRT. With S9, a weakly positive response observed at LBI in the first trial did not repeat in a second trial, and the sister chromatid exchange test with S9 was judged to be negative. This latter result was in agreement with the sister chromatid exchange test with S9 performed at EHRT.

The chromosomal aberrations test performed at EHRT gave positive results without S9. Two trials were performed. No significant increases in chromosomal aberrations were observed in the first trial, but a second trial conducted with higher doses produced positive responses at the two highest doses (1,750 and 2,000 μg/mL). With S9, results of the first trial were again negative, while the second trial showed a strong increase in chromosomal aberrations at the highest scorable dose (1,500 μg/mL). However, because no increase in chromosomal aberrations was seen at this dose level in the first trial, the overall results of the test with S9 were considered to be equivocal. At LBI, no increase in chromosomal aberrations was observed without S9 (highest dose, 1,250 μg/mL) but with S9, significant increases in chromosomal aberrations were observed at each of the three doses scored. These tests were not repeated.

Methylphenidate hydrochloride did not induce mutations in *Salmonella*, but did induce chromosomal aberrations and sister chromatid exchanges in mammalian cells *in vitro*. The NTP has evaluated these mutagenicity tests with respect to their predictive value for rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). A strong correlation was found to exist among the potential electrophilicity of a chemical (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rats and mice at single or multiple tissue sites (Ashby and Tennant, 1991). Although a positive result in the *Salmonella* test was shown to be a good predictor of carcinogenicity in rodents (89% of *Salmonella* mutagens were carcinogens in rats and/or mice), the negative predictivity was less precise. Approximately 50% of nonmutagens were also found to be noncarcinogens. Positive results in cultured Chinese hamster ovary cell cytogenetic studies are less predictive than positive results in the *Salmonella* assay for rodent carcinogenicity: 64% of chemicals that induced sister chromatid exchanges and 73% of chemicals that induce chromosomal aberrations were positive in the rodent bioassay. It is also important to note that no combination of *in vitro* genetic toxicity tests improved upon the predictivity of the *Salmonella* assay.

DISCUSSION AND CONCLUSIONS

Methylphenidate hydrochloride is used in the treatment of attention-deficit disorders and narcolepsy. Because there is little information on the long-term effects of this drug, the National Cancer Institute and the Food and Drug Administration nominated it for toxicity and carcinogenicity testing. The studies performed by the National Toxicology Program were designed primarily to determine the carcinogenic response of rodents to long-term administration of the chemical.

In the 14-day and 13-week studies, the principal chemical-related findings were toxicity to the mouse liver and lower mean body weight gain in rats and mice. Liver toxicity has not been reported as a common side effect in humans, and there have been no studies reporting any definitive liver lesions associated with the intake of methylphenidate (Goodman, 1972; Barkley *et al.*, 1990; *Goodman and Gilman's*, 1990). Quantitative differences in rodent and human methylphenidate metabolites occur (Faraj *et al.*, 1974), and these differences or the higher dose levels used in these rodent studies may account for the toxicity observed.

Decreases in feed consumption by rats and mice were reported during the first or second week of methylphenidate hydrochloride treatment, but after 1 or 2 weeks feed consumption was similar among exposed and control groups. This is consistent with studies reported in the literature that show that any anorexic effects of methylphenidate are transient. When methylphenidate hydrochloride is given to rodents, feed consumption is reduced for several hours after drug administration (Karczmar and Howard, 1959; Roskowski and Kelley, 1963; Warawa *et al.*, 1975), but when feed is available on a 24-hour *ad libitum* basis, methylphenidate at oral doses up to 12 mg/kg has no effect on daily consumption by rats (Barone *et al.*, 1979).

Hyperactivity was reported during the first weeks of treatment in male and female rats and male mice exposed to 4,000 ppm in the 14-day studies and in 2,000 ppm female rats in the 13-week studies, but no increase in activity was reported in rats or mice at the lower dose levels used in the 2-year studies. Other rodent studies have shown an increase in locomotive activity within 1 to 2 hours of methylphenidate treatment (Smith and Isaac, 1980; Wargin *et al.*, 1983). The dose-response relationships for motor activity are complex and sometimes seem contradictory. In rats methylphenidate increases spontaneous motor activity and stereotyped behavior after intraperitoneal doses of 5 to 20 mg/kg, and these effects are correlated with increased levels of dopamine in the brain. Other studies have shown that while ambulation in rats is increased at 8 mg/kg (intraperitoneal injection), a 16 mg/kg dose does not produce the same degree of increased activity, and the behavioral effects can vary with dose level (Hughes and Greig, 1976). With increasing dose, spontaneous motor activity decreased but stereotyped behavior increased (Bhattacharyya *et al.*, 1980). At doses of 3.2 and 6.4 mg/kg, methylphenidate increases locomotive activity in rats within 1 hour after intraperitoneal administration, but not after oral administration, probably because higher plasma levels of the drug are reached after intraperitoneal administration (Smith and Isaac, 1980; Wargin *et al.*, 1983). Increases in activity or stereotyped behavior occur in rodents within several hours after oral administration of methylphenidate at higher dose levels (40 to 100 mg/kg) (Fog, 1969; Pedersen and Christensen, 1972).

Tolerance to the therapeutic effects of methylphenidate has been reported in children, although the mechanism for such an effect is not known (Swanson *et al.*, 1986). While oral doses of 62 mg/kg of methylphenidate cause increased spontaneous motor activity in rats for the first few days of treatment, tolerance appears to develop by day 4 to 6 of treatment (Fregly and Black, 1964). The failure to observe hyperactivity in the 2-year studies may be due to the fact that these studies were conducted at lower doses than the 14-day and 13-week studies; any increase in activity would probably correspond to the maximum intake of chemical in the feed at night, and tolerance to the hyperactive effects of the drug may develop.

There have been conflicting reports in the literature as to whether methylphenidate affects growth

patterns in children (Roche *et al.*, 1979; Mattes and Gittelman, 1983), and because of this concern measurements of bone density and length were included in the 13-week rat study. There were no treatment-related effects on bone density or length at 13 weeks at doses up to 2,000 ppm (80 mg/kg per day) in rats. Other studies show depression of skeletal growth at subcutaneous doses of 35 and 100 mg/kg administered twice daily to neonatal or juvenile rats. These effects were reversible upon discontinuation of treatment (Greeley and Kizer, 1980). A small reduction in femur length was observed in rats treated with 35 mg/kg methylphenidate twice a day from 5 days of age to 24 days, but not in 55-day-old rats similarly treated. The reduction in growth observed in the younger rats was reversible upon cessation of treatment (Pizzi *et al.*, 1987). Dosing of animals in the NTP studies started when the animals were 7 to 8 weeks old, and these older animals may not be sensitive to an effect, if any, of methylphenidate on bone growth. In addition, administration of the chemical in feed probably results in lower plasma levels of the drug than occur with subcutaneous or bolus oral administration.

Studies on side effects from methylphenidate treatment have focused on the effects on growth and changes in hormone levels. Schultz *et al.* (1982) reported no significant differences in 24-hour growth hormone or prolactin profiles in children treated with methylphenidate for a mean of 15 months, while other investigators found increases in serum growth hormone and decreases in serum prolactin levels after methylphenidate treatment (Weizman *et al.*, 1987; Shaywitz *et al.*, 1990). Rats administered 1, 3, 10, 35, or 100 mg/kg methylphenidate hydrochloride subcutaneously twice daily for 21 days had depressed serum prolactin levels (males and females) and growth hormone levels (females) (Greeley and Kizer, 1980). The effect of methylphenidate hydrochloride on growth in children remains an area of ongoing clinical study (Whalen and Henker, 1991; Kelley and Aylward, 1992).

In the 2-year feed studies of methylphenidate hydrochloride, there were no treatment-related effects on survival in rats or mice. There were increases in the absolute and/or relative liver weights of exposed mice. In exposed rats there were lower mean body weights which progressed with length of exposure. The final mean body weights of 500 and 1,000 ppm male and female rats were 5% to 22% lower than those of the controls. The body weight effect in mice was less than that in rats; the final mean body weights of 500 ppm male and female mice were 3% and 7% lower than those of the controls. In these 2-year studies feed consumption by control and exposed groups was similar, indicating that the effect of methylphenidate hydrochloride on body weight was probably due to pharmacologic effects. The estimated doses of methylphenidate hydrochloride delivered to rats and mice were 40 to 60 times human dose levels based on a body weight comparison (Table 17).

In the 2-year rat study there was no indication that tolerance to the body weight effects developed, which is consistent with the findings for amphetamine (NTP, 1991). In humans, older patients respond to lower levels of the drug than younger patients (Gurian and Rosowsky, 1990), and the progression of the body weight effect in the 2-year rat study may be related to differences in how the animal responds to the drug as it ages. In the 2-year mouse study the body weight effects were less severe and higher doses may have been tolerated.

There was no evidence of carcinogenic activity in male or female rats, but in mice there was some evidence of carcinogenic activity based on an increased incidence in hepatocellular neoplasms in 500 ppm male and female mice. In addition, in high-dose mice there was an increase in the incidence of eosinophilic foci and total foci in the liver, and an increase in the number of animals with multiple hepatocellular adenomas. While the incidence of hepatocellular carcinomas alone was not increased, the combined incidence of hepatocellular adenomas, carcinomas, or hepatoblastomas (males) was increased in high-dose mice.

Hepatoblastomas [thought to arise from liver stem cells (Shiojiri *et al.*, 1991)] were found in one low-dose, one mid-dose, and five high-dose male mice. Hyperplasia, adenoma, and carcinoma represent a biological and morphological continuum in progression of proliferative lesions. It is probable that hepatoblastomas comprise cells that are more primitive, and rather than representing further progression to a more malignant state, simply represent a phenotypic (and possibly genotypic) variant of a malignant

TABLE 17
Comparison of Doses in Methylphenidate Hydrochloride 2-Year Feed Studies[a]

	Males				Females			
Rats								
Dose in ppm	0	100	500	1,000	0	100	500	1,000
Grams feed/day	16.2	16.3	16.0	16.1	12.2	12.2	11.9	11.2
mg methylphenidate/kg body weight	0	4	20	42	0	4	22	47
mg/m^2	0	21	104	218	0	20	114	244
Mice								
Dose in ppm	0	50	250	500	0	50	250	500
Grams feed/day	4.7	4.8	4.7	4.8	5.7	5.6	5.7	5.7
mg methylphenidate/kg body weight	0	5.3	28.3	55.9	0	6.7	34.2	66.5
mg/m^2	0	15	84	168	0	21	102	198
Humans								
mg/kg	0.3–1.0							
mg/m^2	11–37							

[a] The dose is calculated as an average for > 52 weeks. Calculation for body surface area dose based on Freireich *et al.*, 1966; $mg/m^2 = K_m x$ (dose in mg/kg) where K_m is 37 for humans, 5.2 for rats, and 3.0 for mice. (K_m is a conversion based on average height-to-body-weight ratios.)

liver neoplasm. Because the malignant potential of hepatoblastomas and carcinomas appear similar and hepatoblastomas are generally observed within hepatocellular neoplasms (mostly carcinomas), it is appropriate to combine the incidences of hepatoblastoma with those of adenoma and carcinoma when interpreting the carcinogenic potential of a chemical. However, because hepatoblastomas are rare and seen in relatively high numbers only after chemical administration, the presence of these neoplasms appears to indicate that methylphenidate hydrochloride had an effect on the liver, or at least on the hepatocellular neoplasms.

This was considered to represent some evidence of a carcinogenic effect because there was an increase in eosinophilic foci and hepatocellular neoplasms in the high-dose groups of male and female mice. The evidence for carcinogenicity was not considered to be strong enough to place it in the "clear evidence" category because the incidence of hepatocellular neoplasms was increased only in the high dose groups. This incidence of total hepatocellular neoplasms was within the historical control range for males, and was not increased for females.

Methylphenidate was not mutagenic in the *Salmonella typhimurium* assay. This suggests that the mechanism for the formation of the mouse liver neoplasms may be related to mechanisms other than a direct genotoxic effect. In a recent review of long-term rodent studies, 55 of 301 chemicals were found to produce neoplasms only in the mouse liver, and of these 61% were negative in the *S. typhimurium* test (Tennant and Ashby, 1991). The mechanism by which methylphenidate hydrochloride and these other *S. typhimurium* negative chemicals produce mouse liver neoplasms is not known. One proposed mechanism for mouse liver carcinogenicity includes an increase in liver toxicity and subsequent increase in cell proliferation, and an increased potential for expression of endogenous mutations (Nemali *et al.*, 1989; Reddy and Rao, 1989). Alternatively, non-genotoxic agents might promote the growth of preneoplastic foci (Cattley and Popp, 1989). Further research is needed to characterize the mechanism by

which methylphenidate produces mouse liver toxicity and the manner in which this nonmutagenic chemical interacts with components of liver cells.

It is generally accepted that chemical carcinogenesis is a multistep process (Barrett, 1992) and that in the rodent liver carcinogenicity induced by chemicals includes a series of stepwise cellular changes. Foci of altered hepatocytes, as were observed in these studies, are considered to be preneoplastic lesions (Bannasch and Zerban, 1992). The evidence for this is based on studies conducted primarily in the rat which show that foci are rapidly induced by hepatocarcinogens, and the numbers of induced foci are related to the dose of the carcinogen (Emmelot and Scherer, 1980). Foci increase in number and size with continued carcinogen exposure or with time after cessation of exposure to certain carcinogens (Rabes and Szymkowiak, 1979; Barbason and Betz, 1981). Foci of altered hepatocytes are characterized by enhanced cell proliferation which increases with time (Rabes, 1988). It is this property of enhanced cell proliferation found in the focal liver lesions that may facilitate the clonal expansion of initiated cells.

A series of genetic changes is proposed to occur during multistep carcinogenesis, and an early change found in carcinogenesis has been mutations in *ras* genes (Barrett, 1992). Richardson *et al.* (1992) reported on the molecular events in murine hepatocarcinogenesis in hepatic foci, adenomas, and carcinomas that arose spontaneously in control B6C3F$_1$ mice as measured in tissues obtained from archival pathology specimens. In this study it was found that the H-*ras* oncogene was activated in 29% of hepatocellular foci, 44% of hepatocellular adenomas, and 42% of hepatocellular carcinomas but in only 7% of normal liver tissue. The increase in *ras* oncogene activation in hepatocellular foci may represent an early change which may be one step in the evolution from a normal cell to a neoplastic cell. The oncogene changes from spontaneous and chemical-induced liver neoplasms may vary (Reynolds *et al.*, 1987; Fox *et al.*, 1990); at this time, information on oncogene changes with methylphenidate treatment are not available.

Treatment with methylphenidate hydrochloride reduced the incidence of mammary gland fibroadenomas in the female rat (control, 15/50; 100 ppm, 13/50; 500 ppm, 6/50; 1,000 ppm, 5/50), a neoplasm that occurs naturally in this animal [historical range for this neoplasm in control female rats is 8% to 58% with a mean of 39% (484/1,251)]. Mean body weights were also reduced in the mid- and high-dose female rats by 11% and 22%, respectively. Increases in serum prolactin levels potentiate the formation of chemical-induced mammary gland neoplasms in rodents, and prolactin lowering drugs inhibit the growth of these neoplasms (Briand, 1983; Kleinberg, 1987). Methylphenidate has been reported to lower serum prolactin levels (Greeley and Kizer, 1980), and the lower incidence of spontaneous mammary gland fibroadenomas in female rats may be related to these hormonal effects of methylphenidate. Amphetamine also reduces the incidence of mammary gland fibroadenomas in the female rat (NTP, 1991) and is also thought to have the potential to lower serum prolactin levels (Ravitz and Moore, 1977).

The role of prolactin in the growth of mammary gland neoplasms is still under study (Kleinberg, 1987; Musey *et al.*, 1987). Secretion of pituitary prolactin is regulated by a hypothalamic factor known as prolactin-inhibiting factor (PIF). Hypothalamic PIF is controlled by dopaminergic neurons, and increases in dopamine levels such as seen with amphetamine and methylphenidate may increase the release of PIF, which would result in decreases in serum prolactin (Archer, 1977; Leong *et al.*, 1983). It has been suggested that increases in estrogen and prolactin levels will result in an increase in the rate of DNA synthesis in the mammary gland and a concomitant increase in the susceptibility to tumorigenesis (Blankenstein *et al.*, 1984). Using *in vitro* strains of human breast neoplasms, prolactin was shown to have a growth promoting effect on estrogen-receptor positive breast cell lines (Manni *et al.*, 1986). The dopaminergic activity of methylphenidate would be anticipated to increase release of dopamine, increase hypothalamus release of PIF, and decrease serum prolactin concentration (Costall and Naylor, 1974; Leong *et al.*, 1983), and these neuroendocrine effects of methylphenidate are one hypothesis for the observed decrease in mammary gland neoplasms.

An alternative hypothesis for the decrease in mammary gland neoplasms is offered by Rao *et al.* (1987), who found that decreases in rat body weight were associated with a decrease in the incidences of naturally occurring benign neoplasms including neoplasms of the mammary gland in female rats. Because methylphenidate caused lower body weights in dosed female rats, the decreases in the incidence

of mammary gland neoplasms may also be related to this lower body weight. Other studies report that increased levels of dietary fat are associated with increases in the incidence of mammary gland neoplasms (Cave and Jurkowski, 1984; Welsch, 1985; Bruning, 1987).

The incidence of benign or malignant pheochromocytomas of the adrenal medulla (18/49, 7/48, 5/49, 10/50) was marginally decreased in treated male rats by pairwise comparison but not by the trend statistic. The incidence for this neoplasm was within the historical range for this neoplasm in controls and it was uncertain if this effect was related to chemical treatment.

Methylphenidate and amphetamine are related drugs (Figure 6; Julien, 1975) used in the treatment of attention-deficit hyperactivity disorders (Pelham *et al.*, 1990). In the NTP long-term studies of these drugs, both chemicals caused lower body weights and decreased incidence of mammary gland neoplasms in the female rats. The lower body weights and the spectrum of decreases in naturally occurring neoplasms were more marked in the amphetamine studies, in which there was no evidence of carcinogenic activity in either rats or mice. Amphetamine treatment caused decreased incidences of total neoplasms in rats and mice, of the incidence of adrenal pheochromocytomas in male rats, of mammary gland fibroadenomas and uterine polyps in female rats, of pituitary gland adenomas in male and female rats and female mice, and of harderian gland adenomas, liver neoplasms, and lung neoplasms in male and female mice. Hyperactivity was noted throughout the day for rodents on amphetamine treatment, while this side effect was not observed in the methylphenidate studies. This is consistent with other studies which show that amphetamine causes increased activity in rats at lower doses than observed with methylphenidate (Hughes and Greig, 1976; Pechnik *et al.*, 1979), and that depletion of rat brain monoamine markers lasts for up to 18 hours after treatment with amphetamine but is of short duration with methylphenidate (Zaczek *et al.*, 1989).

CONCLUSIONS

Under the conditions of these 2-year feed studies there was *no evidence of carcinogenic activity** of methylphenidate hydrochloride in male or female F344/N rats receiving 100, 500, or 1,000 ppm. There was *some evidence of carcinogenic activity* of methylphenidate hydrochloride in male and female B6C3F$_1$ mice based on the occurrence of hepatocellular neoplasms.

Treatment of female rats with methylphenidate hydrochloride was associated with a decrease in the incidence of mammary gland fibroadenomas. Administration of methylphenidate hydrochloride to male and female mice resulted in increased incidences of eosinophilic foci.

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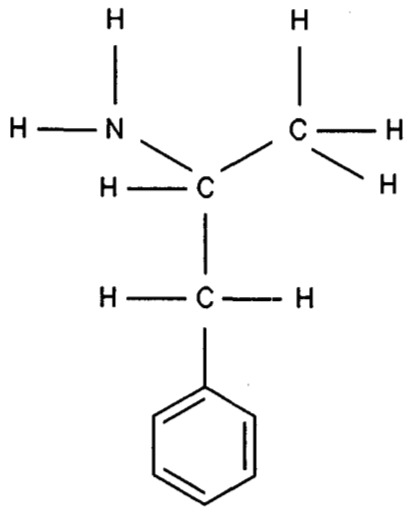
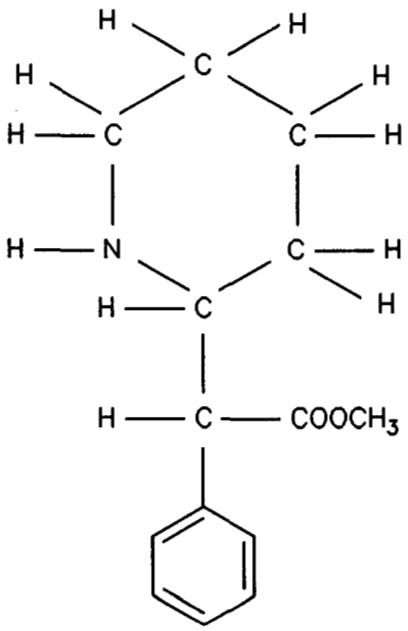
* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.



Amphetamine



Methylphenidate (Ritalin)

FIGURE 6
Structural Formulas of Amphetamine and Methylphenidate (Ritalin)
(Julien, 1975)

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF METHYLPHENIDATE HYDROCHLORIDE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	100 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	9
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths		1		
Moribund	14	9	7	9
Natural deaths	8	7	9	8
Survivors				
Died last week of study				1
Terminal sacrifice	28	33	34	33
Animals examined microscopically	70	70	70	70
9-Month Interim Evaluation				
Genital System[b]				
Testes	(10)	(10)	(10)	(9)
Interstitial cell, adenoma				1 (11%)
15-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adenoma		1 (10%)		
Adrenal medulla	(10)	(10)	(10)	(10)
Pheochromocytoma benign				1 (10%)
Islets, pancreatic	(10)	(10)	(10)	(10)
Adenoma			1 (10%)	
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma	1 (10%)	1 (10%)		1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, adenoma		1 (10%)		1 (10%)
General Body System				
None				
Genital System				
Preputial gland	(10)	(10)	(10)	(10)
Adenoma		1 (10%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
15-Month Interim Evaluation (continued)				
Genital System (continued)				
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	7 (70%)	7 (70%)	8 (80%)	8 (80%)
Interstitial cell, adenoma	2 (20%)	3 (30%)		2 (20%)
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)			
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Intestine large, colon	(46)	(46)	(46)	(47)
Intestine large, rectum	(48)	(47)	(48)	(50)
Intestine large, cecum	(46)	(44)	(44)	(44)
Lipoma		1 (2%)		
Polyp				1 (2%)
Intestine small, duodenum	(46)	(49)	(46)	(48)
Intestine small, jejunum	(45)	(46)	(44)	(46)
Intestine small, ileum	(46)	(43)	(42)	(45)
Liver	(50)	(50)	(50)	(51)
Hepatocellular adenoma		2 (4%)		
Histiocytic sarcoma				1 (2%)
Mesentery	(5)	(6)	(14)	(14)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(49)	(50)	(49)	(51)
Acinus, adenoma			2 (4%)	1 (2%)
Stomach, glandular	(48)	(50)	(48)	(51)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Endocrine System				
Adrenal medulla	(49)	(48)	(49)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)	1 (2%)	
Pheochromocytoma benign	12 (24%)	5 (10%)	5 (10%)	10 (20%)
Bilateral, pheochromocytoma benign	5 (10%)	1 (2%)		
Islets, pancreatic	(49)	(50)	(50)	(51)
Adenoma	1 (2%)			2 (4%)
Carcinoma		2 (4%)		2 (4%)
Parathyroid gland	(48)	(46)	(49)	(47)
Adenoma				1 (2%)
Pituitary gland	(48)	(49)	(48)	(51)
Pars distalis, adenoma	10 (21%)	10 (20%)	7 (15%)	10 (20%)
Pars distalis, adenoma, multiple	1 (2%)			
Pars distalis, carcinoma	1 (2%)			
Thyroid gland	(50)	(49)	(50)	(50)
Schwannoma malignant, metastatic, skin			1 (2%)	
Bilateral, C-cell, adenoma				1 (2%)
C-cell, adenoma	4 (8%)	4 (8%)	6 (12%)	7 (14%)
C-cell, carcinoma	1 (2%)		2 (4%)	1 (2%)
Follicular cell, adenoma	1 (2%)			
Follicular cell, carcinoma		1 (2%)	1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Coagulating gland				(1)
Adenoma				1 (100%)
Epididymis	(50)	(49)	(50)	(51)
Preputial gland	(50)	(47)	(50)	(51)
Adenoma	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Carcinoma		2 (4%)	4 (8%)	2 (4%)
Prostate	(49)	(50)	(49)	(51)
Seminal vesicle	(48)	(50)	(49)	(51)
Testes	(50)	(49)	(50)	(51)
Bilateral, interstitial cell, adenoma	43 (86%)	40 (82%)	43 (86%)	43 (84%)
Interstitial cell, adenoma	3 (6%)	6 (12%)	4 (8%)	3 (6%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Hematopoietic System				
Blood		(1)		
Bone marrow	(49)	(50)	(50)	(51)
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Lymph node	(11)	(18)	(15)	(11)
Mediastinal, histiocytic sarcoma				1 (9%)
Pancreatic, histiocytic sarcoma				1 (9%)
Lymph node, mandibular	(49)	(49)	(48)	(51)
Histiocytic sarcoma				1 (2%)
Lymph node, mesenteric	(49)	(50)	(48)	(50)
Histiocytic sarcoma				1 (2%)
Spleen	(50)	(50)	(50)	(51)
Hemangiosarcoma	2 (4%)			
Histiocytic sarcoma				1 (2%)
Thymus	(41)	(47)	(47)	(49)
Histiocytic sarcoma				1 (2%)
Integumentary System				
Mammary gland	(38)	(36)	(37)	(44)
Fibroadenoma	1 (3%)	2 (6%)	1 (3%)	2 (5%)
Skin	(50)	(50)	(50)	(51)
Basal cell adenoma		2 (4%)		
Fibroma	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Fibrosarcoma	1 (2%)			
Keratoacanthoma	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Sarcoma		1 (2%)	1 (2%)	
Squamous cell papilloma	1 (2%)		1 (2%)	
Subcutaneous tissue, schwannoma malignant			1 (2%)	
Musculoskeletal System				
Bone	(49)	(50)	(50)	(51)
Chordoma			1 (2%)	
Osteosarcoma			1 (2%)	
Skeletal muscle	(1)		(6)	
Nervous System				
Brain	(50)	(50)	(50)	(51)
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)		
Histiocytic sarcoma				1 (2%)
Schwannoma malignant, metastatic, skin			1 (2%)	
Nose	(50)	(49)	(49)	(51)
Polyp				1 (2%)
Squamous cell carcinoma				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Special Senses System				
Ear	(3)			(1)
Carcinoma, metastatic, pituitary gland	1 (33%)			
Zymbal's gland			(1)	
Carcinoma			1 (100%)	
Urinary System				
Kidney	(49)	(50)	(50)	(48)
Lipoma				1 (2%)
Sarcoma	1 (2%)			
Renal tubule, adenoma		1 (2%)		
Urinary bladder	(43)	(44)	(43)	(45)
Papilloma				1 (2%)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(51)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	29 (58%)	25 (50%)	17 (34%)	23 (45%)
Mesothelioma malignant	1 (2%)		3 (6%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
9-Month interim evaluation				1
15-Month interim evaluation	9	10	8	10
2-Year study	48	47	48	46
Total primary neoplasms				
9-Month interim evaluation				1
15-Month interim evaluation	11	14	9	13
2-Year study	124	112	109	123
Total animals with benign neoplasms				
9-Month interim evaluation				1
15-Month interim evaluation	9	10	8	10
2-Year study	47	47	47	46
Total benign neoplasms				
9-Month interim evaluation				1
15-Month interim evaluation	11	14	9	13
2-Year study	87	80	76	90
Total animals with malignant neoplasms				
2-Year study	32	28	27	30
Total malignant neoplasms				
2-Year study	37	32	33	33
Total animals with metastatic neoplasms				
2-Year study	1		4	1
Total metastatic neoplasms				
2-Year study	1		5	1

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] No neoplasms were observed at any other site in any animal at the 9-month interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm

Number of Days on Study	3 0 4	3 9 1	4 5 9	5 2 4	5 4 9	5 5 0	5 6 6	5 9 4	6 1 2	6 3 2	6 3 2	6 3 5	6 3 9	6 6 5	6 7 2	6 7 7	6 9 7	6 9 5	7 0 8	7 1 1	7 1 5	7 3 7	7 3 5	7 3 5
Carcass ID Number	0 2 1	0 3 4	0 0 1	0 0 6	0 4 0	0 5 5	0 1 3	0 5 4	0 6 5	0 0 2	0 0 3	0 6 8	0 2 3	0 4 8	0 5 7	0 6 4	0 6 9	0 1 1	0 2 6	0 4 6	0 1 2	0 1 4	0 2 4	0 2 5	0 2 7
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											+		+											
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								
Pheochromocytoma benign												X				X	X	X			X	X		
Bilateral, pheochromocytoma benign													X											
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pars distalis, adenoma									X						X			X						
Pars distalis, adenoma, multiple																								
Pars distalis, carcinoma							X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								
C-cell, carcinoma																								
Follicular cell, adenoma															X									
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma			X	X																				

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 3 0	0 3 2	0 3 6	0 3 7	0 3 8	0 3 9	0 4 1	0 5 0	0 5 3	0 5 6	0 5 9	0 6 0	0 0 5	0 0 8	0 1 0	0 1 5	0 1 6	0 4 3	0 4 4	0 4 5	0 6 1	0 6 2	0 6 6	0 6 7	0 7 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery											+								+		+					5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																X										1
Pheochromocytoma benign			X		X	X															X	X		X		12
Bilateral, pheochromocytoma benign				X									X	X				X								5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X				X			X					X						X		X		X			10
Pars distalis, adenoma, multiple														X												1
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X		X						X										X			4
C-cell, carcinoma	X																									1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X										X	2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	43
Interstitial cell, adenoma													X													3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	3 0 4	3 9 1	4 5 9	5 2 4	5 4 9	5 5 0	5 6 6	5 9 4	6 1 2	6 3 2	6 3 2	6 3 5	6 3 9	6 6 5	6 7 2	6 7 7	6 7 7	6 9 5	6 9 8	7 0 1	7 1 5	7 1 7	7 3 5	7 3 5	7 3 5
Carcass ID Number	0 2 1	0 3 4	0 0 1	0 0 6	0 4 0	0 5 5	0 1 3	0 5 4	0 6 5	0 0 2	0 0 3	0 6 8	0 2 3	0 4 8	0 5 7	0 6 4	0 6 9	0 1 1	0 2 6	0 4 6	0 1 2	0 1 4	0 2 4	0 2 5	0 2 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node					+			+					+	+		+				+		+	+		
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	M	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma				X																					
Fibrosarcoma																									
Keratoacanthoma																									
Squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve								+																	
Spinal cord								+																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear							+	+																	
Carcinoma, metastatic, pituitary gland							X																		
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Sarcoma													X												
Ureter																					+				
Urinary bladder	+	A	+	+	+	+	+	+	A	+	+	M	+	A	A	+	+	+	+	A	+	A	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X		X	X	X		X	X	X	X	X	X			X		X	X	X	
Mesothelioma malignant											X														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 3 0	0 3 2	0 3 6	0 3 7	0 3 8	0 3 9	0 4 1	0 5 0	0 5 3	0 5 6	0 5 9	0 6 0	0 0 5	0 0 8	0 1 0	0 1 5	0 1 6	0 4 3	0 4 4	0 4 5	0 6 1	0 6 2	0 6 6	0 6 7	0 7 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node					+	+							+													11
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													2
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	M	+	+	M	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	38
Fibroadenoma										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Fibrosarcoma																				X						1
Keratoacanthoma						X																				1
Squamous cell papilloma																		X								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear													+													3
Carcinoma, metastatic, pituitary gland																										1
Eye				+																						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																										1
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X	X	X	X	X	X			X		X		X	X			X		X	X			29
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 100 ppm

Number of Days on Study	0 4 3	3 1 5	4 0 9	4 2 9	5 3 3	5 4 7	5 9 6	6 0 0	6 2 3	6 3 9	6 5 0	6 5 0	6 7 5	6 7 6	6 8 7	7 1 7	7 2 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 1 6	0 7 4	1 3 5	0 9 3	1 2 2	1 2 6	1 3 2	1 3 1	1 2 7	0 9 2	0 9 6	1 2 3	0 9 8	0 9 5	0 9 9	0 7 8	1 0 9	0 7 2	0 7 3	0 7 7	0 8 0	0 8 3	0 8 4	0 8 6	0 8 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	+	A	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Lipoma																									
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	+	A	A	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X											
Mesentery								+		+					+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																					X				
Pheochromocytoma benign														X				X							
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X																		
Parathyroid gland	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X			X								X	X				X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X												X					
Follicular cell, carcinoma																	X								
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X		X	X	X	X	X			X			X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma						X							X		X	X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 100 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 9 1	0 9 4	1 0 1	1 0 4	1 0 5	1 0 6	1 1 0	1 1 2	1 1 4	1 1 7	1 1 9	0 7 9	0 8 7	0 8 9	1 2 4	1 2 5	1 2 8	1 3 0	1 3 3	1 3 4	1 3 6	1 3 7	1 3 8	1 3 9	1 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lipoma			X																							1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																									X	2
Mesentery							+					+											+			6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																										1
Pheochromocytoma benign					X	X						X														5
Bilateral, pheochromocytoma benign																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X															2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma						X		X				X				X	X									10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	X																X									4
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																X										1
Carcinoma			X	X																						2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	40
Interstitial cell, adenoma																						X	X			6

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 100 ppm
(continued)

Number of Days on Study	0 4 3	3 1 5	4 0 9	4 2 9	5 3 3	5 4 7	5 9 6	6 0 0	6 2 3	6 3 9	6 5 0	6 5 0	6 7 5	6 7 6	6 8 7	7 1 7	7 2 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 1 6	0 7 4	1 3 5	0 9 3	1 2 2	1 2 6	1 3 2	1 3 1	1 2 7	0 9 2	0 9 6	1 2 3	0 9 8	0 9 5	0 9 9	0 7 8	1 0 9	0 7 2	0 7 3	0 7 7	0 8 0	0 8 3	0 8 4	0 8 6	0 8 8
Hematopoietic System																								
Blood								+																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+			+		+	+		+	+	+		+				+		+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																								
Mammary gland	+	M	+	+	+	+	M	+	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																				X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								
Fibroma																								
Keratoacanthoma																								
Sarcoma									X															
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X			
Nose	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																						M		
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								
Urinary bladder	+	A	A	+	+	A	A	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X		X	X		X	X	X		X	X	X		X		X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 100 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 9 1	0 9 4	1 0 1	1 0 4	1 0 5	1 0 6	1 1 0	1 1 2	1 1 4	1 1 7	1 1 9	0 7 9	0 8 7	0 8 9	1 2 4	1 2 5	1 2 8	1 3 0	1 3 3	1 3 4	1 3 6	1 3 7	1 3 8	1 3 9	1 4 0	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+		+			+		+		+											+		+	18
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Integumentary System																										
Mammary gland	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	36
Fibroadenoma																				X						2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma								X																X		2
Fibroma								X										X				X				3
Keratoacanthoma					X																					1
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+		+																				+	3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																									X	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X	X		X		X	X			X						X	X	X	X	X	X	25

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm

Number of Days on Study	3 2 5	3 8 3	4 0 6	5 4 2	5 6 6	6 2 4	6 3 8	6 5 3	6 7 4	6 7 6	6 7 7	6 8 1	7 0 0	7 0 1	7 2 1	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 5 1	1 5 3	1 6 9	1 7 6	2 0 9	1 5 4	1 8 9	1 5 0	1 8 0	1 9 0	2 0 0	1 8 6	1 6 2	1 6 8	1 6 5	1 7 8	1 9 1	1 9 5	1 9 6	1 9 7	1 9 9	1 4 2	1 4 3	1 4 4	1 4 5
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	A	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	A	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	A	A	A	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic																								
Mesentery								+		+				+		+	+			+			+	
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																								
Salivary glands	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								
Pheochromocytoma benign								X																X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pars distalis, adenoma																		X		X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin							X																	
C-cell, adenoma												X												
C-cell, carcinoma																							X	
Follicular cell, carcinoma																								
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma																				X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Interstitial cell, adenoma				X															X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 4 7	1 4 8	1 4 9	1 5 5	1 5 6	1 6 0	1 6 3	1 7 0	1 7 2	1 7 3	1 7 4	1 7 7	1 7 7	1 8 9	1 9 4	2 0 6	2 0 7	2 0 8	1 5 9	1 8 1	1 8 2	1 8 3	1 8 5	2 0 1	2 0 2	2 0 5	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic										X																	1
Mesentery	+			+					+	+		+							+		+					14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma		X																								X	2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																								X			1
Pheochromocytoma benign									X										X					X			5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X								X							X							X	X	7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																											1
C-cell, adenoma	X			X	X						X		X														6
C-cell, carcinoma					X																						2
Follicular cell, carcinoma											X																1
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X				X																		2
Carcinoma	X											X							X								4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	43
Interstitial cell, adenoma										X														X			4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	3 2 5	3 8 3	4 0 6	5 4 2	5 6 6	6 2 4	6 3 8	6 5 3	6 7 4	6 7 6	6 7 7	6 8 1	7 0 0	7 0 1	7 2 1	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 5 1	1 5 3	1 6 9	1 7 6	2 0 9	1 5 4	1 8 9	1 5 0	1 8 0	1 9 0	2 0 0	1 8 6	1 6 2	1 6 8	1 6 5	1 7 8	1 9 1	1 9 5	1 9 6	1 9 7	1 9 9	1 4 2	1 4 3	1 4 4	1 4 5
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone												X													
Lymph node								+			+		+	+	+						+	+	+		
Lymph node, mandibular	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	+	M	+	M	M	M	+	+	+	M	+	M	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Keratoacanthoma								X											X	X					
Sarcoma				X																					
Squamous cell papilloma																									
Subcutaneous tissue, schwannoma malignant							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma															X										
Osteosarcoma												X													
Skeletal muscle												+		+		+				+					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve															+										
Spinal cord															+										
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic														X											
Schwannoma malignant, metastatic, skin							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+																							
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	A	A	A	A	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X		X	X	X	X								X	X	X		
Mesothelioma malignant														X		X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 4 7	1 4 8	1 4 9	1 5 5	1 5 6	1 6 0	1 6 3	1 7 0	1 7 2	1 7 3	1 7 4	1 7 7	1 8 7	1 9 4	2 0 6	2 0 7	2 0 8	1 5 9	1 8 1	1 8 2	1 8 3	1 8 5	2 0 1	2 0 2	2 0 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Lymph node			+	+				+					+						+	+			+			15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	M	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	37
Fibroadenoma			X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma					X																					1
Keratoacanthoma																X										4
Sarcoma																										1
Squamous cell papilloma																X										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma																										1
Osteosarcoma																										1
Skeletal muscle										+															+	6
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic																										1
Schwannoma malignant, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye								+														+				3
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X						X			X	X						X	X					17
Mesothelioma malignant										X																3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm

Number of Days on Study	1 1 1 3 3 4 5 5 5 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 8 8 8 5 8 3 1 9 9 3 5 7 7 8 8 8 2 2 2 2 2 2 2 2 0 5 7 7 6 9 8 0 8 9 3 5 8 2 2 6 2 9 9 9 9 9 9 9 9
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 4 3 1 3 1 2 1 6 4 7 1 4 4 2 5 4 5 1 1 3 3 4 4 4 5 6 7 7 1 3 3 2 6 9 3 1 8 1 8 5 7 8 6 9 8 9 3 4 5 2
Alimentary System	
Esophagus	+ +
Intestine large, colon	+ A A + + + A + + + + + + + + + + A + + + + + +
Intestine large, rectum	+ + A +
Intestine large, cecum	A A A + + A A + + + + + + + + + A A + + + + + +
Polyp	
Intestine small, duodenum	+ A A + + A + + + + + + + + + + + + + + + + + +
Intestine small, jejunum	+ A A + A A + + + + + + + + + + A + + + + + + +
Intestine small, ileum	A A A + A A + + + + + + + + + + A + + + + + + +
Liver	+ +
Histiocytic sarcoma	X
Mesentery	+ + + + + +
Pancreas	+ +
Acinus, adenoma	
Salivary glands	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Tongue	
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal cortex	+ M +
Adrenal medulla	+ M +
Pheochromocytoma benign	X X
Islets, pancreatic	+ +
Adenoma	X
Carcinoma	
Parathyroid gland	M +
Adenoma	
Pituitary gland	+ +
Pars distalis, adenoma	X X X
Thyroid gland	+ + A +
Bilateral, C-cell, adenoma	
C-cell, adenoma	X X X X
C-cell, carcinoma	
Follicular cell, carcinoma	
General Body System	
None	
Genital System	
Coagulating gland	+
Adenoma	X
Epididymis	+ +
Preputial gland	+ +
Adenoma	
Carcinoma	X X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 5 3	2 5 4	2 6 1	2 6 2	2 6 3	2 6 4	2 6 8	2 7 0	2 7 7	2 7 9	2 8 0	2 1 4	2 2 2	2 2 4	2 2 5	2 2 9	2 3 2	2 3 5	2 4 2	2 5 0	2 5 6	2 5 9	2 6 0	2 7 1	2 7 4	2 7 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Polyp																	X									1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Mesentery	+		+	+		+	+				+					+				+			+			14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinus, adenoma																		X								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tongue															+											1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X								X				X			X	X					X		X	X	10
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma		X																								2
Carcinoma									X				X													2
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma										X																1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma	X				X							X	X				X	X							X	10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																	X									1
C-cell, adenoma												X											X	X		7
C-cell, carcinoma																				X						1
Follicular cell, carcinoma									X																	1
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Adenoma																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma											X															1
Carcinoma																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm
(continued)

Number of Days on Study	1 8 0	1 8 5	1 8 7	3 5 7	3 8 6	4 3 9	5 1 8	5 9 0	5 9 8	6 3 9	6 5 3	6 7 5	6 7 8	6 8 2	6 8 2	6 8 6	7 2 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 4 6	2 3 7	2 1 7	2 3 1	2 1 3	2 2 3	2 1 2	2 6 6	2 4 9	2 7 3	2 1 1	2 4 8	2 4 1	2 2 8	2 5 5	2 4 7	2 5 8	2 1 6	2 1 9	2 3 8	2 3 9	2 4 3	2 4 4	2 4 5	2 5 2
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma						X						X													
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymph node						+	+			+			+			+									
Mediastinal, histiocytic sarcoma						X																			
Pancreatic, histiocytic sarcoma						X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Thymus	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Integumentary System																									
Mammary gland	+	M	M	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma										X									X			X			
Keratoacanthoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Mesothelioma malignant, metastatic, heart																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp																									
Squamous cell carcinoma											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																	+								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	25 3	25 4	26 1	26 2	26 3	26 4	26 8	27 0	27 7	27 9	28 0	28 1	28 4	28 2	28 4	28 5	28 9	29 2	29 5	29 2	29 0	29 6	29 9	30 1	30 7	30 4	30 5	Total Tissues/ Tumors
Genital System (continued)																												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Interstitial cell, adenoma								X																				3
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																												1
Lymph node			+	+	+					+								+								+		11
Mediastinal, histiocytic sarcoma																												1
Pancreatic, histiocytic sarcoma																												1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																												1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																												1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																												1
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+		44
Fibroadenoma														X						X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibroma																												3
Keratoacanthoma																X												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord														+														1
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																												1
Mesothelioma malignant, metastatic, heart																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp																								X				1
Squamous cell carcinoma																												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																												
Ear														+														1
Eye																					+	+						3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm
(continued)

Number of Days on Study	1	1	1	3	3	4	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	
	8	8	8	5	8	3	1	9	9	3	5	7	7	8	8	8	2	2	2	2	2	2	2	2	
	0	5	7	7	6	9	8	0	8	9	3	5	8	2	2	6	2	9	9	9	9	9	9	9	
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	4	3	1	3	1	2	1	6	4	7	1	4	4	2	5	4	5	1	1	3	3	4	4	4	5
	6	7	7	1	3	3	2	6	9	3	1	8	1	8	5	7	8	6	9	8	9	3	4	5	2
Urinary System																									
Kidney	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																								X	
Urinary bladder	+	A	A	+	A	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Leukemia mononuclear							X	X	X				X	X	X		X	X	X		X	X	X	X	X
Mesothelioma malignant											X					X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	25 53	25 54	26 61	26 62	26 63	26 64	26 68	27 00	27 77	27 79	28 00	21 04	22 22	22 24	22 25	23 09	23 02	23 05	24 52	25 20	25 56	25 59	26 60	27 01	27 74	27 75	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lipoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Papilloma																	X										1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Leukemia mononuclear	X			X	X							X			X		X		X		X				X		23
Mesothelioma malignant																											2

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

	0 ppm	100 ppm	500 ppm	1,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	17/49 (35%)	6/48 (13%)	5/49 (10%)	10/50 (20%)
Adjusted rates[b]	50.8%	17.9%	13.8%	30.3%
Terminal rates[c]	12/28 (43%)	5/32 (16%)	4/34 (12%)	10/33 (30%)
First incidence (days)	639	676	653	729 (T)
Life table tests[d]	P=0.122N	P=0.004N	P=0.001N	P=0.033N
Logistic regression tests[d]	P=0.151N	P=0.005N	P=0.001N	P=0.049N
Cochran-Armitage test[d]	P=0.177N			
Fisher exact test[d]		P=0.009N	P=0.003N	P=0.078N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rates	18/49 (37%)	7/48 (15%)	5/49 (10%)	10/50 (20%)
Adjusted rates	53.9%	20.9%	13.8%	30.3%
Terminal rates	13/28 (46%)	6/32 (19%)	4/34 (12%)	10/33 (30%)
First incidence (days)	639	676	653	729 (T)
Life table tests	P=0.069N	P=0.004N	P<0.001N	P=0.019N
Logistic regression tests	P=0.087N	P=0.006N	P<0.001N	P=0.029N
Cochran-Armitage test	P=0.110N			
Fisher exact test		P=0.011N	P=0.002N	P=0.052N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	1/49 (2%)	2/50 (4%)	0/50 (0%)	4/51 (8%)
Adjusted rates	3.6%	5.2%	0.0%	11.4%
Terminal rates	1/28 (4%)	1/33 (3%)	0/34 (0%)	3/34 (9%)
First incidence (days)	729 (T)	596	-[e]	686
Life table tests	P=0.157	P=0.543	P=0.461N	P=0.236
Logistic regression tests	P=0.134	P=0.505	P=0.461N	P=0.204
Cochran-Armitage test	P=0.139			
Fisher exact test		P=0.508	P=0.495N	P=0.194
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	11/48 (23%)	10/49 (20%)	7/48 (15%)	10/51 (20%)
Adjusted rates	34.4%	25.9%	21.2%	28.3%
Terminal rates	8/28 (29%)	6/33 (18%)	7/33 (21%)	9/34 (26%)
First incidence (days)	612	409	729 (T)	675
Life table tests	P=0.306N	P=0.382N	P=0.122N	P=0.327N
Logistic regression tests	P=0.377N	P=0.483N	P=0.142N	P=0.406N
Cochran-Armitage test	P=0.368N			
Fisher exact test		P=0.479N	P=0.217N	P=0.437N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	12/48 (25%)	10/49 (20%)	7/48 (15%)	10/51 (20%)
Adjusted rates	35.9%	25.9%	21.2%	28.3%
Terminal rates	8/28 (29%)	6/33 (18%)	7/33 (21%)	9/34 (26%)
First incidence (days)	566	409	729 (T)	675
Life table tests	P=0.248N	P=0.301N	P=0.083N	P=0.250N
Logistic regression tests	P=0.313N	P=0.387N	P=0.114N	P=0.341N
Cochran-Armitage test	P=0.302N			
Fisher exact test		P=0.383N	P=0.153N	P=0.343N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
Preputial Gland: Carcinoma				
Overall rates	0/50 (0%)	2/47 (4%)	4/50 (8%)	2/51 (4%)
Adjusted rates	0.0%	6.1%	11.8%	5.3%
Terminal rates	0/28 (0%)	2/33 (6%)	4/34 (12%)	0/34 (0%)
First incidence (days)	–	729 (T)	729 (T)	675
Life table tests	P=0.297	P=0.275	P=0.089	P=0.280
Logistic regression tests	P=0.275	P=0.275	P=0.089	P=0.241
Cochran-Armitage test	P=0.265			
Fisher exact test		P=0.232	P=0.059	P=0.252
Preputial Gland: Adenoma or Carcinoma				
Overall rates	2/50 (4%)	3/47 (6%)	6/50 (12%)	3/51 (6%)
Adjusted rates	7.1%	9.1%	17.6%	8.1%
Terminal rates	2/28 (7%)	3/33 (9%)	6/34 (18%)	1/34 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	675
Life table tests	P=0.456	P=0.575	P=0.200	P=0.584
Logistic regression tests	P=0.434	P=0.575	P=0.200	P=0.531
Cochran-Armitage test	P=0.405			
Fisher exact test		P=0.470	P=0.134	P=0.509
Skin: Fibroma				
Overall rates	1/50 (2%)	3/50 (6%)	1/50 (2%)	3/51 (6%)
Adjusted rates	2.1%	9.1%	2.9%	8.1%
Terminal rates	0/28 (0%)	3/33 (9%)	1/34 (3%)	2/34 (6%)
First incidence (days)	524	729 (T)	729 (T)	639
Life table tests	P=0.420	P=0.349	P=0.739N	P=0.346
Logistic regression tests	P=0.379	P=0.305	P=0.750	P=0.316
Cochran-Armitage test	P=0.383			
Fisher exact test		P=0.309	P=0.753N	P=0.316
Skin: Keratoacanthoma				
Overall rates	1/50 (2%)	1/50 (2%)	4/50 (8%)	1/51 (2%)
Adjusted rates	3.6%	3.0%	10.9%	2.9%
Terminal rates	1/28 (4%)	1/33 (3%)	3/34 (9%)	1/34 (3%)
First incidence (days)	729 (T)	729 (T)	653	729 (T)
Life table tests	P=0.536	P=0.725N	P=0.240	P=0.718N
Logistic regression tests	P=0.503	P=0.725N	P=0.206	P=0.718N
Cochran-Armitage test	P=0.489			
Fisher exact test		P=0.753N	P=0.181	P=0.748N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Basal Cell Adenoma				
Overall rates	2/50 (4%)	3/50 (6%)	4/50 (8%)	1/51 (2%)
Adjusted rates	7.1%	9.1%	10.9%	2.9%
Terminal rates	2/28 (7%)	3/33 (9%)	3/34 (9%)	1/34 (3%)
First incidence (days)	729 (T)	729 (T)	653	729 (T)
Life table tests	P=0.294N	P=0.575	P=0.426	P=0.432N
Logistic regression tests	P=0.321N	P=0.575	P=0.386	P=0.432N
Cochran-Armitage test	P=0.347N			
Fisher exact test		P=0.500	P=0.339	P=0.492N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
Testes: Adenoma				
Overall rates	46/50 (92%)	46/49 (94%)	47/50 (94%)	46/51 (90%)
Adjusted rates	97.9%	100.0%	100.0%	100.0%
Terminal rates	27/28 (96%)	33/33 (100%)	34/34 (100%)	34/34 (100%)
First incidence (days)	459	429	542	439
Life table tests	P=0.167N	P=0.206N	P=0.153N	P=0.146N
Logistic regression tests	P=0.336	P=0.336	P=0.586	P=0.375
Cochran-Armitage test	P=0.372N			
Fisher exact test		P=0.511	P=0.500	P=0.513N
Thyroid Gland (C-cell): Adenoma				
Overall rates	4/50 (8%)	4/49 (8%)	6/50 (12%)	8/50 (16%)
Adjusted rates	14.3%	11.5%	16.9%	22.5%
Terminal rates	4/28 (14%)	3/32 (9%)	5/34 (15%)	7/34 (21%)
First incidence (days)	729 (T)	600	681	639
Life table tests	P=0.139	P=0.577N	P=0.494	P=0.277
Logistic regression tests	P=0.106	P=0.634N	P=0.472	P=0.222
Cochran-Armitage test	P=0.092			
Fisher exact test		P=0.631	P=0.370	P=0.178
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	5/50 (10%)	4/49 (8%)	7/50 (14%)	9/50 (18%)
Adjusted rates	17.9%	11.5%	19.8%	25.4%
Terminal rates	5/28 (18%)	3/32 (9%)	6/34 (18%)	8/34 (24%)
First incidence (days)	729 (T)	600	681	639
Life table tests	P=0.124	P=0.424N	P=0.519	P=0.308
Logistic regression tests	P=0.093	P=0.484N	P=0.499	P=0.250
Cochran-Armitage test	P=0.078			
Fisher exact test		P=0.513N	P=0.380	P=0.194
All Organs: Mononuclear Cell Leukemia				
Overall rates	29/50 (58%)	25/50 (50%)	17/50 (34%)	23/51 (45%)
Adjusted rates	69.9%	60.6%	41.7%	55.7%
Terminal rates	16/28 (57%)	17/33 (52%)	11/34 (32%)	16/34 (47%)
First incidence (days)	549	533	638	518
Life table tests	P=0.060N	P=0.149N	P=0.006N	P=0.069N
Logistic regression tests	P=0.176N	P=0.263N	P=0.016N	P=0.286N
Cochran-Armitage test	P=0.097N			
Fisher exact test		P=0.274N	P=0.013N	P=0.136N
All Organs: Malignant Mesothelioma				
Overall rates	1/50 (2%)	0/50 (0%)	3/50 (6%)	2/51 (4%)
Adjusted rates	2.4%	0.0%	8.3%	5.1%
Terminal rates	0/28 (0%)	0/33 (0%)	1/34 (3%)	0/34 (0%)
First incidence (days)	632	–	701	653
Life table tests	P=0.214	P=0.500N	P=0.369	P=0.525
Logistic regression tests	P=0.188	P=0.493N	P=0.315	P=0.511
Cochran-Armitage test	P=0.191			
Fisher exact test		P=0.500N	P=0.309	P=0.508

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
All Organs: Benign Neoplasms				
Overall rates	47/50 (94%)	47/50 (94%)	47/50 (94%)	46/51 (90%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	33/33 (100%)	34/34 (100%)	34/34 (100%)
First incidence (days)	459	409	542	439
Life table tests	P=0.114N	P=0.202N	P=0.109N	P=0.102N
Logistic regression tests	P=0.527	P=0.548	P=0.829N	P=0.535
Cochran-Armitage test	P=0.262N			
Fisher exact test		P=0.661N	P=0.661N	P=0.369N
All Organs: Malignant Neoplasms				
Overall rates	32/50 (64%)	28/50 (56%)	27/50 (54%)	30/51 (59%)
Adjusted rates	73.7%	64.8%	59.8%	66.6%
Terminal rates	17/28 (61%)	18/33 (55%)	16/34 (47%)	19/34 (56%)
First incidence (days)	549	533	406	439
Life table tests	P=0.265N	P=0.153N	P=0.086N	P=0.200N
Logistic regression tests	P=0.392	P=0.420N	P=0.321N	P=0.456
Cochran-Armitage test	P=0.414N			
Fisher exact test		P=0.270N	P=0.208N	P=0.371N
All Organs: Benign or Malignant Neoplasms				
Overall rates	48/50 (96%)	47/50 (94%)	48/50 (96%)	46/51 (90%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	33/33 (100%)	34/34 (100%)	34/34 (100%)
First incidence (days)	459	409	406	439
Life table tests	P=0.100N	P=0.160N	P=0.115N	P=0.077N
Logistic regression tests	P=0.603N	P=0.729N	P=0.785	P=0.785
Cochran-Armitage test	P=0.180N			
Fisher exact test		P=0.500N	P=0.691N	P=0.226N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE A4
Historical Incidence of Adrenal Medulla Pheochromocytomas in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence at TSI Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	12/50	1/50	13/50
Acetaminophen	16/44	1/44	17/44
HC Yellow 4	19/50	2/50	19/50
Pentaerythritol tetranitrate	19/49	0/49	19/49
Quercetin	12/50	1/50	13/50
Turmeric oleoresin	14/47	0/47	14/47
Overall Historical Incidence			
Total	414/1,234 (33.5%)	48/1,234 (3.9%)	445/1,234[b] (36.1%)
Standard deviation	11.6%	4.8%	11.0%
Range	10%-63%	0%-20%	14%-63%

[a] Data as of 20 August 1992
[b] Includes three complex pheochromocytomas

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	100 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	9
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths		1		
Moribund	14	9	7	9
Natural deaths	8	7	9	8
Survivors				
Died last week of study				1
Terminal sacrifice	28	33	34	33
Animals examined microscopically	70	70	70	70
9-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(9)
Parasite metazoan	2 (20%)		1 (10%)	1 (11%)
Intestine large, rectum	(10)	(10)	(10)	(9)
Parasite metazoan	5 (50%)	3 (30%)	4 (40%)	3 (33%)
Intestine large, cecum	(10)	(10)	(10)	(9)
Parasite metazoan	1 (10%)	2 (20%)	2 (20%)	1 (11%)
Liver	(10)	(10)	(10)	(9)
Developmental malformation	1 (10%)			3 (33%)
Hepatodiaphragmatic nodule	1 (10%)			1 (11%)
Bile duct, hyperplasia		1 (10%)	2 (20%)	
Mesentery	(1)			
Fat, necrosis	1 (100%)			
Pancreas	(10)	(10)	(10)	(8)
Inflammation, chronic, focal				1 (13%)
Acinus, atrophy	1 (10%)	1 (10%)	3 (30%)	2 (25%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(9)
Cardiomyopathy	6 (60%)	2 (20%)	4 (40%)	4 (44%)
Inflammation, chronic, focal	2 (20%)	6 (60%)	5 (50%)	3 (33%)
Atrium, dilatation				1 (11%)
Endocrine System				
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, cyst				1 (11%)
Pars distalis, hyperplasia, focal	1 (10%)	1 (10%)	3 (30%)	3 (33%)
General Body System				
None				

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
9-Month Interim Evaluation (continued)				
Genital System				
Preputial gland	(10)	(10)	(10)	(9)
Abscess	1 (10%)	1 (10%)		
Inflammation, chronic, focal	8 (80%)	8 (80%)	8 (80%)	9 (100%)
Testes	(10)	(10)	(10)	(9)
Bilateral, interstitial cell, hyperplasia	1 (10%)	1 (10%)	2 (20%)	3 (33%)
Interstitial cell, hyperplasia		1 (10%)		1 (11%)
Seminiferous tubule, atrophy		1 (10%)		
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(9)
Hyperplasia				1 (11%)
Lymph node	(1)		(1)	
Mediastinal, congestion	1 (100%)		1 (100%)	
Lymph node, mesenteric	(10)	(10)	(10)	(9)
Congestion	1 (10%)			
Giant cell	8 (80%)	10 (100%)	10 (100%)	8 (89%)
Thymus	(10)	(10)	(10)	(9)
Depletion lymphoid				4 (44%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Hyperplasia, adenomatous	1 (10%)			
Peribronchial, inflammation, chronic	10 (100%)	10 (100%)	9 (90%)	9 (100%)
Nose	(10)	(10)	(10)	(9)
Inflammation, acute				1 (11%)
Inflammation, chronic, focal	10 (100%)	10 (100%)	10 (100%)	7 (78%)
Metaplasia, squamous	4 (40%)	1 (10%)		1 (11%)
Special Senses System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
9-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(9)
Nephropathy	3 (30%)	3 (30%)	4 (40%)	2 (22%)
Renal tubule, regeneration	5 (50%)	4 (40%)	6 (60%)	1 (11%)
Urinary bladder	(10)	(10)	(10)	(9)
Calculus microscopic observation only	4 (40%)	1 (10%)	2 (20%)	
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(9)	(10)
Parasite metazoan	1 (10%)		1 (11%)	3 (30%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)	3 (30%)	2 (20%)	3 (30%)
Intestine large, cecum	(10)	(10)	(10)	(10)
Parasite metazoan				1 (10%)
Intestine small, ileum	(10)	(10)	(10)	(10)
Peyer's patch, hyperplasia			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus	4 (40%)	4 (40%)	3 (30%)	2 (20%)
Fatty change			1 (10%)	
Granuloma		1 (10%)		
Hepatodiaphragmatic nodule		1 (10%)		
Bile duct, hyperplasia	6 (60%)	7 (70%)	3 (30%)	4 (40%)
Mesentery		(1)		
Fat, necrosis		1 (100%)		
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy	3 (30%)	6 (60%)	3 (30%)	5 (50%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	8 (80%)	9 (90%)	8 (80%)	6 (60%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Cytoplasmic alteration	1 (10%)			
Adrenal medulla	(10)	(10)	(10)	(10)
Hyperplasia, focal			1 (10%)	
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, hyperplasia, focal	3 (30%)	4 (40%)	6 (60%)	4 (40%)
Pars distalis, inflammation, chronic, focal		1 (10%)		
Pars intermedia, cyst	1 (10%)			
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia	1 (10%)			1 (10%)
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Preputial gland	(10)	(10)	(10)	(10)
Abscess		2 (20%)		
Cyst		1 (10%)	1 (10%)	
Inflammation, chronic	10 (100%)	8 (80%)	9 (90%)	10 (100%)
Prostate	(10)	(10)	(10)	(10)
Inflammation, acute			1 (10%)	
Inflammation, chronic	1 (10%)			
Inflammation, focal		1 (10%)		
Seminal vesicle	(10)	(10)	(10)	(10)
Atrophy			1 (10%)	
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, hyperplasia	1 (10%)		2 (20%)	
Seminiferous tubule, atrophy	1 (10%)			1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hyperplasia		1 (10%)		
Lymph node		(1)		
Mediastinal, congestion		1 (100%)		
Lymph node, mandibular	(10)	(10)	(10)	(10)
Congestion	1 (10%)			1 (10%)
Spleen	(10)	(10)	(10)	(10)
Depletion lymphoid				1 (10%)
Thymus	(8)	(10)	(10)	(10)
Hyperplasia, lymphoid		1 (10%)		
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Ulcer			1 (10%)	
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Nose	(10)	(10)	(10)	(10)
Fungus	2 (20%)	4 (40%)		1 (10%)
Inflammation, acute	2 (20%)	4 (40%)		1 (10%)
Inflammation, chronic	8 (80%)	6 (60%)	10 (100%)	9 (90%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
15-Month Interim Evaluation (continued)				
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	7 (70%)	9 (90%)	9 (90%)	8 (80%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic, focal			1 (10%)	
2-Year Study				
Alimentary System				
Intestine large, colon	(46)	(46)	(46)	(47)
Parasite metazoan	5 (11%)	8 (17%)	9 (20%)	5 (11%)
Intestine large, rectum	(48)	(47)	(48)	(50)
Parasite metazoan	4 (8%)	9 (19%)	9 (19%)	6 (12%)
Intestine large, cecum	(46)	(44)	(44)	(44)
Edema	2 (4%)			
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Parasite metazoan	2 (4%)	2 (5%)	1 (2%)	1 (2%)
Intestine small, jejunum	(45)	(46)	(44)	(46)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Intestine small, ileum	(46)	(43)	(42)	(45)
Autolysis				1 (2%)
Liver	(50)	(50)	(50)	(51)
Angiectasis, focal	2 (4%)	7 (14%)	3 (6%)	5 (10%)
Atrophy		1 (2%)	2 (4%)	
Basophilic focus	35 (70%)	42 (84%)	38 (76%)	37 (73%)
Clear cell focus	10 (20%)	8 (16%)	14 (28%)	6 (12%)
Cyst	2 (4%)	1 (2%)		
Developmental malformation	2 (4%)	1 (2%)	3 (6%)	4 (8%)
Eosinophilic focus	2 (4%)	1 (2%)		4 (8%)
Fatty change	9 (18%)	5 (10%)	3 (6%)	6 (12%)
Fibrosis, focal	1 (2%)		1 (2%)	
Granuloma			3 (6%)	1 (2%)
Hepatodiaphragmatic nodule	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Infarct		1 (2%)		
Mixed cell focus			1 (2%)	1 (2%)
Necrosis, focal	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Proliferation	1 (2%)			
Thrombosis		1 (2%)	1 (2%)	
Bile duct, dilatation		1 (2%)		
Bile duct, hyperplasia	18 (36%)	23 (46%)	14 (28%)	18 (35%)
Lymphatic, angiectasis, focal	2 (4%)	1 (2%)	4 (8%)	3 (6%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(5)	(6)	(14)	(14)
Accessory spleen	1 (20%)		1 (7%)	1 (7%)
Cyst			1 (7%)	
Fibrosis			1 (7%)	1 (7%)
Artery, inflammation, chronic				1 (7%)
Artery, thrombosis				1 (7%)
Fat, hemorrhage	1 (20%)			
Fat, necrosis	2 (40%)	4 (67%)	10 (71%)	11 (79%)
Pancreas	(49)	(50)	(49)	(51)
Angiectasis		1 (2%)		
Autolysis, focal				1 (2%)
Pigmentation, focal			1 (2%)	
Acinus, atrophy	17 (35%)	21 (42%)	16 (33%)	17 (33%)
Acinus, hyperplasia, focal	2 (4%)	2 (4%)	1 (2%)	
Artery, hypertrophy				1 (2%)
Artery, inflammation, chronic		1 (2%)	2 (4%)	
Vein, thrombosis	1 (2%)			
Pharynx		(1)		
Palate, inflammation, chronic		1 (100%)		
Salivary glands	(50)	(50)	(49)	(51)
Atrophy	1 (2%)	1 (2%)		
Hyperplasia		1 (2%)		1 (2%)
Thrombosis	1 (2%)			
Stomach, forestomach	(49)	(50)	(50)	(51)
Cyst epithelial inclusion			1 (2%)	
Hyperkeratosis	1 (2%)			1 (2%)
Inflammation, chronic, focal		1 (2%)		
Ulcer	3 (6%)	1 (2%)		
Stomach, glandular	(48)	(50)	(48)	(51)
Erosion	8 (17%)	5 (10%)	3 (6%)	3 (6%)
Hyperplasia, lymphoid	4 (8%)	2 (4%)	2 (4%)	
Ulcer				1 (2%)
Mucosa, inflammation, acute	1 (2%)			
Submucosa, fibrosis		1 (2%)		
Tongue				(1)
Hyperkeratosis, focal				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Cardiomyopathy	42 (84%)	39 (78%)	37 (74%)	35 (69%)
Hypertrophy				1 (2%)
Mineralization	4 (8%)		1 (2%)	1 (2%)
Artery, inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Atrium, dilatation	1 (2%)	1 (2%)		1 (2%)
Atrium, thrombosis	6 (12%)		3 (6%)	1 (2%)
Ventricle, dilatation		1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Cytoplasmic alteration, focal	2 (4%)	4 (8%)	1 (2%)	2 (4%)
Hyperplasia			2 (4%)	
Hyperplasia, focal		1 (2%)		
Hypertrophy	1 (2%)			
Vacuolization cytoplasmic	3 (6%)	2 (4%)	1 (2%)	
Adrenal medulla	(49)	(48)	(49)	(50)
Hemorrhage	1 (2%)	1 (2%)		
Hyperplasia, focal	16 (33%)	12 (25%)	16 (33%)	22 (44%)
Islets, pancreatic	(49)	(50)	(50)	(51)
Hyperplasia	4 (8%)		1 (2%)	
Parathyroid gland	(48)	(46)	(49)	(47)
Ectopic thymus	1 (2%)			
Hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)	
Pituitary gland	(48)	(49)	(48)	(51)
Pars distalis, angiectasis	1 (2%)	2 (4%)		1 (2%)
Pars distalis, cyst	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Pars distalis, hemorrhage		1 (2%)		1 (2%)
Pars distalis, hyperplasia, focal	6 (13%)	9 (18%)	8 (17%)	9 (18%)
Pars intermedia, cyst				1 (2%)
Pars intermedia, hyperplasia, focal			1 (2%)	
Thyroid gland	(50)	(49)	(50)	(50)
Ultimobranchial cyst		1 (2%)		
C-cell, hyperplasia	4 (8%)	6 (12%)	8 (16%)	6 (12%)
Follicle, cyst		2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(49)	(50)	(51)
Atrophy				1 (2%)
Depletion cellular	2 (4%)	2 (4%)	2 (4%)	6 (12%)
Dilatation				1 (2%)
Fibrosis				1 (2%)
Spermatocele			1 (2%)	
Preputial gland	(50)	(47)	(50)	(51)
Abscess	6 (12%)	1 (2%)		3 (6%)
Cyst	4 (8%)	4 (9%)	1 (2%)	2 (4%)
Ectasia	5 (10%)	2 (4%)	1 (2%)	3 (6%)
Hyperplasia	1 (2%)			
Inflammation, acute		5 (11%)	1 (2%)	
Inflammation, chronic	7 (14%)	3 (6%)	2 (4%)	5 (10%)
Metaplasia, squamous				1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Genital System (continued)				
Prostate	(49)	(50)	(49)	(51)
Atrophy	18 (37%)	11 (22%)	12 (24%)	18 (35%)
Congestion			1 (2%)	
Dilatation	2 (4%)	1 (2%)	1 (2%)	
Hyperplasia, focal				1 (2%)
Inflammation, acute	1 (2%)		1 (2%)	
Inflammation, chronic				1 (2%)
Seminal vesicle	(48)	(50)	(49)	(51)
Atrophy	36 (75%)	36 (72%)	37 (76%)	41 (80%)
Cyst			1 (2%)	
Dilatation	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Testes	(50)	(49)	(50)	(51)
Hemorrhage, focal		1 (2%)		
Bilateral, interstitial cell, hyperplasia	2 (4%)		1 (2%)	1 (2%)
Interstitial cell, hyperplasia	1 (2%)	4 (8%)	2 (4%)	
Seminiferous tubule, atrophy	2 (4%)	4 (8%)	2 (4%)	2 (4%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(51)
Granuloma			1 (2%)	
Hyperplasia	22 (45%)	18 (36%)	23 (46%)	20 (39%)
Myelofibrosis	1 (2%)		2 (4%)	2 (4%)
Lymph node	(11)	(18)	(15)	(11)
Inguinal, lymphatic, angiectasis		1 (6%)		
Lumbar, lymphatic, angiectasis			1 (7%)	
Mediastinal, granuloma		1 (6%)		
Mediastinal, pigmentation		1 (6%)		
Mediastinal, lymphatic, angiectasis	4 (36%)	2 (11%)	3 (20%)	2 (18%)
Pancreatic, hyperplasia, lymphoid		1 (6%)		
Pancreatic, lymphatic, angiectasis	2 (18%)	4 (22%)	4 (27%)	2 (18%)
Renal, pigmentation			1 (7%)	
Renal, lymphatic, angiectasis			1 (7%)	
Lymph node, mandibular	(49)	(49)	(48)	(51)
Angiectasis	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Congestion		1 (2%)		3 (6%)
Depletion lymphoid			1 (2%)	
Infiltration cellular, plasma cell	2 (4%)	1 (2%)		1 (2%)
Lymphatic, angiectasis	1 (2%)		2 (4%)	1 (2%)
Lymph node, mesenteric	(49)	(50)	(48)	(50)
Angiectasis	5 (10%)	5 (10%)	2 (4%)	3 (6%)
Congestion				1 (2%)
Depletion lymphoid	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Lymphatic, angiectasis	1 (2%)	2 (4%)	3 (6%)	3 (6%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(50)	(50)	(51)
Congestion	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Depletion lymphoid	3 (6%)	2 (4%)	6 (12%)	5 (10%)
Fibrosis	14 (28%)	17 (34%)	9 (18%)	11 (22%)
Hematopoietic cell proliferation	3 (6%)	2 (4%)	1 (2%)	
Hemorrhage				1 (2%)
Hypertrophy	1 (2%)			
Infarct	2 (4%)	7 (14%)		1 (2%)
Inflammation, acute				1 (2%)
Necrosis, focal	1 (2%)			1 (2%)
Pigmentation, hemosiderin				3 (6%)
Thrombosis	1 (2%)	1 (2%)		
Capsule, congestion, focal	1 (2%)			
Capsule, fibrosis	2 (4%)	1 (2%)	1 (2%)	
Thymus	(41)	(47)	(47)	(49)
Congestion				1 (2%)
Cyst			2 (4%)	
Depletion lymphoid	1 (2%)		2 (4%)	1 (2%)
Hemorrhage, focal		1 (2%)		
Lymphatic, angiectasis				1 (2%)
Integumentary System				
Mammary gland	(38)	(36)	(37)	(44)
Lactation	14 (37%)	14 (39%)	12 (32%)	12 (27%)
Skin	(50)	(50)	(50)	(51)
Abscess			1 (2%)	
Acanthosis		1 (2%)		
Cyst epithelial inclusion	1 (2%)			
Edema				1 (2%)
Fibrosis, focal	2 (4%)		1 (2%)	1 (2%)
Inflammation, focal, granulomatous		1 (2%)		
Ulcer	1 (2%)			1 (2%)
Hair follicle, cyst		1 (2%)		
Subcutaneous tissue, hemorrhage				1 (2%)
Musculoskeletal System				
Bone	(49)	(50)	(50)	(51)
Callus	1 (2%)			
Hyperostosis	5 (10%)	2 (4%)	3 (6%)	3 (6%)
Proliferation	1 (2%)			
Skeletal muscle	(1)		(6)	
Fibrosis			2 (33%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(51)
Compression	2 (4%)			2 (4%)
Hemorrhage	1 (2%)	2 (4%)		3 (6%)
Meninges, hemorrhage				1 (2%)
Peripheral nerve	(1)		(1)	
Degeneration			1 (100%)	
Spinal cord	(1)		(1)	(1)
Degeneration			1 (100%)	
Hemorrhage, focal	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Angiectasis	3 (6%)			
Congestion		1 (2%)		
Granuloma			3 (6%)	
Hemorrhage, focal	1 (2%)	1 (2%)		1 (2%)
Infiltration cellular, focal, histiocyte	5 (10%)			1 (2%)
Peribronchial, inflammation, chronic	1 (2%)			2 (4%)
Pleura, inflammation, chronic, focal		1 (2%)		
Nose	(50)	(49)	(49)	(51)
Fungus	16 (32%)	14 (29%)	16 (33%)	14 (27%)
Hyperkeratosis	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, basal cell	2 (4%)			
Inflammation, acute	2 (4%)	5 (10%)	1 (2%)	7 (14%)
Inflammation, chronic	2 (4%)	1 (2%)	3 (6%)	6 (12%)
Metaplasia, squamous				1 (2%)
Respiratory epithelium, necrosis		1 (2%)		
Special Senses System				
Eye	(1)	(3)	(3)	(3)
Cataract		1 (33%)	3 (100%)	3 (100%)
Retina, degeneration	1 (100%)	2 (67%)		1 (33%)
Urinary System				
Kidney	(49)	(50)	(50)	(48)
Abscess	1 (2%)			
Autolysis				1 (2%)
Cyst		2 (4%)		1 (2%)
Glomerulosclerosis		1 (2%)	1 (2%)	
Mineralization	1 (2%)			
Necrosis, focal	1 (2%)			
Nephropathy	46 (94%)	45 (90%)	46 (92%)	47 (98%)
Medulla, casts		1 (2%)		
Papilla, necrosis	1 (2%)			
Pelvis, epithelium, hyperplasia				1 (2%)
Renal tubule, degeneration, granular	2 (4%)	2 (4%)	2 (4%)	
Renal tubule, pigmentation, bile	3 (6%)	2 (4%)	5 (10%)	4 (8%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Urinary System (continued)				
Ureter	(1)			
Hyperplasia	1 (100%)			
Urinary bladder	(43)	(44)	(43)	(45)
Calculus microscopic observation only	1 (2%)		1 (2%)	
Ectasia			1 (2%)	
Hemorrhage		1 (2%)	1 (2%)	
Ulcer	1 (2%)			
Transitional epithelium, hyperplasia	1 (2%)			

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF METHYLPHENIDATE HYDROCHLORIDE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	100 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation[b]	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	13	12	10	7
Natural deaths	6	6	4	4
Survivors				
Died last week of study	2	2		1
Terminal sacrifice	29	30	36	38
Animals examined microscopically	70	70	70	70
15-Month Interim Evaluation				
Alimentary System				
Stomach, forestomach	(10)	(10)	(10)	(10)
Squamous cell papilloma		1 (10%)		
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, adenoma	2 (20%)	1 (10%)	2 (20%)	
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, adenoma	1 (10%)			
General Body System				
None				
Genital System				
Uterus	(10)	(10)	(10)	(10)
Polyp stromal			4 (40%)	1 (10%)
Polyp stromal, two				1 (10%)
Hematopoietic System				
None				
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Keratoacanthoma				1 (10%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma		1 (10%)		
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Renal tubule				
Adenoma		1 (10%)		
2-Year Study				
Alimentary System				
Intestine large, colon	(47)	(47)	(49)	(49)
Fibroma				1 (2%)
Intestine small, duodenum	(47)	(46)	(50)	(49)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Intestine small, jejunum	(47)	(43)	(48)	(48)
Intestine small, ileum	(46)	(43)	(47)	(48)
Sarcoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma		1 (2%)		
Sarcoma stromal, metastatic, uterus	1 (2%)			
Mesentery	(4)	(6)	(9)	(3)
Sarcoma stromal, metastatic, uterus	1 (25%)			
Pancreas	(50)	(49)	(50)	(50)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(49)	(50)	(50)
Stomach, glandular	(50)	(49)	(50)	(50)
Tongue			(1)	(1)
Squamous cell papilloma			1 (100%)	1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal medulla	(50)	(49)	(50)	(50)
Pheochromocytoma malignant		1 (2%)	2 (4%)	
Pheochromocytoma benign	3 (6%)	3 (6%)	3 (6%)	3 (6%)
Islets, pancreatic	(50)	(49)	(50)	(50)
Adenoma		2 (4%)	1 (2%)	2 (4%)
Parathyroid gland	(47)	(46)	(48)	(46)
Adenoma		1 (2%)		
Pituitary gland	(50)	(49)	(50)	(49)
Pars distalis, adenoma	26 (52%)	29 (59%)	15 (30%)	22 (45%)
Pars distalis, adenoma, multiple		3 (6%)	5 (10%)	3 (6%)
Pars distalis, carcinoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	3 (6%)	8 (16%)	7 (14%)	4 (8%)
C-cell, carcinoma	1 (2%)	2 (4%)		1 (2%)
Follicular cell, adenoma		1 (2%)		
General Body System				
None				
Genital System				
Clitoral gland	(45)	(48)	(49)	(49)
Adenoma	1 (2%)	1 (2%)	1 (2%)	
Ovary	(50)	(50)	(50)	(50)
Adenoma, tubular			1 (2%)	
Granulosa cell tumor benign	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Leiomyoma				1 (2%)
Polyp stromal	5 (10%)	9 (18%)	7 (14%)	7 (14%)
Sarcoma stromal	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Vagina	(1)	(1)	(4)	(1)
Hematopoietic System				
Blood	(2)		(1)	(1)
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(8)	(6)	(11)	(6)
Lymph node, mandibular	(50)	(50)	(50)	(49)
Fibrosarcoma, metastatic, skin		1 (2%)		
Lymph node, mesenteric	(50)	(49)	(50)	(50)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Spleen	(50)	(49)	(50)	(50)
Thymus	(48)	(48)	(50)	(47)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(49)	(50)	(48)	(50)
Adenocarcinoma	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Adenoma			1 (2%)	
Fibroadenoma	10 (20%)	12 (24%)	6 (13%)	3 (6%)
Fibroadenoma, multiple	5 (10%)	1 (2%)		2 (4%)
Fibrosarcoma	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)	1 (2%)		1 (2%)
Fibroma		2 (4%)		
Fibrosarcoma		1 (2%)		
Sarcoma		1 (2%)	1 (2%)	
Trichoepithelioma	1 (2%)			
Pinna, neurofibroma				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)
Nervous System				
Brain	(50)	(50)	(49)	(50)
Astrocytoma malignant		1 (2%)		
Carcinoma, metastatic, pituitary gland			1 (2%)	
Spinal cord			(1)	(1)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		2 (4%)		
Carcinoma, metastatic, thyroid gland		1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)		
Squamous cell carcinoma, metastatic, ear	1 (2%)			
Special Senses System				
Ear	(1)			
Squamous cell carcinoma, metastatic, ear	1 (100%)			
Zymbal's gland	(1)	(1)	(1)	
Carcinoma			1 (100%)	
Urinary System				
Kidney	(50)	(49)	(48)	(49)
Lipoma			1 (2%)	
Renal tubule, adenoma				2 (4%)
Urinary bladder	(47)	(44)	(47)	(48)
Papilloma			1 (2%)	1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Leukemia mononuclear	13 (26%)	14 (28%)	14 (28%)	13 (26%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	3	4	5	3
2-Year study	46	47	45	43
Total primary neoplasms				
15-Month interim evaluation	3	4	6	3
2-Year study	74	101	71	72
Total animals with benign neoplasms				
15-Month interim evaluation	3	4	5	3
2-Year study	40	44	37	35
Total benign neoplasms				
15-Month interim evaluation	3	4	6	3
2-Year study	56	76	50	54
Total animals with malignant neoplasms				
2-Year study	18	22	20	17
Total malignant neoplasms				
2-Year study	18	25	21	18
Total animals with metastatic neoplasms				
2-Year study	2	3	1	
Total metastatic neoplasms				
2-Year study	7	4	1	

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] No neoplasms were observed at any site in any animal at the 9-month interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm

Number of Days on Study	2 6 0	4 5 0	5 5 1	5 6 3	5 7 5	6 1 3	6 4 8	6 4 9	6 5 0	6 6 0	6 6 0	6 6 2	6 6 8	6 7 5	6 7 7	6 8 0	6 8 4	7 2 8	7 2 9	7 4 6	7 4 7	7 4 7	7 4 7	7 4 7
Carcass ID Number	3 4 3	3 0 2	3 4 1	3 1 4	3 4 9	3 4 8	3 0 7	3 5 7	3 5 6	3 2 9	3 3 4	3 3 9	3 6 2	3 4 7	3 1 1	3 1 3	3 5 3	3 3 0	3 0 9	3 2 3	3 2 6	3 3 7	3 3 1	3 3 2
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus				X																				
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus				X																				
Mesentery				+							+									+				
Sarcoma stromal, metastatic, uterus				X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus				X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X				X		X	X		X	X			X		X	X	X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X	X															
C-cell, carcinoma																								
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Adenoma																						X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign									X															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal													X											X
Sarcoma stromal			X	X																				
Vagina														+										

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm (continued)

Number of Days on Study	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	
Carcass ID Number	3 3 6	3 3 7	3 4 2	3 4 4	3 4 5	3 5 1	3 5 2	3 5 4	3 5 5	3 5 9	3 6 0	3 6 1	3 6 4	3 6 5	3 9 8	3 0 1	3 0 4	3 0 5	3 0 8	3 0 9	3 1 2	3 1 6	3 1 7	3 1 8	3 1 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma stromal, metastatic, uterus																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Mesentery													+													4
Sarcoma stromal, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X										X									3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X	X	X	X	X	X		X	X					X	X			X	X	X		26
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X																									3
C-cell, carcinoma																							X			1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																				X	X			X		5
Sarcoma stromal																										2
Vagina																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm (continued)

Number of Days on Study	2 4 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7
	6 5 5 6 7 1 4 4 5 6 6 6 6 7 7 8 8 2 2 4 4 4 4 4
	0 0 1 3 5 3 8 9 0 0 0 2 8 5 7 0 4 8 9 6 7 7 7 7
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 2 3 3 3 3 3
	4 0 4 1 4 4 0 5 5 2 3 3 6 4 1 1 5 3 0 9 2 2 2 3 3
	3 2 1 4 9 8 7 7 6 9 4 9 2 7 1 3 3 5 3 9 3 6 7 1 2
Hematopoietic System	
Blood	+ +
Bone marrow	+ +
Lymph node	+ + + + + + + + + +
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ +
Sarcoma stromal, metastatic, uterus	X
Spleen	+ +
Thymus	+ + + + + + + + + + + + + M + + + + + M + + + + +
Integumentary System	
Mammary gland	+ + + + + + + + + + + + + + + + + + + M + + + + +
Adenocarcinoma	
Fibroadenoma	X X X X X
Fibroadenoma, multiple	X
Fibrosarcoma	
Skin	+ +
Basal cell adenoma	X
Trichoepithelioma	X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Squamous cell carcinoma, metastatic, ear	X
Nose	+ +
Trachea	+ +
Special Senses System	
Ear	+
Squamous cell carcinoma, metastatic, ear	X
Eye	+ +
Harderian gland	
Zymbal's gland	+
Urinary System	
Kidney	+ +
Urinary bladder	+ + + + A + + + + + A + + + + + A + + + + + + + +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X X X X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm (continued)

Number of Days on Study	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	7 4 8	
Carcass ID Number	3 3 6	3 3 7	3 4 2	3 4 4	3 4 5	3 5 1	3 5 2	3 5 4	3 5 5	3 5 9	3 6 0	3 6 1	3 6 4	3 6 5	3 9 8	3 0 1	3 0 4	3 0 5	3 0 8	3 0 9	3 1 2	3 1 6	3 1 7	3 1 8	3 1 9	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma				X																						1
Fibroadenoma													X	X				X					X		X	10
Fibroadenoma, multiple		X					X				X											X				5
Fibrosarcoma		X																								1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Trichoepithelioma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, ear																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Squamous cell carcinoma, metastatic, ear																										1
Eye																										2
Harderian gland																	+									1
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X																13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 100 ppm

Number of Days on Study	4 5 0	4 8 8	4 9 4	5 7 9	6 1 9	6 3 2	6 6 0	6 7 1	6 8 1	6 8 5	6 9 9	7 1 2	7 1 3	7 1 8	7 2 0	7 2 1	7 2 8	7 2 9	7 4 1	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	3 6 8	4 2 6	3 8 7	4 3 2	4 2 2	4 0 0	3 7 8	3 9 9	4 1 2	3 7 6	4 3 4	3 7 0	4 2 4	4 3 5	4 3 6	3 0 6	3 6 6	3 8 4	4 0 1	3 8 1	3 6 9	3 7 1	3 7 2	3 7 3	3 7 5	3 7 7
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	+	+	+	+	+	+	A	A	A	+	+	+	A	A	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	A	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									X	
Mesentery									+									+		+						+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Pheochromocytoma malignant																										
Pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenoma																								X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																									X	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Pars distalis, adenoma	X			X		X		X		X	X	X		X	X	X			X		X				X	
Pars distalis, adenoma, multiple		X																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X				X																
C-cell, carcinoma																										
Follicular cell, adenoma																										
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X															
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X			X				X				X		X				X						X
Sarcoma stromal																										
Vagina						+																				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 100 ppm (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	
Carcass ID Number	3 7 9	4 0 2	3 7 4	3 8 2	3 8 3	3 8 8	3 9 0	3 9 3	3 9 8	4 0 3	4 0 5	4 0 8	4 1 1	4 1 5	4 1 6	4 2 3	4 3 1	4 1 3	4 1 9	4 2 0	4 2 1	4 2 8	4 2 9	4 3 0	4 3 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery						+			+																	6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant	X																									1
Pheochromocytoma benign					X			X				X														3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X																							2
Parathyroid gland	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X					X	X	X		X	X				X	X	X	X	X	X	X	X	X	29
Pars distalis, adenoma, multiple						X										X										3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X									X								X		X			X	X	8
C-cell, carcinoma					X													X								2
Follicular cell, adenoma																X										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal											X		X													9
Sarcoma stromal		X																								1
Vagina																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 100 ppm (continued)

Number of Days on Study	4 5 0	4 8 8	4 9 4	5 7 9	6 1 9	6 3 2	6 6 0	6 7 1	6 8 1	6 8 5	6 9 9	7 1 2	7 1 3	7 1 8	7 2 0	7 2 1	7 2 8	7 2 9	7 4 1	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	3 6 8	4 2 6	3 8 7	4 3 2	4 2 2	4 0 0	3 7 8	3 9 9	4 1 2	3 7 6	3 3 4	4 7 0	3 2 4	4 3 5	4 0 6	3 6 6	3 8 4	4 0 1	3 8 1	3 6 9	3 7 1	3 7 2	3 7 3	3 7 5	3 7 7
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+				+									+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																							X	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma											X						X							X
Fibroadenoma															X	X			X			X		
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								
Fibroma																								
Fibrosarcoma																							X	
Sarcoma				X																				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																								
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X				
Carcinoma, metastatic, thyroid gland																								
Fibrosarcoma, metastatic, skin																							X	
Pheochromocytoma malignant, metastatic, adrenal medulla																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																								+
Zymbal's gland																					+			
Urinary System																								
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	A	A	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X		X		X								X		X			X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 100 ppm (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	
Carcass ID Number	3 7 9	4 0 2	3 7 4	3 8 2	3 8 3	3 8 8	3 9 0	3 9 3	3 9 8	4 0 3	4 0 5	4 0 8	4 1 1	4 1 5	4 1 6	4 2 3	4 3 1	4 1 3	4 1 9	4 2 0	4 2 1	4 2 8	4 2 9	4 3 0	4 3 3	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+		+															+		6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma										X																4
Fibroadenoma	X		X				X				X							X		X			X	X		12
Fibroadenoma, multiple																			X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma					X																					1
Fibroma	X							X																		2
Fibrosarcoma																										1
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle								+																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant					X																					1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				2
Carcinoma, metastatic, thyroid gland																		X								1
Fibrosarcoma, metastatic, skin																										1
Pheochromocytoma malignant, metastatic, adrenal medulla	X																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X		X	X				X												X	X	14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm

Number of Days on Study	2 8 8	4 2 5	4 6 6	5 3 9	5 4 6	5 6 7	5 8 8	6 3 8	6 4 6	6 7 5	6 7 5	6 8 8	7 3 0	7 3 0	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2
Carcass ID Number	4 6 5	4 3 6	4 6 7	4 9 9	4 7 8	4 4 3	4 8 4	4 8 0	5 0 5	4 3 7	4 6 9	4 5 5	4 6 2	4 8 2	4 4 0	4 4 4	4 4 5	4 4 8	4 4 9	4 5 3	4 5 4	4 5 6	4 5 7	4 5 8	4 5 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery								+						+			+			+					+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign					X																	X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X			X			X				X					X				
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X				X		X					
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, tubular																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X											X						X				X	
Sarcoma stromal																									
Vagina						+					+											+			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm (continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	4 6 0	4 6 1	4 6 4	4 6 8	4 7 1	4 7 2	4 7 3	4 7 4	4 8 6	4 8 8	4 8 9	4 7 6	4 7 9	4 8 1	4 8 3	4 9 1	4 9 2	4 9 5	4 9 6	4 9 7	4 9 8	5 0 0	5 0 1	5 0 2	5 0 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+										+		+	+												9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue						+																				1
Squamous cell papilloma						X																				1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant							X													X						2
Pheochromocytoma benign																		X								3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X				X		X	X			X	X	X			X					X	15
Pars distalis, adenoma, multiple			X					X						X							X		X			5
Pars distalis, carcinoma																								X		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X	X								X														X	7
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, tubular																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X													X						X				7
Sarcoma stromal																						X				1
Vagina																						+				4

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm (continued)

Number of Days on Study	2	4	4	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	8	2	6	3	4	6	8	3	4	7	7	8	3	3	4	4	4	4	4	4	4	4	4	4
	8	5	6	9	6	7	8	8	6	5	5	8	0	0	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	4	4	4	4	4	4	4	4	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	6	3	6	9	7	4	8	8	0	3	6	5	6	8	4	4	4	4	4	5	5	5	5	5
	5	6	7	9	8	3	4	0	5	7	9	5	2	2	0	4	5	8	9	3	4	6	7	8	9
Hematopoietic System																								
Blood										+														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+				+		+	+					+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma															X									
Adenoma																								
Fibroadenoma								X															X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma							X																	
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+			
Nervous System																								
Brain	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																								
Spinal cord																								
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Zymbal's gland										+														
Carcinoma										X														
Urinary System																								
Kidney	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																X								
Urinary bladder	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X						X		X	X			X	X						X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm (continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	4 6 0	4 6 1	4 6 4	4 6 8	4 7 1	4 7 2	4 7 3	4 7 4	4 8 6	4 8 8	4 8 9	4 7 6	4 7 9	4 8 1	4 8 3	4 9 1	4 9 2	4 9 5	4 9 6	4 9 7	4 9 8	5 0 0	5 0 1	5 0 2	5 0 3	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+			+			+		+				+					+				11
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										1
Adenoma						X																				1
Fibroadenoma				X									X				X							X		6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland																								X		1
Spinal cord													+													1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lipoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma							X																			1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X		X		X		X			X						14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm

Number of Days on Study	4 0 4	4 4 2	5 3 0	5 5 9	5 9 1	6 1 9	6 3 7	6 5 8	6 6 9	6 7 6	7 1 4	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1
Carcass ID Number	5 0 9	5 1 2	5 6 3	5 5 3	5 4 0	5 5 8	5 6 6	5 4 3	5 7 2	5 6 9	5 6 5	5 2 2	5 2 3	5 2 4	5 2 5	5 2 9	5 5 2	5 1 0	5 1 3	5 1 4	5 1 5	5 1 6	5 1 7	5 1 8	5 1 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																	X								
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											+														+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																								+	
Squamous cell papilloma																								X	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign															X		X		X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X				X	X					X	X		X	X	X	X	X				X			
Pars distalis, adenoma, multiple																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X									
C-cell, carcinoma										X															
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																		X							
Polyp stromal						X					X								X						
Sarcoma stromal																									
Vagina																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm (continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	5 2 8	5 3 0	5 3 1	5 3 2	5 3 3	5 3 4	5 3 5	5 4 8	5 5 6	5 6 1	5 6 4	5 6 7	5 6 8	5 7 0	5 7 3	5 7 4	5 7 5	5 3 6	5 4 2	5 4 5	5 4 6	5 5 5	5 5 9	5 6 0	5 6 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroma			X																							1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+																							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																		X						2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X		X		X				X	X	X				X		X		X	X			22
Pars distalis, adenoma, multiple									X							X										3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X											X	X		4
C-cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Polyp stromal	X										X						X						X			7
Sarcoma stromal								X																		1
Vagina													+													1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm (continued)

Number of Days on Study	4	4	5	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	4	3	5	9	1	3	5	6	7	1	3	3	3	3	3	3	4	4	4	4	4	4	4
	4	2	0	9	1	9	7	8	9	6	4	7	7	7	7	7	8	1	1	1	1	1	1	1
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	0	1	6	5	4	5	6	4	7	6	6	2	2	2	2	2	5	1	1	1	1	1	1	1
	9	2	3	3	0	8	6	3	2	9	5	2	3	4	5	9	2	0	3	4	5	6	7	8	9
Hematopoietic System																								
Blood			+																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+		+	+						+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma						X																		
Fibroadenoma				X								X												
Fibroadenoma, multiple						X							X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								
Pinna, neurofibroma																		X						
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma		X																						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+																	
Spinal cord							+																	
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye							+																	
Harderian gland																								
Urinary System																								
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																			X					
Urinary bladder	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X	X	X	X									X			X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride: 1,000 ppm (continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	5 2 8	5 3 0	5 3 1	5 3 2	5 3 3	5 3 4	5 3 5	5 4 8	5 5 6	5 6 1	5 6 4	5 6 7	5 6 8	5 7 0	5 7 3	5 7 4	5 7 5	5 3 6	5 4 2	5 4 5	5 4 6	5 5 5	5 5 9	5 6 0	5 6 2	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+													+					6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Fibroadenoma																					X					3
Fibroadenoma, multiple																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma												X														1
Pinna, neurofibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye									+																	2
Harderian gland									+													+				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																					X					2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma																						X				1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X	X					X				X					X							13

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

	0 ppm	100 ppm	500 ppm	1,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	3/50 (6%)	3/49 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rates[b]	9.7%	9.7%	7.6%	7.7%
Terminal rates[c]	3/31 (10%)	3/31 (10%)	2/36 (6%)	3/39 (8%)
First incidence (days)	737 (T)	737 (T)	546	737 (T)
Life table tests[d]	P=0.449N	P=0.665	P=0.607N	P=0.553N
Logistic regression tests[d]	P=0.550N	P=0.665	P=0.661N	P=0.553N
Cochran-Armitage test[d]	P=0.570N			
Fisher exact test[d]		P=0.651	P=0.661N	P=0.661N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rates	3/50 (6%)	4/49 (8%)	5/50 (10%)	3/50 (6%)
Adjusted rates	9.7%	12.9%	13.0%	7.7%
Terminal rates	3/31 (10%)	4/31 (13%)	4/36 (11%)	3/39 (8%)
First incidence (days)	737 (T)	737 (T)	546	737 (T)
Life table tests	P=0.396N	P=0.500	P=0.427	P=0.553N
Logistic regression tests	P=0.506N	P=0.500	P=0.363	P=0.553N
Cochran-Armitage test	P=0.535N			
Fisher exact test		P=0.489	P=0.357	P=0.661N
Mammary Gland: Fibroadenoma				
Overall rates	15/50 (30%)	13/50 (26%)	6/50 (12%)	5/50 (10%)
Adjusted rates	45.3%	38.0%	15.9%	11.7%
Terminal rates	13/31 (42%)	11/32 (34%)	5/36 (14%)	3/39 (8%)
First incidence (days)	680	720	638	559
Life table tests	P<0.001N	P=0.361N	P=0.010N	P=0.003N
Logistic regression tests	P=0.002N	P=0.280N	P=0.014N	P=0.008N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.412N	P=0.024N	P=0.011N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	15/50 (30%)	13/50 (26%)	7/50 (14%)	5/50 (10%)
Adjusted rates	45.3%	38.0%	18.6%	11.7%
Terminal rates	13/31 (42%)	11/32 (34%)	6/36 (17%)	3/39 (8%)
First incidence (days)	680	720	638	559
Life table tests	P<0.001N	P=0.361N	P=0.019N	P=0.003N
Logistic regression tests	P=0.002N	P=0.280N	P=0.026N	P=0.008N
Cochran-Armitage test	P=0.004N			
Fisher exact test		P=0.412N	P=0.045N	P=0.011N
Mammary Gland: Carcinoma				
Overall rates	1/50 (2%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rates	3.2%	11.3%	2.8%	2.2%
Terminal rates	1/31 (3%)	2/32 (6%)	1/36 (3%)	0/39 (0%)
First incidence (days)	737 (T)	699	737 (T)	619
Life table tests	P=0.212N	P=0.203	P=0.728N	P=0.733N
Logistic regression tests	P=0.257N	P=0.202	P=0.728N	P=0.755
Cochran-Armitage test	P=0.263N			
Fisher exact test		P=0.181	P=0.753N	P=0.753N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
Mammary Gland: Adenoma or Carcinoma				
Overall rates	1/50 (2%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rates	3.2%	11.3%	5.6%	2.2%
Terminal rates	1/31 (3%)	2/32 (6%)	2/36 (6%)	0/39 (0%)
First incidence (days)	737 (T)	699	737 (T)	619
Life table tests	P=0.244N	P=0.203	P=0.552	P=0.733N
Logistic regression tests	P=0.299N	P=0.202	P=0.552	P=0.755
Cochran-Armitage test	P=0.307N			
Fisher exact test		P=0.181	P=0.500	P=0.753N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rates	16/50 (32%)	17/50 (34%)	8/50 (16%)	5/50 (10%)
Adjusted rates	48.3%	46.9%	21.3%	11.7%
Terminal rates	14/31 (45%)	13/32 (41%)	7/36 (19%)	3/39 (8%)
First incidence (days)	680	699	638	559
Life table tests	P<0.001N	P=0.561	P=0.019N	P=0.002N
Logistic regression tests	P<0.001N	P=0.527N	P=0.027N	P=0.004N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.500	P=0.050N	P=0.006N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	26/50 (52%)	32/49 (65%)	20/50 (40%)	25/49 (51%)
Adjusted rates	64.4%	75.5%	50.9%	59.1%
Terminal rates	17/31 (55%)	21/31 (68%)	17/36 (47%)	21/38 (55%)
First incidence (days)	551	450	567	404
Life table tests	P=0.035N	P=0.238	P=0.074N	P=0.216N
Logistic regression tests	P=0.153N	P=0.152	P=0.138N	P=0.493N
Cochran-Armitage test	P=0.174N			
Fisher exact test		P=0.127	P=0.158N	P=0.541N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	26/50 (52%)	32/49 (65%)	21/50 (42%)	25/49 (51%)
Adjusted rates	64.4%	75.5%	53.5%	59.1%
Terminal rates	17/31 (55%)	21/31 (68%)	18/36 (50%)	21/38 (55%)
First incidence (days)	551	450	567	404
Life table tests	P=0.036N	P=0.238	P=0.101N	P=0.216N
Logistic regression tests	P=0.162N	P=0.152	P=0.188N	P=0.493N
Cochran-Armitage test	P=0.183N			
Fisher exact test		P=0.127	P=0.212N	P=0.541N
Thyroid Gland (C-cell): Adenoma				
Overall rates	3/50 (6%)	8/50 (16%)	7/50 (14%)	4/50 (8%)
Adjusted rates	7.7%	22.5%	18.9%	10.3%
Terminal rates	1/31 (3%)	6/32 (19%)	6/36 (17%)	4/39 (10%)
First incidence (days)	649	660	730	737 (T)
Life table tests	P=0.304N	P=0.124	P=0.215	P=0.589
Logistic regression tests	P=0.414N	P=0.107	P=0.167	P=0.515
Cochran-Armitage test	P=0.443N			
Fisher exact test		P=0.100	P=0.159	P=0.500

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	4/50 (8%)	10/50 (20%)	7/50 (14%)	5/50 (10%)
Adjusted rates	10.8%	28.5%	18.9%	12.4%
Terminal rates	2/31 (6%)	8/32 (25%)	6/36 (17%)	4/39 (10%)
First incidence (days)	649	660	730	676
Life table tests	P=0.228N	P=0.094	P=0.337	P=0.603
Logistic regression tests	P=0.334N	P=0.085	P=0.276	P=0.516
Cochran-Armitage test	P=0.364N			
Fisher exact test		P=0.074	P=0.262	P=0.500
Uterus: Stromal Polyp				
Overall rates	5/50 (10%)	9/50 (18%)	7/50 (14%)	7/50 (14%)
Adjusted rates	15.2%	22.8%	17.9%	16.9%
Terminal rates	4/31 (13%)	4/32 (13%)	5/36 (14%)	5/39 (13%)
First incidence (days)	668	494	466	619
Life table tests	P=0.436N	P=0.236	P=0.477	P=0.522
Logistic regression tests	P=0.514	P=0.195	P=0.384	P=0.414
Cochran-Armitage test	P=0.510			
Fisher exact test		P=0.194	P=0.380	P=0.380
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	7/50 (14%)	10/50 (20%)	7/50 (14%)	8/50 (16%)
Adjusted rates	18.7%	25.5%	17.9%	19.3%
Terminal rates	4/31 (13%)	5/32 (16%)	5/36 (14%)	6/39 (15%)
First incidence (days)	551	494	466	619
Life table tests	P=0.340N	P=0.344	P=0.527N	P=0.578N
Logistic regression tests	P=0.492N	P=0.274	P=0.612	P=0.501
Cochran-Armitage test	P=0.490N			
Fisher exact test		P=0.298	P=0.613N	P=0.500
All Organs: Mononuclear Cell Leukemia				
Overall rates	13/50 (26%)	14/50 (28%)	14/50 (28%)	13/50 (26%)
Adjusted rates	30.0%	35.1%	32.6%	29.5%
Terminal rates	3/31 (10%)	8/32 (25%)	8/36 (22%)	8/39 (21%)
First incidence (days)	575	488	425	637
Life table tests	P=0.341N	P=0.559	P=0.567N	P=0.437N
Logistic regression tests	P=0.435	P=0.301	P=0.497	P=0.229
Cochran-Armitage test	P=0.508N			
Fisher exact test		P=0.500	P=0.500	P=0.590N
All Organs: Benign Neoplasms				
Overall rates	40/50 (80%)	44/50 (88%)	37/50 (74%)	35/50 (70%)
Adjusted rates	92.9%	93.5%	85.9%	79.4%
Terminal rates	28/31 (90%)	29/32 (91%)	30/36 (83%)	30/39 (77%)
First incidence (days)	450	450	466	404
Life table tests	P=0.002N	P=0.430	P=0.099N	P=0.016N
Logistic regression tests	P=0.024N	P=0.261	P=0.309N	P=0.126N
Cochran-Armitage test	P=0.033N			
Fisher exact test		P=0.207	P=0.318N	P=0.178N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
All Organs: Malignant Neoplasms				
Overall rates	19/50 (38%)	22/50 (44%)	20/50 (40%)	17/50 (34%)
Adjusted rates	41.8%	52.4%	44.9%	36.9%
Terminal rates	6/31 (19%)	13/32 (41%)	12/36 (33%)	10/39 (26%)
First incidence (days)	551	488	425	442
Life table tests	P=0.139N	P=0.437	P=0.520N	P=0.275N
Logistic regression tests	P=0.405N	P=0.179	P=0.318	P=0.489
Cochran-Armitage test	P=0.260N			
Fisher exact test		P=0.342	P=0.500	P=0.418N
All Organs: Benign or Malignant Neoplasms				
Overall rates	47/50 (94%)	47/50 (94%)	45/50 (90%)	43/50 (86%)
Adjusted rates	95.9%	94.0%	91.8%	87.7%
Terminal rates	29/31 (94%)	29/32 (91%)	32/36 (89%)	33/39 (85%)
First incidence (days)	450	450	425	404
Life table tests	P=0.016N	P=0.418N	P=0.156N	P=0.033N
Logistic regression tests	P=0.065N	P=0.621N	P=0.357N	P=0.136N
Cochran-Armitage test	P=0.070N			
Fisher exact test		P=0.661N	P=0.357N	P=0.159N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.

TABLE B4
Historical Incidence of Mammary Gland Fibroadenomas in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at TSI Mason Research Institute	
1-Amino-2,4-dibromoanthraquinone	21/50
Acetaminophen	19/50
HC Yellow 4	28/50
Pentaerythritol tetranitrate	27/50
Quercetin	29/50
Turmeric oleoresin	13/50
Overall Historical Incidence	
Total	484/1,251 (38.7%)
Standard deviation	13.5%
Range	8%-58%

[a] Data as of 20 August 1992

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	100 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	13	12	10	7
Natural deaths	6	6	4	4
Survivors				
Died last week of study	2	2		1
Terminal sacrifice	29	30	36	38
Animals examined microscopically	70	70	70	70
9-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)	1 (10%)	1 (10%)	1 (10%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan		1 (10%)		1 (10%)
Intestine large, cecum	(10)	(10)	(10)	(10)
Parasite metazoan		1 (10%)	2 (20%)	1 (10%)
Intestine small, ileum	(10)	(10)	(10)	(10)
Parasite metazoan			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus				2 (20%)
Granuloma		1 (10%)	4 (40%)	2 (20%)
Hepatodiaphragmatic nodule	1 (10%)			
Bile duct, hyperplasia			1 (10%)	
Mesentery		(1)		
Fat, necrosis		1 (100%)		
Pancreas	(10)	(10)	(10)	(10)
Inflammation, chronic, focal				2 (20%)
Acinus, atrophy	1 (10%)	1 (10%)	1 (10%)	1 (10%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Inflammation, chronic, focal	2 (20%)	5 (50%)	6 (60%)	4 (40%)
Endocrine System				
Islets, pancreatic	(10)	(10)	(10)	(10)
Hypoplasia		1 (10%)	2 (20%)	4 (40%)
Pituitary gland	(10)	(10)	(9)	(9)
Pars distalis, cyst	4 (40%)	3 (30%)	1 (11%)	1 (11%)
Pars distalis, hyperplasia, focal				1 (11%)
Thyroid gland	(10)	(10)	(10)	(10)
Inflammation, chronic, focal				1 (10%)

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
9-Month Interim Evaluation (continued)				
General Body System				
None				
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Abscess		1 (10%)		
Cyst				1 (10%)
Inflammation, chronic, focal	6 (60%)	8 (80%)	9 (90%)	8 (80%)
Ovary	(10)	(10)	(10)	(10)
Cyst			2 (20%)	
Uterus	(10)	(10)	(10)	(10)
Dilatation	2 (20%)	1 (10%)	6 (60%)	1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Myelofibrosis		2 (20%)	1 (10%)	
Lymph node				(2)
Pancreatic, giant cell				2 (100%)
Pancreatic, pigmentation, hemosiderin				2 (100%)
Lymph node, mandibular	(10)	(10)	(10)	(10)
Congestion				1 (10%)
Giant cell	1 (10%)	1 (10%)	1 (10%)	
Lymph node, mesenteric	(10)	(10)	(8)	(10)
Giant cell	9 (90%)	10 (100%)	8 (100%)	10 (100%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
Brain	(10)	(10)	(10)	(10)
Choroid plexus, inflammation, chronic				1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Granuloma	1 (10%)			
Peribronchial, inflammation, chronic	10 (100%)	10 (100%)	9 (90%)	10 (100%)
Nose	(10)	(10)	(9)	(10)
Inflammation, chronic, focal	10 (100%)	10 (100%)	9 (100%)	8 (80%)
Metaplasia, squamous	2 (20%)	1 (10%)		1 (10%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
9-Month Interim Evaluation (continued)				
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization, focal	2 (20%)	5 (50%)	7 (70%)	
Nephropathy	1 (10%)			
Renal tubule, regeneration	1 (10%)	2 (20%)	1 (10%)	2 (20%)
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan	2 (20%)	3 (30%)		
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	3 (30%)	2 (20%)	1 (10%)	4 (40%)
Intestine large, cecum	(10)	(10)	(10)	(10)
Parasite metazoan			1 (10%)	2 (20%)
Liver	(10)	(10)	(10)	(10)
Angiectasis, focal			1 (10%)	
Basophilic focus	7 (70%)	9 (90%)	5 (50%)	7 (70%)
Clear cell focus	1 (10%)			
Developmental malformation		1 (10%)		
Granuloma		2 (20%)	2 (20%)	2 (20%)
Hepatodiaphragmatic nodule			1 (10%)	
Bile duct, hyperplasia	3 (30%)	1 (10%)	4 (40%)	1 (10%)
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy	1 (10%)	1 (10%)	2 (20%)	1 (10%)
Salivary glands	(10)	(10)	(10)	(10)
Inflammation, chronic, focal		1 (10%)		
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	3 (30%)	1 (10%)	1 (10%)	
Coronary artery, inflammation, chronic		1 (10%)		
Myocardium, inflammation, chronic, focal		2 (20%)		1 (10%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Congestion			1 (10%)	
Adrenal medulla	(10)	(10)	(10)	(10)
Hyperplasia, focal		1 (10%)		
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, angiectasis	1 (10%)	1 (10%)	1 (10%)	1 (11%)
Pars distalis, angiectasis, focal	1 (10%)			
Pars distalis, cyst		2 (20%)	1 (10%)	1 (11%)
Pars distalis, hyperplasia	2 (20%)			1 (11%)
Pars distalis, hyperplasia, focal	2 (20%)	3 (30%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
15-Month Interim Evaluation (continued)				
Endocrine System (continued)				
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia	2 (20%)	3 (30%)	2 (20%)	
General Body System				
None				
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Abscess		1 (10%)		
Dilatation	1 (10%)			
Inflammation, chronic	8 (80%)	6 (60%)	6 (60%)	9 (90%)
Ovary	(10)	(10)	(10)	(10)
Inflammation, chronic, focal	1 (10%)			
Uterus	(10)	(10)	(10)	(10)
Dilatation	1 (10%)	1 (10%)	1 (10%)	
Endometrium, fibrosis	1 (10%)			
Hematopoietic System				
Lymph node			(1)	
Mediastinal, congestion			1 (100%)	
Thymus	(10)	(10)	(10)	(8)
Cyst				1 (13%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
Brain	(10)	(10)	(10)	(10)
Capillary, inflammation, chronic				2 (20%)
Respiratory System				
Nose	(10)	(10)	(10)	(10)
Fungus	1 (10%)			1 (10%)
Inflammation, acute	1 (10%)		1 (10%)	1 (10%)
Inflammation, chronic	9 (90%)	10 (100%)	10 (100%)	8 (80%)
Metaplasia, squamous	1 (10%)			
Special Senses System				
Harderian gland	(1)			
Hyperplasia	1 (100%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	8 (80%)	7 (70%)	6 (60%)	7 (70%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic, focal	1 (10%)			1 (10%)
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Angiectasis		1 (2%)		1 (2%)
Intestine large, colon	(47)	(47)	(49)	(49)
Parasite metazoan	5 (11%)	3 (6%)	6 (12%)	3 (6%)
Intestine large, rectum	(49)	(47)	(50)	(50)
Parasite metazoan	4 (8%)	2 (4%)	3 (6%)	1 (2%)
Intestine large, cecum	(46)	(45)	(49)	(48)
Autolysis	1 (2%)			
Dilatation	1 (2%)			
Inflammation, chronic				1 (2%)
Parasite metazoan	3 (7%)	2 (4%)	2 (4%)	5 (10%)
Intestine small, ileum	(46)	(43)	(47)	(48)
Abscess				1 (2%)
Liver	(50)	(50)	(50)	(50)
Abscess	2 (4%)			
Angiectasis	1 (2%)		4 (8%)	4 (8%)
Atrophy		1 (2%)		
Basophilic focus	35 (70%)	39 (78%)	36 (72%)	39 (78%)
Clear cell focus	10 (20%)	8 (16%)	4 (8%)	10 (20%)
Depletion glycogen		1 (2%)		
Developmental malformation	1 (2%)			
Eosinophilic focus			1 (2%)	
Fatty change	8 (16%)	6 (12%)	5 (10%)	7 (14%)
Granuloma	3 (6%)	2 (4%)	1 (2%)	4 (8%)
Hemorrhage	1 (2%)	1 (2%)		
Hepatodiaphragmatic nodule	6 (12%)	3 (6%)	4 (8%)	6 (12%)
Hepatodiaphragmatic nodule, multiple				1 (2%)
Mineralization, focal				1 (2%)
Necrosis, focal	1 (2%)	5 (10%)		1 (2%)
Pigmentation, bile	1 (2%)			
Bile duct, hyperplasia	1 (2%)			
Mesentery	(4)	(6)	(9)	(3)
Accessory spleen				1 (33%)
Inflammation, granulomatous		1 (17%)		
Fat, necrosis	3 (75%)	5 (83%)	8 (89%)	2 (67%)
Pancreas	(50)	(49)	(50)	(50)
Ectopic liver		2 (4%)		
Acinus, atrophy	11 (22%)	9 (18%)	15 (30%)	11 (22%)
Acinus, hyperplasia, focal		1 (2%)		
Artery, inflammation, chronic		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Salivary glands	(50)	(50)	(50)	(50)
Depletion cellular	2 (4%)			
Hyperplasia	1 (2%)		1 (2%)	
Hypoplasia	1 (2%)			
Inflammation, chronic, focal		1 (2%)		
Stomach, forestomach	(50)	(49)	(50)	(50)
Acanthosis				1 (2%)
Diverticulum				1 (2%)
Hyperkeratosis		1 (2%)		
Hyperplasia, squamous	2 (4%)			
Inflammation, subacute		1 (2%)		
Ulcer	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(50)	(49)	(50)	(50)
Depletion cellular		1 (2%)	1 (2%)	1 (2%)
Edema, focal				1 (2%)
Erosion	5 (10%)	8 (16%)	3 (6%)	5 (10%)
Hypoplasia	1 (2%)			
Ulcer			1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	22 (44%)	22 (44%)	23 (46%)	26 (52%)
Dilatation	1 (2%)			1 (2%)
Mineralization				1 (2%)
Pigmentation		1 (2%)		
Artery, mineralization			1 (2%)	
Perivascular, inflammation				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Atrophy				1 (2%)
Cytoplasmic alteration, focal	3 (6%)	8 (16%)	8 (16%)	3 (6%)
Hyperplasia, focal	1 (2%)		3 (6%)	
Mineralization, focal				1 (2%)
Vacuolization cytoplasmic	3 (6%)		2 (4%)	2 (4%)
Adrenal medulla	(50)	(49)	(50)	(50)
Fibrosis		1 (2%)		
Hyperplasia, focal	7 (14%)	3 (6%)	3 (6%)	2 (4%)
Necrosis				1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(50)
Hyperplasia		1 (2%)		
Hypoplasia		1 (2%)		
Parathyroid gland	(47)	(46)	(48)	(46)
Hyperplasia		1 (2%)		
Hyperplasia, focal	2 (4%)	1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(50)	(49)	(50)	(49)
Hemorrhage	1 (2%)	1 (2%)		
Pars distalis, angiectasis	4 (8%)	2 (4%)	1 (2%)	1 (2%)
Pars distalis, cyst	7 (14%)	2 (4%)	5 (10%)	6 (12%)
Pars distalis, hyperplasia, focal	12 (24%)	13 (27%)	12 (24%)	10 (20%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	12 (24%)	9 (18%)	12 (24%)	12 (24%)
General Body System				
None				
Genital System				
Clitoral gland	(45)	(48)	(49)	(49)
Abscess		2 (4%)		
Cyst	4 (9%)	4 (8%)	1 (2%)	2 (4%)
Depletion cellular		2 (4%)		
Dilatation	9 (20%)	4 (8%)	5 (10%)	9 (18%)
Inflammation, acute	4 (9%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, chronic	5 (11%)	2 (4%)	5 (10%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	1 (2%)
Atrophy				1 (2%)
Cyst	1 (2%)		4 (8%)	2 (4%)
Uterus	(50)	(50)	(50)	(50)
Abscess	1 (2%)			
Angiectasis			1 (2%)	1 (2%)
Atrophy			1 (2%)	2 (4%)
Cyst				2 (4%)
Dilatation	4 (8%)	4 (8%)	3 (6%)	5 (10%)
Thrombosis		2 (4%)	1 (2%)	
Endometrium, cyst	1 (2%)	1 (2%)		1 (2%)
Endometrium, fibrosis			2 (4%)	
Endometrium, hyperplasia, cystic	2 (4%)		1 (2%)	
Vagina	(1)	(1)	(4)	(1)
Dilatation	1 (100%)		1 (25%)	
Exudate		1 (100%)	1 (25%)	
Hematopoietic System				
Blood	(2)		(1)	(1)
Bacterium				1 (100%)
Hypochromasia			1 (100%)	
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia	17 (34%)	11 (22%)	15 (30%)	12 (24%)
Myelofibrosis		1 (2%)		2 (4%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node	(8)	(6)	(11)	(6)
Inguinal, congestion				1 (17%)
Lumbar, congestion				1 (17%)
Lumbar, hyperplasia			1 (9%)	
Mediastinal, angiectasis		1 (17%)	1 (9%)	
Mediastinal, congestion	1 (13%)		1 (9%)	1 (17%)
Mediastinal, hematopoietic cell proliferation			1 (9%)	
Mediastinal, lymphatic, angiectasis			1 (9%)	
Pancreatic, angiectasis		1 (17%)		1 (17%)
Pancreatic, congestion	1 (13%)			
Pancreatic, granuloma			1 (9%)	
Pancreatic, infiltration cellular, histiocyte				1 (17%)
Pancreatic, lymphatic, angiectasis			1 (9%)	2 (33%)
Lymph node, mandibular	(50)	(50)	(50)	(49)
Congestion	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Cyst		1 (2%)		
Infiltration cellular, plasma cell	1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)			1 (2%)
Inflammation, acute		1 (2%)		
Lymphatic, angiectasis			1 (2%)	2 (4%)
Lymph node, mesenteric	(50)	(49)	(50)	(50)
Congestion	3 (6%)	1 (2%)	3 (6%)	4 (8%)
Depletion lymphoid	1 (2%)			1 (2%)
Giant cell	1 (2%)			
Granuloma	1 (2%)			1 (2%)
Spleen	(50)	(49)	(50)	(50)
Autolysis	1 (2%)			
Congestion	1 (2%)			
Depletion lymphoid	4 (8%)	1 (2%)	6 (12%)	9 (18%)
Fibrosis, focal	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Granuloma	1 (2%)		1 (2%)	
Hematopoietic cell proliferation	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Infarct	1 (2%)		1 (2%)	
Necrosis, focal		1 (2%)		
Pigmentation, hemosiderin	1 (2%)			
Capsule, fibrosis	1 (2%)			1 (2%)
Thymus	(48)	(48)	(50)	(47)
Cyst				2 (4%)
Depletion lymphoid	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia			1 (2%)	
Lymphatic, angiectasis		1 (2%)		
Integumentary System				
Mammary gland	(49)	(50)	(48)	(50)
Galactocele	9 (18%)	5 (10%)	2 (4%)	1 (2%)
Galactocele, multiple	1 (2%)	1 (2%)		
Lactation	35 (71%)	36 (72%)	27 (56%)	25 (50%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(50)
Acanthosis		1 (2%)		
Cyst epithelial inclusion		1 (2%)		
Fibrosis			1 (2%)	
Hyperkeratosis	1 (2%)		1 (2%)	
Perivascular, inflammation, chronic			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	6 (12%)	9 (18%)	12 (24%)	8 (16%)
Skeletal muscle	(1)	(1)	(1)	
Ectopic tissue	1 (100%)		1 (100%)	
Nervous System				
Brain	(50)	(50)	(49)	(50)
Abscess				1 (2%)
Compression	4 (8%)	6 (12%)	4 (8%)	4 (8%)
Congestion	1 (2%)			
Hemorrhage	1 (2%)	4 (8%)	2 (4%)	4 (8%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Angiectasis		2 (4%)	2 (4%)	
Congestion			1 (2%)	
Emphysema, focal			1 (2%)	
Hemorrhage, focal			1 (2%)	
Mineralization, focal				1 (2%)
Necrosis, focal	3 (6%)			
Alveolar epithelium, metaplasia	2 (4%)		1 (2%)	1 (2%)
Pleura, fibrosis, focal			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Fungus	3 (6%)	4 (8%)	3 (6%)	2 (4%)
Inflammation, acute	1 (2%)	1 (2%)	4 (8%)	9 (18%)
Inflammation, chronic	1 (2%)	2 (4%)	6 (12%)	6 (12%)
Special Senses System				
Eye	(2)	(1)		(2)
Cataract		1 (100%)		1 (50%)
Retina, degeneration	1 (50%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	100 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(49)	(48)	(49)
Abscess				1 (2%)
Bacterium				1 (2%)
Cyst		1 (2%)	1 (2%)	1 (2%)
Glomerulosclerosis		2 (4%)		1 (2%)
Mineralization	19 (38%)	22 (45%)	20 (42%)	20 (41%)
Nephropathy	37 (74%)	42 (86%)	33 (69%)	33 (67%)
Pigmentation				1 (2%)
Renal tubule, degeneration, granular	1 (2%)	1 (2%)	1 (2%)	
Renal tubule, necrosis, focal	1 (2%)			
Renal tubule, pigmentation, bile	4 (8%)	6 (12%)	1 (2%)	2 (4%)
Urinary bladder	(47)	(44)	(47)	(48)
Hemorrhage				2 (4%)
Hyperplasia, focal		1 (2%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF METHYLPHENIDATE HYDROCHLORIDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	50 ppm	250 ppm	500 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	2	2	4	4
Natural deaths	3	3	2	5
Survivors				
Died last week of study			1	
Terminal sacrifice	45	45	43	41
Animals examined microscopically	70	70	70	70
9-Month Interim Evaluation				
Alimentary System[b]				
Liver	(10)	(10)	(10)	(10)
Hepatocellular adenoma			1 (10%)	
15-Month Interim Evaluation				
Alimentary System[c]				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma				1 (10%)
Hepatocellular adenoma	2 (20%)		1 (10%)	1 (10%)
Hepatocellular adenoma, multiple				1 (10%)
Respiratory System				
Lung	(10)	(9)	(10)	(10)
Alveolar/bronchiolar adenoma		1 (11%)		
2-Year Study				
Alimentary System				
Intestine large, cecum	(48)	(49)	(48)	(47)
Intestine small, duodenum	(48)	(48)	(48)	(48)
Intestine small, jejunum	(48)	(48)	(47)	(46)
Intestine small, ileum	(47)	(48)	(48)	(46)
Sarcoma		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Hemangioma			1 (2%)	
Hemangiosarcoma	3 (6%)	2 (4%)	1 (2%)	
Hepatoblastoma		1 (2%)		4 (8%)
Hepatoblastoma, multiple			1 (2%)	1 (2%)
Hepatocellular carcinoma	8 (16%)	8 (16%)	15 (30%)	10 (20%)
Hepatocellular carcinoma, multiple	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Hepatocellular adenoma	13 (26%)	8 (16%)	10 (20%)	15 (30%)
Hepatocellular adenoma, multiple	5 (10%)	10 (20%)	6 (12%)	14 (28%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Sarcoma		1 (2%)		
Mesentery	(1)	(3)	(1)	(2)
Hepatoblastoma, metastatic, liver				1 (50%)
Sarcoma		1 (33%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(49)	(50)	(50)
Hemangiosarcoma, metastatic, spleen				1 (2%)
Sarcoma		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)		
Stomach, glandular	(48)	(49)	(50)	(47)
Sarcoma		1 (2%)		
Tongue	(3)		(1)	(2)
Squamous cell papilloma	1 (33%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, prostate		1 (2%)		
Hemangiosarcoma		1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(49)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	
Capsule, adenoma	1 (2%)	2 (4%)		
Adrenal medulla	(48)	(48)	(49)	(48)
Pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(50)	(48)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(48)	(48)	(44)	(44)
Pars intermedia, adenoma				1 (2%)
Pars intermedia, carcinoma			1 (2%)	
Thyroid gland	(50)	(50)	(49)	(50)
Follicular cell, adenoma	1 (2%)	1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Prostate	(50)	(50)	(49)	(48)
Adenocarcinoma		1 (2%)		
Sarcoma		1 (2%)		
Seminal vesicle	(50)	(49)	(50)	(50)
Sarcoma		2 (4%)		
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma			2 (4%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	1 (2%)	2 (4%)
Histiocytic sarcoma		1 (2%)		
Mast cell tumor NOS				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node	(3)	(5)	(1)	(2)
Mediastinal, histiocytic sarcoma		1 (20%)		
Mediastinal, sarcoma		2 (40%)		
Pancreatic, sarcoma		1 (20%)		
Lymph node, mandibular	(49)	(47)	(49)	(49)
Lymph node, mesenteric	(48)	(48)	(45)	(47)
Histiocytic sarcoma		1 (2%)		
Sarcoma		2 (4%)		
Spleen	(50)	(49)	(49)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)	3 (6%)
Histiocytic sarcoma		1 (2%)		
Mast cell tumor NOS				1 (2%)
Sarcoma		1 (2%)		
Thymus	(38)	(41)	(38)	(38)
Sarcoma		1 (2%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Fibroma				1 (2%)
Hemangiosarcoma				1 (2%)
Lipoma			1 (2%)	
Sarcoma	2 (4%)			
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, prostate		1 (2%)		
Alveolar/bronchiolar adenoma	13 (26%)	6 (12%)	5 (10%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		2 (4%)	
Alveolar/bronchiolar carcinoma	4 (8%)	5 (10%)	2 (4%)	1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)			1 (2%)
Hepatoblastoma, metastatic, liver				1 (2%)
Hepatocellular carcinoma, metastatic, liver	4 (8%)		4 (8%)	
Histiocytic sarcoma		1 (2%)		1 (2%)
Sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Harderian gland	(5)	(2)		(2)
Adenoma	4 (80%)	1 (50%)		1 (50%)
Carcinoma	1 (20%)			1 (50%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Urinary bladder	(48)	(48)	(48)	(47)
Systemic Lesions				
Multiple organs[d]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Lymphoma malignant lymphocytic		1 (2%)		1 (2%)
Lymphoma malignant mixed	3 (6%)	4 (8%)	3 (6%)	8 (16%)
Neoplasm Summary				
Total animals with primary neoplasms[e]				
9-Month interim evaluation			1	
15-Month interim evaluation	2	1	1	3
2-Year study	41	35	33	43
Total primary neoplasms				
9-Month interim evaluation			1	
15-Month interim evaluation	2	1	1	3
2-Year study	67	72	56	74
Total animals with benign neoplasms				
9-Month interim evaluation			1	
15-Month interim evaluation	2	1	1	2
2-Year study	31	23	23	33
Total benign neoplasms				
9-Month interim evaluation			1	
15-Month interim evaluation	2	1	1	2
2-Year study	43	30	29	38
Total animals with malignant neoplasms				
15-Month interim evaluation				1
2-Year study	19	24	22	24
Total malignant neoplasms				
15-Month interim evaluation				1
2-Year study	24	42	27	34
Total animals with metastatic neoplasms				
2-Year study	5	2	5	4
Total metastatic neoplasms				
2-Year study	5	3	5	4
Total animals with uncertain neoplasms benign or malignant				
2-Year study				1
Total uncertain neoplasms				
2-Year study				2

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] No neoplasms were observed at any other site in any animal at the 9-month interim evaluation.
[c] No neoplasms were observed at any other site in any animal at the 15-month interim evaluation.
[d] Number of animals with any tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm

Number of Days on Study	5 3 7	6 1 7	6 3 9	6 4 0	6 7 9	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1
Carcass ID Number	0 1 6	0 6 0	0 0 7	0 6 7	0 1 0	0 1 2	0 0 3	0 0 5	0 0 9	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 7	0 2 9	0 3 2	0 3 3
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	A	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hepatocellular carcinoma	X		X		X																			
Hepatocellular carcinoma, multiple																								
Hepatocellular adenoma						X			X	X	X		X	X			X	X			X		X	
Hepatocellular adenoma, multiple					X		X																	
Mesentery							+																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Stomach, glandular	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue														+										
Squamous cell papilloma														X										
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Capsule, adenoma																								
Adrenal medulla	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	
Carcass ID Number	0 3 6	0 3 8	0 3 9	0 4 0	0 4 2	0 4 3	0 4 4	0 4 5	0 4 7	0 4 8	0 4 9	0 5 1	0 5 3	0 5 4	0 5 5	0 5 7	0 5 8	0 5 9	0 6 1	0 6 2	0 6 3	0 6 4	0 6 6	0 6 8	0 6 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																	X				X				X	3
Hepatocellular carcinoma		X																		X	X	X	X			8
Hepatocellular carcinoma, multiple						X					X															2
Hepatocellular adenoma																X					X	X				13
Hepatocellular adenoma, multiple						X		X						X												5
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma	X																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue													+										+			3
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																	1
Capsule, adenoma	X																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	M	M	M	+	+	+	+	M	M	+	+	+	+	M	+	39
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma												X														1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	5 3 7	6 1 7	6 3 9	6 4 0	6 7 9	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1
Carcass ID Number	0 1 6	0 6 0	0 0 7	0 6 7	0 1 0	0 1 2	0 0 3	0 0 5	0 0 9	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 7	0 2 9	0 3 2	0 3 3
Hematopoietic System																								
Blood					+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+			+																		
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Thymus	+	+	M	M	+	+	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma				X																				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X	X						X			X						X					X	X	
Alveolar/bronchiolar adenoma, multiple										X														
Alveolar/bronchiolar carcinoma																								
Carcinoma, metastatic, harderian gland																								
Hepatocellular carcinoma, metastatic, liver																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland														+										
Adenoma														X										
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed		X																	X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	
Carcass ID Number	0 3 6	0 3 8	0 3 9	0 4 0	0 4 2	0 4 3	0 4 4	0 4 5	0 4 7	0 4 8	0 4 9	0 5 1	0 5 3	0 5 4	0 5 5	0 5 7	0 5 8	0 5 9	0 6 1	0 6 2	0 6 3	0 6 4	0 6 6	0 6 8	0 6 9	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										17
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														1
Thymus	+	+	+	+	+	M	+	M	+	+	M	M	+	+	M	+	M	+	+	M	+	+	M	+	+	38
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																		X								2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X	X				X				X			X								X		13
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma													X			X		X					X			4
Carcinoma, metastatic, harderian gland																				X						1
Hepatocellular carcinoma, metastatic, liver		X				X					X													X		4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland			+																+	+		+				5
Adenoma			X																X			X				4
Carcinoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed												X														3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm

Number of Days on Study	6 2 8	6 7 4	7 0 7	7 0 8	7 2 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	0 7 6	0 8 1	0 7 9	1 1 5	1 2 8	0 7 2	0 7 3	0 7 4	0 7 8	0 8 2	0 8 3	0 8 4	0 8 5	0 8 7	0 8 8	0 8 9	0 9 0	0 9 4	0 9 5	1 0 1	1 0 2	1 0 3	1 0 5	1 0 6	1 1 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X					X			
Hepatoblastoma																									
Hepatocellular carcinoma			X												X						X				X
Hepatocellular carcinoma, multiple							X																		
Hepatocellular adenoma					X					X	X														
Hepatocellular adenoma, multiple														X	X						X				X
Histiocytic sarcoma		X																							
Sarcoma																									
Mesentery											+														
Sarcoma																									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, prostate	X																								
Hemangiosarcoma																						X			
Endocrine System																									
Adrenal cortex	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma									X																
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	
Carcass ID Number	1 1 6	1 1 8	1 0 7	1 0 8	1 0 9	1 1 0	1 1 1	1 1 2	1 1 3	1 2 1	1 2 2	1 2 3	1 2 4	1 2 5	1 3 0	1 3 1	1 3 2	1 3 3	1 3 4	1 3 5	1 3 6	1 3 7	1 3 8	1 3 9	1 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																X										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatoblastoma																								X		1
Hepatocellular carcinoma	X	X										X	X													8
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma									X					X	X	X	X									8
Hepatocellular adenoma, multiple		X						X		X									X		X			X		10
Histiocytic sarcoma																										1
Sarcoma																X										1
Mesentery										+		+														3
Sarcoma												X														1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																X										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma														X												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																X										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, prostate																										1
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma		X													X											2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma										X																1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	M	M	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm
(continued)

Number of Days on Study	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	7	0	0	2	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	8	4	7	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
	7	8	7	1	2	7	7	7	7	8	8	8	8	8	8	8	9	9	9	0	0	0	0	1
	6	1	9	5	8	2	3	4	8	2	3	4	5	7	8	9	0	4	5	1	2	3	5	6	4
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	X																							
Sarcoma																								
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X									
Histiocytic sarcoma		X																						
Lymph node		+														+								
Mediastinal, histiocytic sarcoma		X																						
Mediastinal, sarcoma																								
Pancreatic, sarcoma																								
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Sarcoma																								
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Sarcoma																								
Thymus	A	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								
Integumentary System																								
Mammary gland	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, prostate	X																							
Alveolar/bronchiolar adenoma						X				X				X			X							
Alveolar/bronchiolar carcinoma														X					X					
Histiocytic sarcoma		X																						
Sarcoma																								
Sarcoma, metastatic, mesentery																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	
Carcass ID Number	1 1 6	1 1 8	1 0 7	1 0 8	1 0 9	1 1 0	1 1 1	1 1 2	1 1 3	1 2 1	1 2 2	1 2 3	1 2 4	1 2 5	1 3 0	1 3 1	1 3 2	1 3 3	1 3 4	1 3 5	1 3 6	1 3 7	1 3 8	1 3 9	1 4 0	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenocarcinoma																										1	
Sarcoma																X										1	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Sarcoma																X	X									2	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hemangiosarcoma																										1	
Histiocytic sarcoma																										1	
Lymph node				+												+	+									5	
Mediastinal, histiocytic sarcoma																										1	
Mediastinal, sarcoma																X	X									2	
Pancreatic, sarcoma																	X									1	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Histiocytic sarcoma																										1	
Sarcoma																X	X									2	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Histiocytic sarcoma																										1	
Sarcoma																X										1	
Thymus	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	41	
Sarcoma																X										1	
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenocarcinoma, metastatic, prostate																										1	
Alveolar/bronchiolar adenoma	X																			X						6	
Alveolar/bronchiolar carcinoma				X				X									X									5	
Histiocytic sarcoma																										1	
Sarcoma																X										1	
Sarcoma, metastatic, mesentery												X														1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm
(continued)

Number of Days on Study	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	7	0	0	2	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	8	4	7	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
	7	8	7	1	2	7	7	7	7	8	8	8	8	8	8	8	9	9	9	0	0	0	0	0	1
	6	1	9	5	8	2	3	4	8	2	3	4	5	7	8	9	0	4	5	1	2	3	5	6	4
Special Senses System																									
Ear				+																					
Harderian gland															+										
Adenoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Urinary bladder	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed				X												X									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	
Carcass ID Number	1 1 6	1 1 8	1 0 7	1 0 8	1 0 9	1 1 0	1 1 1	1 1 2	1 1 3	1 2 1	1 2 2	1 2 3	1 2 4	1 2 5	1 3 0	1 3 1	1 3 2	1 3 3	1 3 4	1 3 5	1 3 6	1 3 7	1 3 8	1 3 9	1 4 0	Total Tissues/ Tumors
Special Senses System																										
Ear																										1
Harderian gland	+																									2
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic															X											1
Lymphoma malignant mixed		X																							X	4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm

Number of Days on Study	5 4 1	5 8 5	6 0 1	6 1 0	6 2 6	7 1 0	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 4 0	7 4 0
Carcass ID Number	1 6 7	1 5 5	2 0 1	2 0 9	2 0 4	2 0 7	1 7 3	1 5 9	1 6 2	1 6 5	1 6 6	1 6 8	1 6 9	1 4 1	1 4 5	1 4 6	1 4 7	1 4 9	1 5 1	1 5 2	1 5 3	1 5 4	1 6 0	1 7 0	1 7 1
Alimentary System																								
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	M	M	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								X
Hemangiosarcoma							X																	
Hepatoblastoma, multiple																								
Hepatocellular carcinoma	X		X	X	X	X	X	X									X					X		X
Hepatocellular carcinoma, multiple														X				X						
Hepatocellular adenoma				X					X				X	X			X							X
Hepatocellular adenoma, multiple											X							X						
Mesentery																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									+															
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X															
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		
Parathyroid gland	+	+	M	M	+	M	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	M	+	M	+	+	M	+	+
Pars intermedia, carcinoma		X																						
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Prostate	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	1 7 5	1 7 6	1 7 7	1 7 8	1 7 9	1 8 0	1 8 2	1 8 3	1 8 4	1 8 5	1 8 6	1 8 8	1 8 9	1 9 2	1 9 4	1 9 5	1 9 6	1 9 7	1 9 8	1 9 9	2 0 0	2 0 3	2 0 5	2 0 8	2 1 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma																										1
Hepatoblastoma, multiple																	X									1
Hepatocellular carcinoma				X											X			X						X	X	15
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma		X										X							X						X	10
Hepatocellular adenoma, multiple						X									X		X					X				6
Mesentery									+																	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	M	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	M	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pars intermedia, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																+										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma				X					X																	2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm
(continued)

Number of Days on Study	5 4 1	5 8 5	6 0 1	6 1 0	6 2 6	7 1 0	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 4 0	7 4 0
Carcass ID Number	1 6 7	1 5 5	2 0 1	2 0 9	2 0 4	2 0 7	1 7 3	1 5 9	1 6 2	1 6 5	1 6 6	1 6 8	1 6 9	1 4 1	1 4 5	1 4 6	1 4 7	1 4 9	1 5 1	1 5 2	1 5 3	1 5 4	1 6 0	1 7 0	1 7 1
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																	
Lymph node																								
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Hemangiosarcoma							X																	
Thymus	M	+	+	M	+	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	M	+	+	+
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																			X					
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland		X																						
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X				X					X					X			
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma													X											
Hepatocellular carcinoma, metastatic, liver				X				X							X				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
None																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary Bladder	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed					X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	1 7 5	1 7 6	1 7 7	1 7 8	1 7 9	1 8 0	1 8 2	1 8 3	1 8 4	1 8 5	1 8 6	1 8 8	1 8 9	1 9 2	1 9 4	1 9 5	1 9 6	1 9 7	1 9 8	1 9 9	2 0 0	2 0 3	2 0 5	2 0 8	2 1 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node								+																		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	M	+	38
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			5
Alveolar/bronchiolar adenoma, multiple																			X						X	2
Alveolar/bronchiolar carcinoma																				X						2
Hepatocellular carcinoma, metastatic, liver																										4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed				X				X																		3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm

Number of Days on Study	5 7 4	6 1 8	6 2 6	6 4 7	6 5 4	6 8 4	6 8 7	7 0 0	7 0 7	7 3 0	7 3 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 1 1	2 4 1	2 7 5	2 7 0	2 2 0	2 6 1	2 1 7	2 7 3	2 7 9	2 1 2	2 1 4	2 1 6	2 1 5	2 2 5	2 2 6	2 2 7	2 2 8	2 2 9	2 3 1	2 3 3	2 3 8	2 5 5	2 5 6	2 5 8	2 5 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatoblastoma, multiple																			X						
Hepatocellular carcinoma	X	X	X						X					X				X	X						
Hepatocellular carcinoma, multiple						X																			
Hepatocellular adenoma		X	X	X							X				X	X		X				X			
Hepatocellular adenoma, multiple							X										X		X					X	
Histiocytic sarcoma									X																
Mesentery																									
Hepatoblastoma, metastatic, liver																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue													+										+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Parathyroid gland	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	I	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma				X																					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 6 0	2 6 4	2 6 6	2 6 8	2 7 4	2 7 8	2 8 0	2 3 5	2 6 9	2 7 1	2 7 2	2 7 6	2 7 7	2 4 2	2 4 3	2 4 9	2 5 2	2 1 8	2 2 3	2 2 4	2 3 9	2 4 0	2 4 5	2 4 7	2 4 6 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma									X				X	X			X									4
Hepatoblastoma, multiple																										1
Hepatocellular carcinoma													X								X		X			10
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma					X	X	X				X			X		X							X			15
Hepatocellular adenoma, multiple			X					X	X			X	X				X	X	X			X			X	14
Histiocytic sarcoma																										1
Mesentery													+	+												2
Hepatoblastoma, metastatic, liver														X												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tongue																										2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	M	+	+	+	+	+	+	+	M	+	M	+	M	+	M	M	M	+	+	M	+	M	M	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	44
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	5 7 4	6 1 8	6 2 6	6 4 7	6 5 4	6 8 4	6 8 7	7 0 0	7 0 7	7 3 0	7 3 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 1 1	2 4 1	2 7 5	2 7 0	2 2 0	2 6 1	2 1 7	2 7 3	2 7 9	2 1 2	2 1 4	2 1 6	2 1 5	2 2 5	2 2 6	2 2 7	2 2 8	2 2 9	2 3 1	2 3 3	2 3 8	2 5 5	2 5 6	2 5 8	2 5 9
Hematopoietic System																									
Blood														+	+	+	+								
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Mast cell tumor NOS																		X							
Lymph node					+								+												
Lymph node, mandibular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X														X					
Mast cell tumor NOS																		X							
Thymus	+	+	M	M	+	+	M	M	M	I	+	+	+	I	+	M	+	M	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Hemangiosarcoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve								+																	
Spinal cord								+																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X			X											
Alveolar/bronchiolar carcinoma						X																			
Carcinoma, metastatic, harderian gland														X											
Hepatoblastoma, metastatic, liver																			X						
Histiocytic sarcoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland														+											
Adenoma																									
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 6 0	2 6 4	2 6 6	2 6 8	2 7 4	2 7 8	2 8 0	2 3 5	2 6 9	2 7 1	2 7 2	2 7 6	2 7 7	2 4 2	2 4 3	2 4 9	2 5 2	2 1 8	2 2 3	2 2 4	2 3 9	2 4 0	2 4 5	2 4 7	2 4 2	Total Tissues/ Tumors
Hematopoietic System																										
Blood																		+	+	+						7
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma	X																									2
Mast cell tumor NOS																										1
Lymph node																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									3
Mast cell tumor NOS																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	38
Integumentary System																										
Mammary gland	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma		X																								1
Hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X								X										X	5
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, harderian gland																										1
Hepatoblastoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland				+																						2
Adenoma				X																						1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	1	2	4	5	8	8	0	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4	8	6	7	4	4	7	0	7	0	0	0	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	4	7	7	2	6	1	7	7	1	1	1	1	2	2	2	2	2	3	3	3	5	5	5	5
	1	1	5	0	0	1	7	3	9	2	4	6	5	5	6	7	8	9	1	3	8	5	6	8	9
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed							X						X			X		X							X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 6 0	2 6 4	2 6 6	2 6 8	2 7 4	2 7 8	2 8 0	2 3 5	2 6 9	2 7 1	2 7 2	2 7 6	2 7 7	2 7 4	2 4 3	2 4 9	2 5 2	2 1 8	2 2 3	2 2 4	2 3 9	2 4 0	2 4 5	2 4 7	2 4 6	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed								X												X		X				8

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride

	0 ppm	50 ppm	250 ppm	500 ppm
Harderian Gland: Adenoma				
Overall rates[a]	4/50 (8%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rates[b]	8.9%	2.2%	0.0%	2.4%
Terminal rates[c]	4/45 (9%)	1/45 (2%)	0/44 (0%)	1/41 (2%)
First incidence (days)	730 (T)	730 (T)	–[e]	730 (T)
Life table tests[d]	P=0.152N	P=0.180N	P=0.066N	P=0.209N
Logistic regression tests[d]	P=0.152N	P=0.180N	P=0.066N	P=0.209N
Cochran-Armitage test[d]	P=0.134N			
Fisher exact test[d]		P=0.181N	P=0.059N	P=0.181N
Harderian Gland: Adenoma or Carcinoma				
Overall rates	5/50 (10%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rates	11.1%	2.2%	0.0%	4.9%
Terminal rates	5/45 (11%)	1/45 (2%)	0/44 (0%)	2/41 (5%)
First incidence (days)	730 (T)	730 (T)	–	730 (T)
Life table tests	P=0.247N	P=0.104N	P=0.036N	P=0.256N
Logistic regression tests	P=0.247N	P=0.104N	P=0.036N	P=0.256N
Cochran-Armitage test	P=0.218N			
Fisher exact test		P=0.102N	P=0.028N	P=0.218N
Liver: Hemangiosarcoma				
Overall rates	3/50 (6%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rates	6.7%	4.4%	2.3%	0.0%
Terminal rates	3/45 (7%)	2/45 (4%)	1/44 (2%)	0/41 (0%)
First incidence (days)	730 (T)	730 (T)	730 (T)	–
Life table tests	P=0.073N	P=0.500N	P=0.314N	P=0.138N
Logistic regression tests	P=0.073N	P=0.500N	P=0.314N	P=0.138N
Cochran-Armitage test	P=0.063N			
Fisher exact test		P=0.500N	P=0.309N	P=0.121N
Liver: Hepatocellular Adenoma				
Overall rates	18/50 (36%)	18/50 (36%)	16/50 (32%)	29/50 (58%)
Adjusted rates	39.1%	39.1%	35.5%	64.2%
Terminal rates	17/45 (38%)	17/45 (38%)	15/44 (34%)	25/41 (61%)
First incidence (days)	679	720	610	618
Life table tests	P=0.004	P=0.579N	P=0.449N	P=0.010
Logistic regression tests	P=0.009	P=0.524N	P=0.437N	P=0.020
Cochran-Armitage test	P=0.012			
Fisher exact test		P=0.582N	P=0.417N	P=0.022
Liver: Hepatocellular Carcinoma				
Overall rates	10/50 (20%)	9/50 (18%)	17/50 (34%)	11/50 (22%)
Adjusted rates	20.7%	19.5%	34.7%	23.4%
Terminal rates	7/45 (16%)	8/45 (18%)	12/44 (27%)	6/41 (15%)
First incidence (days)	537	707	541	574
Life table tests	P=0.224	P=0.494N	P=0.095	P=0.442
Logistic regression tests	P=0.396	P=0.598N	P=0.101	P=0.564
Cochran-Armitage test	P=0.284			
Fisher exact test		P=0.500N	P=0.088	P=0.500

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	24/50 (48%)	23/50 (46%)	26/50 (52%)	34/50 (68%)
Adjusted rates	49.9%	48.9%	53.0%	70.7%
Terminal rates	21/45 (47%)	21/45 (47%)	21/44 (48%)	27/41 (66%)
First incidence (days)	537	707	541	574
Life table tests	P=0.006	P=0.494N	P=0.389	P=0.022
Logistic regression tests	P=0.016	P=0.505N	P=0.444	P=0.037
Cochran-Armitage test	P=0.012			
Fisher exact test		P=0.500N	P=0.421	P=0.034
Liver: Hepatoblastoma				
Overall rates	0/50 (0%)	1/50 (2%)	1/50 (2%)	5/50 (10%)
Adjusted rates	0.0%	2.2%	2.3%	12.2%
Terminal rates	0/45 (0%)	1/45 (2%)	1/44 (2%)	5/41 (12%)
First incidence (days)	–	730 (T)	730 (T)	730 (T)
Life table tests	P=0.004	P=0.500	P=0.496	P=0.026
Logistic regression tests	P=0.004	P=0.500	P=0.496	P=0.026
Cochran-Armitage test	P=0.006			
Fisher exact test		P=0.500	P=0.500	P=0.028
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rates	10/50 (20%)	10/50 (20%)	18/50 (36%)	14/50 (28%)
Adjusted rates	20.7%	21.7%	36.7%	30.0%
Terminal rates	7/45 (16%)	9/45 (20%)	13/44 (30%)	9/41 (22%)
First incidence (days)	537	707	541	574
Life table tests	P=0.084	P=0.589N	P=0.067	P=0.206
Logistic regression tests	P=0.171	P=0.509	P=0.068	P=0.274
Cochran-Armitage test	P=0.114			
Fisher exact test		P=0.598N	P=0.059	P=0.241
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rates	24/50 (48%)	23/50 (46%)	26/50 (52%)	34/50 (68%)
Adjusted rates	49.9%	48.9%	53.0%	70.7%
Terminal rates	21/45 (47%)	21/45 (47%)	21/44 (48%)	27/41 (66%)
First incidence (days)	537	707	541	574
Life table tests	P=0.006	P=0.494N	P=0.389	P=0.022
Logistic regression tests	P=0.016	P=0.505N	P=0.444	P=0.037
Cochran-Armitage test	P=0.012			
Fisher exact test		P=0.500N	P=0.421	P=0.034
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	14/50 (28%)	6/50 (12%)	7/50 (14%)	5/50 (10%)
Adjusted rates	29.6%	13.3%	15.9%	12.2%
Terminal rates	12/45 (27%)	6/45 (13%)	7/44 (16%)	5/41 (12%)
First incidence (days)	537	730 (T)	730 (T)	730 (T)
Life table tests	P=0.068N	P=0.042N	P=0.082N	P=0.035N
Logistic regression tests	P=0.046N	P=0.053N	P=0.068N	P=0.020N
Cochran-Armitage test	P=0.045N			
Fisher exact test		P=0.039N	P=0.070N	P=0.020N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	4/50 (8%)	5/50 (10%)	2/50 (4%)	1/50 (2%)
Adjusted rates	8.9%	11.1%	4.5%	2.2%
Terminal rates	4/45 (9%)	5/45 (11%)	2/44 (5%)	0/41 (0%)
First incidence (days)	730 (T)	730 (T)	730 (T)	684
Life table tests	P=0.075N	P=0.500	P=0.348N	P=0.205N
Logistic regression tests	P=0.067N	P=0.500	P=0.348N	P=0.181N
Cochran-Armitage test	P=0.061N			
Fisher exact test		P=0.500	P=0.339N	P=0.181N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	16/50 (32%)	10/50 (20%)	9/50 (18%)	6/50 (12%)
Adjusted rates	33.9%	22.2%	20.5%	14.1%
Terminal rates	14/45 (31%)	10/45 (22%)	9/44 (20%)	5/41 (12%)
First incidence (days)	537	730 (T)	730 (T)	684
Life table tests	P=0.033N	P=0.130N	P=0.097N	P=0.028N
Logistic regression tests	P=0.021N	P=0.148N	P=0.083N	P=0.014N
Cochran-Armitage test	P=0.019N			
Fisher exact test		P=0.127N	P=0.083N	P=0.014N
Spleen: Hemangiosarcoma				
Overall rates	1/50 (2%)	0/49 (0%)	1/49 (2%)	3/50 (6%)
Adjusted rates	2.2%	0.0%	2.3%	7.0%
Terminal rates	1/45 (2%)	0/45 (0%)	1/43 (2%)	2/41 (5%)
First incidence (days)	730 (T)	–	730 (T)	684
Life table tests	P=0.065	P=0.500N	P=0.751	P=0.283
Logistic regression tests	P=0.075	P=0.500N	P=0.751	P=0.304
Cochran-Armitage test	P=0.077			
Fisher exact test		P=0.505N	P=0.747	P=0.309
All Organs: Hemangiosarcoma				
Overall rates	4/50 (8%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rates	8.9%	6.7%	2.3%	7.0%
Terminal rates	4/45 (9%)	3/45 (7%)	1/44 (2%)	2/41 (5%)
First incidence (days)	730 (T)	730 (T)	730 (T)	684
Life table tests	P=0.436N	P=0.500N	P=0.187N	P=0.543N
Logistic regression tests	P=0.413N	P=0.500N	P=0.187N	P=0.510N
Cochran-Armitage test	P=0.391N			
Fisher exact test		P=0.500N	P=0.181N	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	4/50 (8%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rates	8.9%	6.7%	4.5%	7.0%
Terminal rates	4/45 (9%)	3/45 (7%)	2/44 (5%)	2/41 (5%)
First incidence (days)	730 (T)	730 (T)	730 (T)	684
Life table tests	P=0.473N	P=0.500N	P=0.348N	P=0.543N
Logistic regression tests	P=0.450N	P=0.500N	P=0.348N	P=0.510N
Cochran-Armitage test	P=0.425N			
Fisher exact test		P=0.500N	P=0.339N	P=0.500N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rates	3/50 (6%)	5/50 (10%)	3/50 (6%)	9/50 (18%)
Adjusted rates	6.4%	10.8%	6.6%	20.7%
Terminal rates	2/45 (4%)	4/45 (9%)	2/44 (5%)	7/41 (17%)
First incidence (days)	617	708	626	654
Life table tests	P=0.038	P=0.363	P=0.645	P=0.052
Logistic regression tests	P=0.056	P=0.307	P=0.639N	P=0.064
Cochran-Armitage test	P=0.050			
Fisher exact test		P=0.357	P=0.661N	P=0.061
All Organs: Benign Neoplasms				
Overall rates	31/50 (62%)	23/50 (46%)	23/50 (46%)	33/50 (66%)
Adjusted rates	64.5%	50.0%	51.1%	73.1%
Terminal rates	28/45 (62%)	22/45 (49%)	22/44 (50%)	29/41 (71%)
First incidence (days)	537	720	610	618
Life table tests	P=0.075	P=0.086N	P=0.106N	P=0.239
Logistic regression tests	P=0.150	P=0.074N	P=0.086N	P=0.411
Cochran-Armitage test	P=0.179			
Fisher exact test		P=0.080N	P=0.080N	P=0.418
All Organs: Malignant Neoplasms				
Overall rates	19/50 (38%)	24/50 (48%)	22/50 (44%)	24/50 (48%)
Adjusted rates	38.0%	48.9%	44.0%	49.8%
Terminal rates	14/45 (31%)	20/45 (44%)	16/44 (36%)	17/41 (41%)
First incidence (days)	537	628	541	574
Life table tests	P=0.198	P=0.244	P=0.329	P=0.166
Logistic regression tests	P=0.453	P=0.158	P=0.383	P=0.274
Cochran-Armitage test	P=0.288			
Fisher exact test		P=0.210	P=0.342	P=0.210
All Organs: Benign or Malignant Neoplasms				
Overall rates	41/50 (82%)	35/50 (70%)	33/50 (66%)	43/50 (86%)
Adjusted rates	82.0%	70.0%	66.0%	87.7%
Terminal rates	36/45 (80%)	30/45 (67%)	27/44 (61%)	35/41 (85%)
First incidence (days)	537	628	541	574
Life table tests	P=0.094	P=0.163N	P=0.129N	P=0.195
Logistic regression tests	P=0.282	P=0.118N	P=0.045N	P=0.434
Cochran-Armitage test	P=0.206			
Fisher exact test		P=0.121N	P=0.055N	P=0.393

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and spleen; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence at TSI Mason Research Institute				
1-Amino-2,4-dibromoanthraquinone	10/50	9/50	0/50	18/50
Acetaminophen	11/50	7/50	0/50	16/50
HC Yellow 4	8/49	5/49	0/49	13/49
Pentaerythritol tetranitrate	9/48	3/48	0/48	11/48
Turmeric oleoresin	25/50	12/50	0/50	30/50
Overall Historical Incidence				
Total	312/1,366 (22.8%)	223/1,366 (16.3%)	0/1,366	485/1,366 (35.5%)
Standard deviation	13.8%	7.2%		14.3%
Range	4%-60%	3%-29%		10%-68%

[a] Data as of 20 August 1992

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	50 ppm	250 ppm	500 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	2	2	4	4
Natural deaths	3	3	2	5
Survivors				
Died last week of study			1	
Terminal sacrifice	45	45	43	41
Animals examined microscopically	70	70	70	70
9-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Fatty change	4 (40%)	2 (20%)	2 (20%)	4 (40%)
Mesentery	(1)			
Fat, necrosis	1 (100%)			
Salivary glands	(10)	(10)	(10)	(10)
Inflammation, chronic, focal		3 (30%)	2 (20%)	3 (30%)
Stomach, glandular	(10)	(10)	(10)	(10)
Perivascular, inflammation, chronic			1 (10%)	
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Atrophy	1 (10%)			
Islets, pancreatic	(10)	(10)	(9)	(10)
Hyperplasia	3 (30%)	2 (20%)	2 (22%)	1 (10%)
General Body System				
None				
Genital System				
Preputial gland	(1)	(1)	(1)	(1)
Abscess	1 (100%)			
Cyst		1 (100%)	1 (100%)	1 (100%)
Prostate	(10)	(9)	(8)	(9)
Inflammation, chronic, focal			2 (25%)	

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
9-Month Interim Evaluation (continued)				
Hematopoietic System				
None				
Musculoskeletal System				
None				
Nervous System				
Brain	(10)	(10)	(10)	(10)
Mineralization, focal	5 (50%)	3 (30%)	4 (40%)	5 (50%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Congestion		1 (10%)		
Peribronchial, inflammation, chronic	4 (40%)	4 (40%)	7 (70%)	3 (30%)
Nose	(10)	(10)	(10)	(10)
Degeneration, hyaline			3 (30%)	2 (20%)
Inflammation, chronic, focal	10 (100%)	8 (80%)	10 (100%)	10 (100%)
Metaplasia, squamous		1 (10%)	1 (10%)	1 (10%)
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Inflammation, chronic, focal		1 (10%)		
Renal tubule, regeneration	3 (30%)	3 (30%)	2 (20%)	1 (10%)
Urinary bladder	(10)	(10)	(10)	(10)
Calculus micro observation only				1 (10%)
Inflammation, chronic, focal		3 (30%)		
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Basophilic focus			1 (10%)	1 (10%)
Clear cell focus	1 (10%)		1 (10%)	
Eosinophilic focus		1 (10%)		
Fatty change	1 (10%)	4 (40%)	4 (40%)	5 (50%)
Pancreas	(10)	(10)	(10)	(10)
Inflammation, chronic, focal				1 (10%)
Salivary glands	(10)	(10)	(10)	(10)
Inflammation, chronic, focal	2 (20%)	3 (30%)	2 (20%)	5 (50%)
Stomach, glandular	(10)	(10)	(10)	(10)
Inflammation, chronic				1 (10%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
15-Month Interim Evaluation (continued)				
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia, focal	1 (10%)	2 (20%)		
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia	3 (30%)	3 (30%)	2 (20%)	2 (20%)
General Body System				
None				
Genital System				
Preputial gland	(3)	(2)	(5)	(4)
Abscess			1 (20%)	
Atrophy			1 (20%)	
Cyst		1 (50%)	2 (40%)	2 (50%)
Dilatation	3 (100%)	1 (50%)	1 (20%)	2 (50%)
Inflammation, chronic			1 (20%)	
Prostate	(9)	(10)	(10)	(8)
Inflammation, acute				1 (13%)
Inflammation, chronic		1 (10%)	2 (20%)	2 (25%)
Hematopoietic System				
Lymph node, mesenteric	(10)	(8)	(10)	(9)
Hyperplasia, lymphoid		1 (13%)		
Spleen	(9)	(10)	(10)	(10)
Cyst		1 (10%)		
Hematopoietic cell proliferation				1 (10%)
Hyperplasia, lymphoid		1 (10%)		
Thymus	(10)	(9)	(10)	(8)
Cyst	1 (10%)			
Hyperplasia, lymphoid		1 (11%)		
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
Brain	(10)	(10)	(10)	(10)
Mineralization	5 (50%)	8 (80%)	4 (40%)	5 (50%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Nose	(10)	(10)	(10)	(10)
Inflammation, chronic	8 (80%)	8 (80%)	8 (80%)	7 (70%)
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Casts				1 (10%)
Mineralization	2 (20%)			
Renal tubule, regeneration	5 (50%)	6 (60%)	5 (50%)	5 (50%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic, focal	1 (10%)	3 (30%)	2 (20%)	
2-Year Study				
Alimentary System				
Gallbladder	(46)	(47)	(44)	(44)
Ulcer	1 (2%)			
Intestine large, cecum	(48)	(49)	(48)	(47)
Hyperplasia, lymphoid	33 (69%)	18 (37%)	23 (48%)	24 (51%)
Intestine small, jejunum	(48)	(48)	(47)	(46)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, acute	1 (2%)			1 (2%)
Ulcer		1 (2%)		
Intestine small, ileum	(47)	(48)	(48)	(46)
Hyperplasia, lymphoid	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis	4 (8%)	2 (4%)	1 (2%)	
Basophilic focus	1 (2%)	2 (4%)	4 (8%)	
Clear cell focus	4 (8%)	3 (6%)	2 (4%)	6 (12%)
Eosinophilic focus	6 (12%)	8 (16%)	9 (18%)	14 (28%)
Fatty change	7 (14%)	7 (14%)	7 (14%)	15 (30%)
Fatty change, focal	2 (4%)			2 (4%)
Inflammation, chronic, focal		1 (2%)	1 (2%)	1 (2%)
Necrosis, focal	3 (6%)	1 (2%)	4 (8%)	6 (12%)
Thrombosis	1 (2%)		1 (2%)	1 (2%)
Artery, inflammation, acute				1 (2%)
Mesentery	(1)	(3)	(1)	(2)
Cyst			1 (100%)	
Hemorrhage, focal	1 (100%)			
Mineralization				1 (50%)
Fat, necrosis		2 (67%)		1 (50%)
Pancreas	(50)	(49)	(50)	(50)
Hyperplasia, focal		2 (4%)		
Salivary glands	(50)	(50)	(50)	(50)
Inflammation, chronic, focal		1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(49)	(50)	(50)	(50)
Foreign body	1 (2%)			
Hyperkeratosis, focal			1 (2%)	
Ulcer				2 (4%)
Stomach, glandular	(48)	(49)	(50)	(47)
Erosion		1 (2%)	2 (4%)	2 (4%)
Hyperplasia				1 (2%)
Inflammation, acute	1 (2%)			
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Mucosa, hyperplasia, focal		1 (2%)		
Tongue	(3)		(1)	(2)
Hemorrhage, focal	1 (33%)			1 (50%)
Hyperkeratosis, focal			1 (100%)	
Pigmentation, focal	1 (33%)			1 (50%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic, focal				1 (2%)
Mineralization		1 (2%)		
Ventricle, hypertrophy	1 (2%)			
Endocrine System				
Adrenal cortex	(49)	(49)	(50)	(50)
Atrophy	1 (2%)			
Fibrosis				1 (2%)
Hyperplasia, focal	13 (27%)	16 (33%)	15 (30%)	13 (26%)
Capsule, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Capsule, hyperplasia, focal		1 (2%)		
Adrenal medulla	(48)	(48)	(49)	(48)
Hyperplasia		1 (2%)		
Hyperplasia, focal			2 (4%)	
Islets, pancreatic	(50)	(48)	(50)	(50)
Atrophy				1 (2%)
Hyperplasia	18 (36%)	22 (46%)	18 (36%)	17 (34%)
Pituitary gland	(48)	(48)	(44)	(44)
Pars distalis, cyst	1 (2%)			
Thyroid gland	(50)	(50)	(49)	(50)
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia	2 (4%)	1 (2%)		
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Atrophy	1 (2%)		1 (2%)	
Inflammation, chronic	1 (2%)			
Spermatocele	1 (2%)	1 (2%)		
Preputial gland	(50)	(50)	(49)	(49)
Cyst	36 (72%)	40 (80%)	39 (80%)	32 (65%)
Depletion cellular				1 (2%)
Dilatation	25 (50%)	24 (48%)	24 (49%)	26 (53%)
Hemorrhage, focal	1 (2%)			
Infiltration cellular, plasma cell				1 (2%)
Inflammation, acute	6 (12%)	8 (16%)	7 (14%)	4 (8%)
Inflammation, chronic	9 (18%)	8 (16%)	8 (16%)	6 (12%)
Prostate	(50)	(50)	(49)	(48)
Atrophy			2 (4%)	1 (2%)
Seminal vesicle	(50)	(49)	(50)	(50)
Depletion cellular	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Dilatation	5 (10%)	5 (10%)	7 (14%)	3 (6%)
Fibrosis			1 (2%)	
Testes	(50)	(50)	(50)	(50)
Hypospermia	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Interstitial cell, hyperplasia				1 (2%)
Seminiferous tubule, atrophy			1 (2%)	2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Hyperplasia, neutrophil		2 (4%)	1 (2%)	3 (6%)
Myelofibrosis	1 (2%)		1 (2%)	1 (2%)
Lymph node	(3)	(5)	(1)	(2)
Mediastinal, infiltration cellular, plasma cell		1 (20%)		
Pancreatic, hyperplasia	2 (67%)			
Renal, lymphatic, angiectasis				1 (50%)
Lymph node, mandibular	(49)	(47)	(49)	(49)
Infiltration cellular, plasma cell				1 (2%)
Lymph node, mesenteric	(48)	(48)	(45)	(47)
Congestion	2 (4%)	3 (6%)	3 (7%)	2 (4%)
Fibrosis				1 (2%)
Hyperplasia	1 (2%)		1 (2%)	
Infiltration cellular, plasma cell				1 (2%)
Thrombosis	1 (2%)			
Spleen	(50)	(49)	(49)	(50)
Congestion	1 (2%)	1 (2%)	1 (2%)	
Depletion lymphoid	5 (10%)	3 (6%)	4 (8%)	1 (2%)
Fibrosis, focal	2 (4%)			
Hematopoietic cell proliferation	6 (12%)	7 (14%)	9 (18%)	7 (14%)
Hyperplasia, lymphoid				1 (2%)
Infiltration cellular, plasma cell				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Ulcer			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis		1 (2%)		1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression				1 (2%)
Hemorrhage, focal				1 (2%)
Mineralization	31 (62%)	34 (68%)	30 (60%)	29 (58%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Congestion			1 (2%)	
Hemorrhage, focal	5 (10%)	1 (2%)	1 (2%)	
Infiltration cellular, histiocyte		1 (2%)		
Inflammation, chronic		1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	1 (2%)	4 (8%)	3 (6%)
Nose	(50)	(50)	(50)	(50)
Inflammation, chronic	47 (94%)	45 (90%)	44 (88%)	45 (90%)
Inflammation, chronic, focal	1 (2%)			
Olfactory epithelium, hyperplasia			1 (2%)	
Special Senses System				
Harderian gland	(5)	(2)		(2)
Hyperplasia		1 (50%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Glomerulosclerosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid	2 (4%)		1 (2%)	
Infarct	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic, focal		1 (2%)		1 (2%)
Metaplasia, osseous			1 (2%)	
Mineralization	14 (28%)	14 (28%)	13 (26%)	18 (36%)
Nephropathy	1 (2%)		2 (4%)	1 (2%)
Renal tubule, degeneration, granular	1 (2%)			2 (4%)
Renal tubule, regeneration	30 (60%)	28 (56%)	33 (66%)	30 (60%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Urinary System (continued)				
Urinary bladder	(48)	(48)	(48)	(47)
Calculus micro observation only		1 (2%)		
Concretion			1 (2%)	1 (2%)
Ectasia			1 (2%)	
Perivascular, inflammation, chronic	1 (2%)			1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF METHYLPHENIDATE HYDROCHLORIDE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	50 ppm	250 ppm	500 ppm
Disposition Summary				
Animals initially in study	69	69	70	70
9-Month interim evaluation[b]	10	9	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	1			
Moribund	6	7	7	6
Natural deaths	5	7	6	
Survivors				
Died last week of study	1	1		
Terminal sacrifice	36	34	37	44
Missing		1		
Animals examined microscopically	69	68	70	70
15-Month Interim Evaluation				
Alimentary System[c]				
Liver	(10)	(10)	(10)	(10)
Hemangioma	1 (10%)	1 (10%)	1 (10%)	1 (10%)
Endocrine System				
Pituitary gland	(9)	(9)	(10)	(10)
Pars distalis, adenoma				1 (10%)
Genital System				
Ovary	(9)	(10)	(10)	(10)
Cystadenoma	1 (11%)			1 (10%)
Respiratory System				
Lung	(10)	(10)	(9)	(10)
Alveolar/bronchiolar adenoma	1 (10%)			
2-Year Study				
Alimentary System				
Gallbladder	(44)	(40)	(43)	(48)
Intestine large, rectum	(46)	(46)	(47)	(50)
Intestine large, cecum	(47)	(44)	(45)	(50)
Intestine small, duodenum	(46)	(43)	(45)	(50)
Polyp adenomatous	1 (2%)			
Intestine small, jejunum	(45)	(44)	(45)	(50)
Adenocarcinoma		1 (2%)		
Hemangioma			1 (2%)	
Intestine small, ileum	(45)	(42)	(45)	(49)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(49)	(48)	(49)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Hepatocellular carcinoma	3 (6%)	3 (6%)	2 (4%)	5 (10%)
Hepatocellular carcinoma, multiple	2 (4%)			1 (2%)
Hepatocellular adenoma	4 (8%)	10 (21%)	7 (14%)	13 (26%)
Hepatocellular adenoma, multiple	2 (4%)		3 (6%)	15 (30%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Mesentery	(6)		(1)	(2)
Sarcoma	1 (17%)			
Pancreas	(48)	(48)	(49)	(50)
Salivary glands	(49)	(49)	(50)	(49)
Stomach, forestomach	(47)	(49)	(49)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(48)	(46)	(48)	(50)
Cardiovascular System				
Heart	(48)	(49)	(50)	(50)
Endocrine System				
Adrenal cortex	(49)	(48)	(49)	(50)
Adenocarcinoma, metastatic, uterus				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Capsule, adenoma				1 (2%)
Adrenal medulla	(49)	(47)	(49)	(50)
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign				1 (2%)
Islets, pancreatic	(48)	(48)	(49)	(50)
Adenoma	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Pituitary gland	(48)	(48)	(49)	(47)
Pars distalis, adenoma	7 (15%)	10 (21%)	15 (31%)	8 (17%)
Pars intermedia, adenoma	1 (2%)			1 (2%)
Thyroid gland	(49)	(48)	(49)	(49)
Follicular cell, adenoma		6 (13%)		4 (8%)
Follicular cell, carcinoma			1 (2%)	
General Body System				
Tissue NOS	(2)			
Hemangiosarcoma	1 (50%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Genital System				
Ovary	(46)	(48)	(49)	(48)
Cystadenoma	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Cystadenoma, multiple		1 (2%)		
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Teratoma NOS	1 (2%)	1 (2%)		
Uterus	(49)	(49)	(49)	(50)
Hemangioma	1 (2%)		1 (2%)	
Histiocytic sarcoma	2 (4%)		1 (2%)	1 (2%)
Leiomyoma	1 (2%)			
Polyp stromal	2 (4%)		6 (12%)	1 (2%)
Endometrium, adenocarcinoma				1 (2%)
Hematopoietic System				
Bone marrow	(49)	(49)	(48)	(50)
Adenocarcinoma, metastatic, uterus				1 (2%)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Lymph node	(7)	(7)	(8)	(5)
Lumbar, histiocytic sarcoma, metastatic, uterus			1 (13%)	
Lumbar, sarcoma, metastatic, skin			1 (13%)	
Lymph node, mandibular	(48)	(45)	(49)	(49)
Carcinoma, metastatic, harderian gland				1 (2%)
Histiocytic sarcoma			1 (2%)	
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Lymph node, mesenteric	(45)	(47)	(47)	(47)
Histiocytic sarcoma			1 (2%)	
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Spleen	(48)	(48)	(49)	(50)
Hemangioma			1 (2%)	
Hemangiosarcoma	2 (4%)		1 (2%)	
Histiocytic sarcoma		1 (2%)	1 (2%)	
Thymus	(47)	(47)	(49)	(49)
Adenocarcinoma, metastatic, uterus				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Integumentary System				
Mammary gland	(40)	(43)	(46)	(44)
Adenocarcinoma			1 (2%)	
Adenocarcinoma, metastatic, uterus				1 (2%)
Adenoma			1 (2%)	
Skin	(49)	(49)	(50)	(50)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Sarcoma		1 (2%)	1 (2%)	1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(49)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Skeletal muscle	(1)			
Nervous System				
Brain	(49)	(49)	(50)	(50)
Adenocarcinoma, metastatic, uterus				1 (2%)
Respiratory System				
Lung	(48)	(49)	(50)	(50)
Adenocarcinoma, metastatic, uterus				1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	4 (8%)	6 (12%)
Alveolar/bronchiolar carcinoma			2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Carcinoma, metastatic, harderian gland				1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)			1 (2%)
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Osteosarcoma, metastatic, uncertain primary site		1 (2%)		
Sarcoma, metastatic, skin			1 (2%)	
Nose	(49)	(49)	(50)	(50)
Carcinoma, metastatic, harderian gland				1 (2%)
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Special Senses System				
Harderian gland	(2)	(1)	(4)	(5)
Adenoma	1 (50%)		3 (75%)	1 (20%)
Carcinoma		1 (100%)		3 (60%)
Urinary System				
Kidney	(49)	(48)	(50)	(50)
Adenocarcinoma, metastatic, uterus				1 (2%)
Urinary bladder	(43)	(40)	(44)	(50)
Hemangioma				1 (2%)
Systemic Lesions				
Multiple organs[d]	(49)	(49)	(50)	(50)
Histiocytic sarcoma	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Lymphoma malignant mixed	11 (22%)	12 (24%)	6 (12%)	14 (28%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Neoplasm Summary				
Total animals with primary neoplasms[e]				
15-Month interim evaluation	3	1	1	3
2-Year study	34	35	40	41
Total primary neoplasms				
15-Month interim evaluation	3	1	1	3
2-Year study	50	57	68	86
Total animals with benign neoplasms				
15-Month interim evaluation	3	1	1	3
2-Year study	19	25	30	35
Total benign neoplasms				
15-Month interim evaluation	3	1	1	3
2-Year study	25	35	46	54
Total animals with malignant neoplasms				
2-Year study	22	20	16	26
Total malignant neoplasms				
2-Year study	24	21	22	32
Total animals with metastatic neoplasms				
2-Year study	2	1	4	3
Total metastatic neoplasms				
2-Year study	2	1	15	11
Total animals with malignant neoplasms of uncertain primary site				
2-Year study		1		
Total animals with uncertain neoplasms benign or malignant				
2-Year study	1	1		
Total uncertain neoplasms				
2-Year study	1	1		

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] No neoplasms were observed at any site in any animal at the 9-month interim evaluation.
[c] No neoplasms were observed at any other site in any animal at the 15-month interim evaluation.
[d] Number of animals with any tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm

Number of Days on Study	0 6 7	3 4 8	5 7 1	5 8 1	6 2 1	6 2 8	6 7 3	6 8 4	6 8 5	7 0 8	7 0 8	7 0 8	7 4 6	7 4 6	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7
Carcass ID Number	3 0 0	3 2 6	3 2 4	3 3 2	3 4 1	3 0 1	3 1 0	3 5 8	3 4 3	3 3 5	3 3 7	3 4 0	3 0 2	3 0 9	3 2 8	3 0 3	3 0 4	3 0 5	3 0 8	3 1 1	3 1 3	3 1 6	3 1 7	3 2 0	3 2 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous															X										
Intestine small, jejunum	+	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma														X											
Hemangiosarcoma									X																
Hepatocellular carcinoma																					X				
Hepatocellular carcinoma, multiple																			X						
Hepatocellular adenoma															X										
Hepatocellular adenoma, multiple																									
Mesentery																								+	
Sarcoma																									
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue						+				+															
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	M	M	+	+	+	M	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X			X						X					X
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS																									
Hemangiosarcoma																									

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	
Carcass ID Number	3 2 3	3 2 5	3 2 8	3 3 0	3 3 1	3 3 3	3 3 6	3 3 8	3 3 9	3 4 2	3 4 4	3 4 5	3 4 6	3 4 8	3 5 0	3 5 5	3 5 6	3 5 9	3 6 0	3 6 1	3 6 2	3 6 3	3 6 4	3 6 5	Total Tissues/ Tumors
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Polyp adenomatous																								1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																								1
Hemangiosarcoma																								1
Hepatocellular carcinoma									X			X												3
Hepatocellular carcinoma, multiple															X									2
Hepatocellular adenoma									X									X			X			4
Hepatocellular adenoma, multiple															X								X	2
Mesentery											+				+		+					+	+	6
Sarcoma															X									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue									+															3
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma														X										1
Parathyroid gland	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma				X													X				X			7
Pars intermedia, adenoma		X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																								
Tissue NOS				+										+										2
Hemangiosarcoma				X																				1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	0 6 7	3 4 8	5 7 1	5 8 1	6 2 1	6 2 8	6 7 3	6 8 4	6 8 5	7 0 8	7 0 8	7 0 8	7 4 6	7 4 6	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7
Carcass ID Number	3 0 0	3 2 6	3 2 4	3 3 2	3 4 1	3 0 1	3 1 0	3 5 8	3 4 3	3 3 5	3 3 7	3 4 0	3 0 2	3 0 9	2 9 8	3 0 3	3 0 4	3 0 5	3 0 8	3 1 1	3 1 3	3 1 6	3 1 7	3 2 0	3 2 2
Genital System																								
Clitoral gland			+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Teratoma NOS			X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Histiocytic sarcoma																	X							
Leiomyoma																			X					
Polyp stromal												X												
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+			+								+								
Lymph node, mandibular	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X										
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear														+										
Harderian gland																+								
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	
Carcass ID Number	3 2 3	3 2 5	3 2 8	3 3 0	3 3 1	3 3 3	3 3 6	3 3 8	3 3 9	3 4 2	3 4 4	3 4 5	3 4 6	3 4 8	3 5 0	3 5 5	3 5 6	3 5 9	3 6 0	3 6 1	3 6 2	3 6 3	3 6 4	3 6 5	Total Tissues/ Tumors
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Ovary	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cystadenoma								X																	1
Teratoma NOS																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																			X						1
Histiocytic sarcoma								X																	2
Leiomyoma																									1
Polyp stromal					X																				2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node				+														+		+					7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma				X																					2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	M	+	M	+	+	+	40
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma						X																			1
Hepatocellular carcinoma, metastatic, liver												X			X										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Ear																									1
Harderian gland																		+							2
Adenoma																		X							1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	43

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	0	3	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	6	4	7	8	2	2	7	8	8	0	0	0	4	4	4	4	4	4	4	4	4	4	4	4	4
	7	8	1	1	1	8	3	4	5	8	8	8	6	6	7	7	7	7	7	7	7	7	7	7	7
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	3	3	3	3	3	3	3	3	3	3
	0	2	2	3	4	0	1	5	4	3	3	4	0	0	9	0	0	0	0	1	1	1	1	2	2
	0	6	4	2	1	1	0	8	3	5	7	0	2	9	8	3	4	5	8	1	3	6	7	0	2
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Lymphoma malignant lymphocytic																									X
Lymphoma malignant mixed					X			X		X		X				X		X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 0 ppm
(continued)

Number of Days on Study	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	7 4 7	
Carcass ID Number	3 2 3	3 2 5	3 2 8	3 3 0	3 3 1	3 3 3	3 3 6	3 3 8	3 3 9	3 4 2	3 4 4	3 4 5	3 4 6	3 4 8	3 5 0	3 5 5	3 5 6	3 5 9	3 6 0	3 6 1	3 6 2	3 6 3	3 6 4	3 6 5	Total Tissues/ Tumors
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma								X																	2
Lymphoma malignant lymphocytic																									1
Lymphoma malignant mixed							X						X	X		X				X					11

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm

Number of Days on Study	1 0 3	1 4 5	1 5 8	3 9 1	4 6 2	5 8 8	6 0 3	6 2 5	6 2 8	6 8 1	6 9 0	6 9 0	6 9 9	7 3 0	7 4 1	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	4 0 6	4 2 8	4 1 5	4 1 2	3 8 9	3 9 9	4 0 9	3 9 7	4 2 1	3 8 4	4 1 4	4 3 4	3 6 6	4 3 5	3 8 0	3 6 8	3 6 9	3 7 1	3 7 2	3 7 7	3 7 8	3 8 9	3 8 2	3 8 6
Alimentary System																								
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	+	+	A	A	A	A	M	+	A	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	A	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	A	+	+	A	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	A	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Intestine small, ileum	A	+	A	+	+	A	A	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																	
Hepatocellular carcinoma														X										
Hepatocellular adenoma						X							X										X	
Histiocytic sarcoma															X									
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X															
Stomach, glandular	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X					X													
Parathyroid gland	+	M	M	M	+	+	M	M	M	+	+	M	M	+	M	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X				X	X			X
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
None																								
Genital System																								
Clitoral gland					+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Ovary	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma				X		X							X											
Cystadenoma, multiple																							X	
Teratoma NOS	X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	
Carcass ID Number	3 8 7	3 9 6	4 0 0	3 8 8	3 9 2	3 9 4	3 9 5	4 0 1	4 0 2	4 0 3	4 0 4	4 0 5	4 0 7	4 0 8	4 1 1	4 1 6	4 1 7	4 2 3	4 2 4	4 2 5	4 2 6	4 2 7	4 2 9	4 3 2	4 3 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma				X																						1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Hepatocellular carcinoma			X																		X					3
Hepatocellular adenoma			X	X		X							X							X	X				X	10
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										2
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	M	M	+	+	M	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Pars distalis, adenoma		X	X		X		X										X		X							10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma						X							X				X				X	X			X	6
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma	X																									4
Cystadenoma, multiple																										1
Teratoma NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm
(continued)

Number of Days on Study	1 0 3	1 4 5	1 5 8	3 9 1	4 6 2	5 8 8	6 0 3	6 2 5	6 2 8	6 8 1	6 9 0	6 9 0	6 9 9	7 3 0	7 4 1	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	4 0 6	4 2 8	4 1 5	4 1 2	3 8 9	3 9 9	4 0 9	3 9 7	4 2 1	3 8 4	4 1 4	4 3 4	3 6 6	3 3 5	3 8 0	3 6 8	3 6 9	3 7 1	3 7 2	3 7 7	3 7 8	3 8 9	3 8 2	3 8 6
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X									
Lymph node								+		+		+									+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X									
Thymus	+	+	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord				+																				
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X								
Osteosarcoma, metastatic, uncertain primary site					X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye		+																						
Harderian gland																					+			
Carcinoma																					X			
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	A	+	+	A	A	A	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X									
Lymphoma malignant lymphocytic								X																
Lymphoma malignant mixed										X		X									X		X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 50 ppm
(continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	7 4 6	
Carcass ID Number	3 8 7	3 9 6	4 0 0	3 8 8	3 9 2	3 9 4	3 9 5	4 0 1	4 0 2	4 0 3	4 0 4	4 0 5	4 0 7	4 0 8	4 1 1	4 1 6	4 1 7	4 2 3	4 2 4	4 2 5	4 2 6	4 2 7	4 2 9	4 3 2	4 3 3	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node						+											+	+								7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	43
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma			X																							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Harderian gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	40
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed						X	X	X						X			X	X		X		X				12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm

Number of Days on Study	0 5 7	1 8 3	4 6 9	5 7 8	6 0 7	6 5 6	6 8 6	6 8 9	6 9 7	7 0 5	7 0 8	7 1 9	7 2 8	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2
Carcass ID Number	4 5 1	4 5 9	4 8 2	4 6 5	4 6 9	4 6 2	4 5 8	4 4 8	4 4 0	4 7 6	4 4 7	4 3 7	4 6 8	4 4 3	4 4 5	4 4 9	4 5 2	4 5 3	4 5 4	4 5 5	4 5 6	4 6 1	4 6 3	4 7 8	4 8 3
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	M	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma														X										
Intestine small, ileum	A	+	+	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hepatocellular carcinoma																							X	
Hepatocellular adenoma														X	X					X		X	X	
Hepatocellular adenoma, multiple								X																
Histiocytic sarcoma						X																		
Histiocytic sarcoma, metastatic, uterus				X																				
Mesentery																						+		
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X					
Stomach, glandular	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X											
Adrenal medulla	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X		X														
Parathyroid gland	+	+	+	M	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X	X		X								X	X				X	
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																								
General Body System																								
None																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm
(continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	4 8 4	4 8 5	4 8 7	4 8 9	4 9 0	4 9 1	4 9 7	4 9 8	4 9 9	5 0 4	5 0 5	4 3 6	4 3 8	4 3 9	4 4 4	4 5 0	4 5 7	4 6 7	4 7 0	4 7 3	4 7 5	4 9 4	4 9 6	5 0 1	5 0 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hemangioma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma		X																								1
Hepatocellular carcinoma						X																				2
Hepatocellular adenoma								X			X															7
Hepatocellular adenoma, multiple			X													X										3
Histiocytic sarcoma																										1
Histiocytic sarcoma, metastatic, uterus																										1
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant										X																1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Parathyroid gland	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Pars distalis, adenoma			X	X	X		X	X		X			X							X					X	15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma														X												1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm
(continued)

Number of Days on Study	0 5 7	1 8 3	4 6 9	5 7 8	6 0 7	6 5 6	6 8 6	6 8 9	6 9 7	7 0 5	7 0 8	7 1 9	7 2 8	7 4 2	7 4 2	7 4 2	7 5 2	7 5 2	7 5 2	7 5 2	7 5 2	7 6 2	7 6 2	7 7 2	7 8 3
Carcass ID Number	4 5 1	4 5 9	4 5 2	4 6 5	4 6 9	4 6 2	4 5 8	4 4 8	4 4 0	4 7 6	4 4 7	4 3 7	4 6 8	4 4 3	4 4 5	4 4 9	4 5 2	4 5 3	4 5 4	4 5 5	4 5 6	4 6 1	4 6 3	4 7 8	4 8 3
Genital System																									
Clitoral gland			+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Histiocytic sarcoma, metastatic, uterus				X																					
Uterus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma						X																			
Histiocytic sarcoma				X																					
Polyp stromal										X										X					
Hematopoietic System																									
Bone marrow	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Lymph node		+		+								+													
Lumbar, histiocytic sarcoma, metastatic, uterus				X																					
Lumbar, sarcoma, metastatic, skin																									
Lymph node, mandibular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Histiocytic sarcoma, metastatic, uterus				X																					
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Histiocytic sarcoma, metastatic, uterus				X																					
Spleen	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									X
Histiocytic sarcoma						X																			
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Histiocytic sarcoma						X																			
Histiocytic sarcoma, metastatic, uterus				X																					
Integumentary System																									
Mammary gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma			X																						
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Sarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm
(continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	4 8 4	4 8 5	4 8 7	4 8 9	4 9 0	4 9 1	4 9 7	4 9 8	4 9 9	5 0 4	5 0 5	4 3 6	4 3 8	4 3 9	4 4 4	4 5 0	4 5 7	4 6 7	4 7 0	4 7 3	4 7 5	4 9 4	4 9 6	5 0 1	5 0 2	Total Tissues/ Tumors
Genital System																									
Clitoral gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																							X			1
Histiocytic sarcoma, metastatic, uterus																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Histiocytic sarcoma																										1
Polyp stromal				X					X								X			X						6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymph node									+	+			+	+							+					8
Lumbar, histiocytic sarcoma, metastatic, uterus																										1
Lumbar, sarcoma, metastatic, skin									X																	1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Histiocytic sarcoma, metastatic, uterus																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Histiocytic sarcoma, metastatic, uterus																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma															X											1
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Histiocytic sarcoma, metastatic, uterus																										1
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Adenocarcinoma																										1
Adenoma													X													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Sarcoma									X																	1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm
(continued)

Number of Days on Study	0 5 7	1 8 3	4 6 9	5 7 8	6 0 7	6 5 6	6 8 6	6 8 9	6 9 7	7 0 5	7 0 8	7 1 9	7 2 8	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2
Carcass ID Number	4 5 1	4 5 9	4 8 2	4 6 5	4 6 9	4 6 2	4 5 8	4 4 8	4 4 0	4 7 6	4 4 7	4 3 7	4 6 8	4 4 3	4 4 5	4 4 9	4 5 2	4 5 3	4 5 4	4 5 5	4 5 6	4 6 1	4 6 3	4 7 8	4 8 3
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						X
Alveolar/bronchiolar carcinoma													X												
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Carcinoma, metastatic, thyroid gland																									
Histiocytic sarcoma, metastatic, uterus				X																					
Sarcoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, uterus				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland											+								+		+				
Adenoma											X										X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	A	A	+	+	+	A	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X		X																			
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed													X												

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 250 ppm
(continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	4 8 4	4 8 5	4 8 7	4 8 9	4 9 0	4 9 1	4 9 7	4 9 8	4 9 9	5 0 4	5 0 5	4 3 6	4 3 8	4 3 9	4 4 4	4 5 0	4 5 7	5 6 7	4 7 0	4 7 3	4 7 5	4 9 4	4 9 6	5 0 1	5 0 2	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X															X										4
Alveolar/bronchiolar carcinoma											X															2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Carcinoma, metastatic, thyroid gland														X												1
Histiocytic sarcoma, metastatic, uterus																										1
Sarcoma, metastatic, skin									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, uterus																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																								+	+	2
Harderian gland					+																					4
Adenoma					X																					3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic																					X					2
Lymphoma malignant mixed		X				X					X	X						X								6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm

Number of Days on Study	6 4 8	6 6 0	6 6 0	6 7 7	6 9 0	6 9 5	7 3 9	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1
Carcass ID Number	5 2 9	5 5 7	5 6 0	5 1 1	5 3 9	5 2 1	5 7 3	5 0 6	5 1 8	5 2 0	5 2 2	5 2 5	5 2 6	5 2 7	5 3 0	5 3 2	5 3 4	5 3 7	5 3 8	5 4 0	5 4 3	5 4 5	5 4 9	5 5 0	5 5 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X																						
Hepatocellular carcinoma, multiple													X												
Hepatocellular adenoma					X			X	X					X				X			X				
Hepatocellular adenoma, multiple										X		X	X			X				X			X	X	
Mesentery												+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																+									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus	X																								
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Parathyroid gland	+	M	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M
Pars distalis, adenoma					X							X		X											
Pars intermedia, adenoma			X																						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Follicular cell, adenoma				X								X													
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Ovary	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Polyp stromal																								X	
Endometrium, adenocarcinoma	X																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	5 5 3	5 5 5	5 5 6	5 5 8	5 5 9	5 6 1	5 6 3	5 6 4	5 6 5	5 6 6	5 6 7	5 6 8	5 7 0	5 7 1	5 7 2	5 0 7	5 0 8	5 1 3	5 1 4	5 1 5	5 1 6	5 1 7	5 3 5	5 6 2	5 6 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X									X				X						X	5
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X		X			X		X					X						X				X			13
Hepatocellular adenoma, multiple				X										X		X	X			X		X		X	X	15
Mesentery																		+								2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Capsule, adenoma																							X			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma				X					X							X					X		X			8
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma									X									X								4
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma				X																						1
Polyp stromal																										1
Endometrium, adenocarcinoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	6 4 8	6 6 0	6 6 0	6 7 7	6 9 0	6 9 5	7 3 9	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1
Carcass ID Number	5 2 9	5 5 7	5 6 0	5 1 1	5 3 9	5 2 1	5 7 3	5 0 6	5 1 8	5 2 0	5 2 2	5 2 5	5 2 6	5 2 7	5 3 0	5 3 2	5 3 4	5 3 7	5 3 8	5 4 0	5 4 3	5 4 5	5 4 9	5 5 0	5 5 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus	X																								
Lymph node					+							+			+									+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland				X																					
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus	X																								
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenocarcinoma, metastatic, uterus	X																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Sarcoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus	X																								
Alveolar/bronchiolar adenoma					X													X							X
Alveolar/bronchiolar carcinoma														X											X
Carcinoma, metastatic, harderian gland				X																					
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland				+																+					
Adenoma																									
Carcinoma				X																X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	5 5 3	5 5 5	5 5 6	5 5 8	5 5 9	5 6 1	5 6 3	5 6 4	5 6 5	5 6 6	5 6 7	5 6 8	5 7 0	5 7 1	5 7 2	5 0 7	5 0 8	5 1 3	5 1 4	5 1 5	5 1 6	5 1 7	5 3 5	5 6 2	5 6 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Lymph node														+												5
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, harderian gland																										1
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uterus																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	44
Adenocarcinoma, metastatic, uterus																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Alveolar/bronchiolar adenoma							X											X					X			6
Alveolar/bronchiolar carcinoma																										2
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																									X	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland						+													+						+	5
Adenoma						X																				1
Carcinoma																									X	3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma				X																						1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	6	6	7	9	9	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	8	0	0	7	0	5	9	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	2	5	6	1	3	2	7	0	1	2	2	2	2	2	3	3	3	3	3	4	4	4	4	5	5
	9	7	0	1	9	1	3	6	8	0	2	5	6	7	0	2	4	7	8	0	3	5	9	0	1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed					X					X		X			X			X	X					X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride: 500 ppm
(continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	5 5 3	5 5 5	5 5 6	5 5 8	5 5 9	5 6 1	5 6 3	5 6 4	5 6 5	5 6 6	5 6 7	5 6 8	5 7 0	5 7 1	5 7 2	5 7 7	5 0 7	5 0 8	5 1 3	5 1 4	5 1 5	5 1 6	5 1 7	5 3 5	5 6 2	5 6 9	Total Tissues/ Tumors
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma				X																							2
Lymphoma malignant lymphocytic							X									X						X					3
Lymphoma malignant mixed				X	X	X				X			X	X			X										14

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride

	0 ppm	50 ppm	250 ppm	500 ppm
Harderian Gland: Adenoma				
Overall rates[a]	1/49 (2%)	0/49 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rates[b]	2.7%	0.0%	7.8%	2.3%
Terminal rates[c]	1/37 (3%)	0/35 (0%)	2/37 (5%)	1/44 (2%)
First incidence (days)	739 (T)	–[e]	708	739 (T)
Life table tests[d]	P=0.455	P=0.511N	P=0.307	P=0.723N
Logistic regression tests[d]	P=0.439	P=0.511N	P=0.313	P=0.723N
Cochran-Armitage test[d]	P=0.395			
Fisher exact test[d]		P=0.500N	P=0.316	P=0.747N
Harderian Gland: Carcinoma				
Overall rates	0/49 (0%)	1/49 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rates	0.0%	2.9%	0.0%	6.6%
Terminal rates	0/37 (0%)	1/35 (3%)	0/37 (0%)	2/44 (5%)
First incidence (days)	–	739 (T)	–	677
Life table tests	P=0.079	P=0.489	–	P=0.152
Logistic regression tests	P=0.065	P=0.489	–	P=0.122
Cochran-Armitage test	P=0.057			
Fisher exact test		P=0.500	–	P=0.125
Harderian Gland: Adenoma or Carcinoma				
Overall rates	1/49 (2%)	1/49 (2%)	3/50 (6%)	4/50 (8%)
Adjusted rates	2.7%	2.9%	7.8%	8.8%
Terminal rates	1/37 (3%)	1/35 (3%)	2/37 (5%)	3/44 (7%)
First incidence (days)	739 (T)	739 (T)	708	677
Life table tests	P=0.107	P=0.749	P=0.307	P=0.233
Logistic regression tests	P=0.088	P=0.749	P=0.313	P=0.200
Cochran-Armitage test	P=0.068			
Fisher exact test		P=0.753N	P=0.316	P=0.187
Liver: Hepatocellular Adenoma				
Overall rates	6/49 (12%)	10/48 (21%)	10/49 (20%)	28/50 (56%)
Adjusted rates	16.2%	26.6%	26.1%	62.2%
Terminal rates	6/37 (16%)	8/35 (23%)	9/37 (24%)	27/44 (61%)
First incidence (days)	739 (T)	588	689	690
Life table tests	P<0.001	P=0.174	P=0.207	P<0.001
Logistic regression tests	P<0.001	P=0.164	P=0.220	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.194	P=0.207	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rates	5/49 (10%)	3/48 (6%)	2/49 (4%)	6/50 (12%)
Adjusted rates	13.5%	8.3%	5.4%	13.2%
Terminal rates	5/37 (14%)	2/35 (6%)	2/37 (5%)	5/44 (11%)
First incidence (days)	739 (T)	730	739 (T)	660
Life table tests	P=0.460	P=0.386N	P=0.215N	P=0.617
Logistic regression tests	P=0.430	P=0.383N	P=0.215N	P=0.575
Cochran-Armitage test	P=0.352			
Fisher exact test		P=0.369N	P=0.218N	P=0.514

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	9/49 (18%)	11/48 (23%)	11/49 (22%)	30/50 (60%)
Adjusted rates	24.3%	28.7%	28.7%	65.2%
Terminal rates	9/37 (24%)	8/35 (23%)	10/37 (27%)	28/44 (64%)
First incidence (days)	739 (T)	588	689	660
Life table tests	P<0.001	P=0.351	P=0.403	P<0.001
Logistic regression tests	P<0.001	P=0.335	P=0.427	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.381	P=0.401	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	1/48 (2%)	1/49 (2%)	4/50 (8%)	6/50 (12%)
Adjusted rates	2.8%	2.9%	10.8%	13.3%
Terminal rates	1/36 (3%)	1/35 (3%)	4/37 (11%)	5/44 (11%)
First incidence (days)	739 (T)	739 (T)	739 (T)	690
Life table tests	P=0.026	P=0.756	P=0.187	P=0.097
Logistic regression tests	P=0.021	P=0.756	P=0.187	P=0.081
Cochran-Armitage test	P=0.012			
Fisher exact test		P=0.747N	P=0.194	P=0.062
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	1/48 (2%)	1/49 (2%)	6/50 (12%)	7/50 (14%)
Adjusted rates	2.8%	2.9%	15.8%	15.5%
Terminal rates	1/36 (3%)	1/35 (3%)	5/37 (14%)	6/44 (14%)
First incidence (days)	739 (T)	739 (T)	728	690
Life table tests	P=0.013	P=0.756	P=0.064	P=0.060
Logistic regression tests	P=0.010	P=0.756	P=0.065	P=0.049
Cochran-Armitage test	P=0.005			
Fisher exact test		P=0.747N	P=0.062	P=0.034
Ovary: Cystadenoma				
Overall rates	1/46 (2%)	5/48 (10%)	1/49 (2%)	1/48 (2%)
Adjusted rates	2.9%	12.3%	2.7%	2.1%
Terminal rates	1/35 (3%)	2/35 (6%)	1/37 (3%)	0/43 (0%)
First incidence (days)	739 (T)	391	739 (T)	677
Life table tests	P=0.153N	P=0.104	P=0.749N	P=0.725N
Logistic regression tests	P=0.207N	P=0.122	P=0.749N	P=0.766N
Cochran-Armitage test	P=0.182N			
Fisher exact test		P=0.112	P=0.737N	P=0.742N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	7/48 (15%)	10/48 (21%)	15/49 (31%)	8/47 (17%)
Adjusted rates	18.3%	29.4%	37.9%	18.5%
Terminal rates	6/37 (16%)	10/34 (29%)	12/36 (33%)	7/42 (17%)
First incidence (days)	708	739 (T)	686	690
Life table tests	P=0.454N	P=0.229	P=0.045	P=0.603
Logistic regression tests	P=0.508N	P=0.234	P=0.047	P=0.563
Cochran-Armitage test	P=0.436			
Fisher exact test		P=0.297	P=0.050	P=0.482

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	0/49 (0%)	6/48 (13%)	0/49 (0%)	4/49 (8%)
Adjusted rates	0.0%	17.1%	0.0%	9.0%
Terminal rates	0/37 (0%)	6/35 (17%)	0/37 (0%)	3/43 (7%)
First incidence (days)	–	739 (T)	–	677
Life table tests	P=0.475	P=0.014	–	P=0.084
Logistic regression tests	P=0.450	P=0.014	–	P=0.066
Cochran-Armitage test	P=0.391			
Fisher exact test		P=0.012	–	P=0.059
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	0/49 (0%)	6/48 (13%)	1/49 (2%)	4/49 (8%)
Adjusted rates	0.0%	17.1%	2.7%	9.0%
Terminal rates	0/37 (0%)	6/35 (17%)	1/37 (3%)	3/43 (7%)
First incidence (days)	–	739 (T)	739 (T)	677
Life table tests	P=0.454	P=0.014	P=0.500	P=0.084
Logistic regression tests	P=0.429	P=0.014	P=0.500	P=0.066
Cochran-Armitage test	P=0.367			
Fisher exact test		P=0.012	P=0.500	P=0.059
Uterus: Stromal Polyp				
Overall rates	2/49 (4%)	0/49 (0%)	6/50 (12%)	1/50 (2%)
Adjusted rates	5.1%	0.0%	15.6%	2.3%
Terminal rates	1/37 (3%)	0/35 (0%)	5/37 (14%)	1/44 (2%)
First incidence (days)	708	–	705	739 (T)
Life table tests	P=0.538	P=0.258N	P=0.139	P=0.449N
Logistic regression tests	P=0.517	P=0.248N	P=0.141	P=0.470N
Cochran-Armitage test	P=0.459			
Fisher exact test		P=0.247N	P=0.141	P=0.492N
All Organs: Hemangioma				
Overall rates	2/49 (4%)	0/49 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rates	5.4%	0.0%	7.5%	2.3%
Terminal rates	2/37 (5%)	0/35 (0%)	2/37 (5%)	1/44 (2%)
First incidence (days)	739 (T)	–	656	739 (T)
Life table tests	P=0.567N	P=0.251N	P=0.504	P=0.440N
Logistic regression tests	P=0.603N	P=0.251N	P=0.508	P=0.440N
Cochran-Armitage test	P=0.571			
Fisher exact test		P=0.247N	P=0.510	P=0.492N
All Organs: Hemangiosarcoma				
Overall rates	3/49 (6%)	1/49 (2%)	2/50 (4%)	0/50 (0%)
Adjusted rates	7.7%	2.3%	5.4%	0.0%
Terminal rates	2/37 (5%)	0/35 (0%)	2/37 (5%)	0/44 (0%)
First incidence (days)	685	603	739 (T)	–
Life table tests	P=0.107N	P=0.326N	P=0.494N	P=0.097N
Logistic regression tests	P=0.125N	P=0.306N	P=0.490N	P=0.110N
Cochran-Armitage test	P=0.130N			
Fisher exact test		P=0.309N	P=0.490N	P=0.117N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

	0 ppm	50 ppm	250 ppm	500 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	4/49 (8%)	1/49 (2%)	5/50 (10%)	1/50 (2%)
Adjusted rates	10.3%	2.3%	12.8%	2.3%
Terminal rates	3/37 (8%)	0/35 (0%)	4/37 (11%)	1/44 (2%)
First incidence (days)	685	603	656	739 (T)
Life table tests	P=0.254N	P=0.200N	P=0.508	P=0.137N
Logistic regression tests	P=0.301N	P=0.184N	P=0.511	P=0.154N
Cochran-Armitage test	P=0.321N			
Fisher exact test		P=0.181N	P=0.513	P=0.175N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rates	12/49 (24%)	13/49 (27%)	8/50 (16%)	17/50 (34%)
Adjusted rates	28.9%	33.8%	20.0%	37.7%
Terminal rates	8/37 (22%)	10/35 (29%)	6/37 (16%)	16/44 (36%)
First incidence (days)	621	625	183	690
Life table tests	P=0.410	P=0.436	P=0.232N	P=0.361
Logistic regression tests	P=0.272	P=0.445	P=0.211N	P=0.272
Cochran-Armitage test	P=0.218			
Fisher exact test		P=0.500	P=0.212N	P=0.207
All Organs: Benign Neoplasms				
Overall rates	19/49 (39%)	25/49 (51%)	30/50 (60%)	35/50 (70%)
Adjusted rates	48.6%	62.1%	71.2%	74.4%
Terminal rates	17/37 (46%)	20/35 (57%)	25/37 (68%)	32/44 (73%)
First incidence (days)	708	391	656	660
Life table tests	P=0.032	P=0.107	P=0.025	P=0.017
Logistic regression tests	P=0.007	P=0.102	P=0.023	P=0.006
Cochran-Armitage test	P=0.001			
Fisher exact test		P=0.155	P=0.028	P=0.002
All Organs: Malignant Neoplasms				
Overall rates	22/49 (45%)	21/49 (43%)	16/50 (32%)	26/50 (52%)
Adjusted rates	52.2%	50.8%	36.5%	54.0%
Terminal rates	17/37 (46%)	15/35 (43%)	10/37 (27%)	22/44 (50%)
First incidence (days)	621	462	183	648
Life table tests	P=0.484N	P=0.558	P=0.167N	P=0.565
Logistic regression tests	P=0.343	P=0.576N	P=0.134N	P=0.403
Cochran-Armitage test	P=0.286			
Fisher exact test		P=0.500N	P=0.133N	P=0.307
All Organs: Benign or Malignant Neoplasms				
Overall rates	34/49 (69%)	36/49 (73%)	40/50 (80%)	41/50 (82%)
Adjusted rates	77.2%	76.6%	85.0%	85.4%
Terminal rates	27/37 (73%)	24/35 (69%)	30/37 (81%)	37/44 (84%)
First incidence (days)	571	103	183	648
Life table tests	P=0.505N	P=0.308	P=0.193	P=0.510
Logistic regression tests	P=0.126	P=0.340	P=0.145	P=0.242
Cochran-Armitage test	P=0.074			
Fisher exact test		P=0.412	P=0.163	P=0.109

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride
(continued)

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at TSI Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	6/50	0/50	6/50
Acetaminophen	3/49	0/49	3/49
H.C. Yellow 4	5/50	1/50	6/50
Pentaerythritol tetranitrate	5/49	1/49	6/49
Turmeric oleoresin	7/50	7/50	13/50
Overall Historical Incidence			
Total	159/1,363 (11.7%)	80/1,363 (5.9%)	223/1,363 (16.4%)
Standard deviation	8.3%	5.5%	10.7%
Range	0%-33%	0%-20%	3%-42%

[a] Data as of 20 August 1992

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	50 ppm	250 ppm	500 ppm
Disposition Summary				
Animals initially in study	69	69	70	70
9-Month interim evaluation	10	9	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	1			
Moribund	6	7	7	6
Natural deaths	5	7	6	
Survivors				
Died last week of study	1	1		
Terminal sacrifice	36	34	37	44
Missing		1		
Animals examined microscopically	69	68	70	70
9-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(9)	(10)	(10)
Eosinophilic focus				1 (10%)
Fatty change			1 (10%)	1 (10%)
Pancreas	(10)	(9)	(10)	(10)
Inflammation, chronic, focal	2 (20%)			1 (10%)
Salivary glands	(10)	(8)	(10)	(10)
Inflammation, chronic, focal	2 (20%)	3 (38%)	2 (20%)	4 (40%)
Stomach, forestomach	(10)	(9)	(10)	(10)
Diverticulum	1 (10%)			
Cardiovascular System				
None				
Endocrine System				
Islets, pancreatic	(10)	(9)	(10)	(10)
Hyperplasia	1 (10%)	3 (33%)		3 (30%)
Hypoplasia			1 (10%)	
General Body System				
None				
Genital System				
Clitoral gland	(1)			
Cyst	1 (100%)			
Ovary	(10)	(9)	(10)	(9)
Cyst		2 (22%)		
Mineralization, focal		1 (11%)	1 (10%)	
Uterus	(10)	(9)	(10)	(10)
Endometrium, hyperplasia, cystic	9 (90%)	8 (89%)	9 (90%)	9 (90%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
9-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mandibular	(10)	(8)	(10)	(10)
Congestion		1 (13%)		
Spleen	(10)	(9)	(9)	(10)
Hematopoietic cell proliferation			1 (11%)	
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
Brain	(10)	(9)	(10)	(10)
Mineralization, focal	2 (20%)		1 (10%)	1 (10%)
Respiratory System				
Lung	(10)	(9)	(10)	(10)
Peribronchial, inflammation, chronic	3 (30%)	1 (11%)	5 (50%)	
Nose	(10)	(9)	(10)	(10)
Degeneration, hyaline	8 (80%)	4 (44%)	7 (70%)	8 (80%)
Inflammation, chronic, focal	10 (100%)	8 (89%)	10 (100%)	10 (100%)
Special Senses System				
None				
Urinary System				
Kidney	(10)	(9)	(10)	(10)
Inflammation, chronic, focal			1 (10%)	
Renal tubule, regeneration			1 (10%)	
Urinary bladder	(10)	(9)	(10)	(10)
Inflammation, chronic, focal	4 (40%)	1 (11%)	5 (50%)	4 (40%)
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Basophilic focus			1 (10%)	
Eosinophilic focus			2 (20%)	1 (10%)
Fatty change			3 (30%)	2 (20%)
Necrosis, focal	2 (20%)	4 (40%)	3 (30%)	3 (30%)
Pancreas	(10)	(10)	(10)	(10)
Inflammation, chronic, focal		2 (20%)	1 (10%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
15-Month Interim Evaluation (continued)				
Alimentary System (continued)				
Salivary glands	(10)	(10)	(10)	(10)
Inflammation, chronic, focal	4 (40%)	4 (40%)	5 (50%)	5 (50%)
Stomach, glandular	(10)	(10)	(10)	(10)
Inflammation, chronic, focal			1 (10%)	
Cardiovascular System				
None				
Endocrine System				
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia		1 (10%)	1 (10%)	2 (20%)
Pituitary gland	(9)	(9)	(10)	(10)
Pars distalis, hyperplasia, focal				1 (10%)
General Body System				
None				
Genital System				
Ovary	(9)	(10)	(10)	(10)
Cyst	1 (11%)	2 (20%)	2 (20%)	1 (10%)
Thrombosis		1 (10%)		
Uterus	(10)	(10)	(10)	(10)
Hydrometra	2 (20%)	1 (10%)		3 (30%)
Endometrium, hyperplasia, cystic	10 (100%)	10 (100%)	9 (90%)	8 (80%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Myelofibrosis	3 (30%)	1 (10%)	1 (10%)	1 (10%)
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation		1 (10%)		
Thymus	(9)	(10)	(9)	(10)
Hyperplasia, lymphoid	1 (11%)			
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
Brain	(10)	(10)	(10)	(10)
Mineralization	6 (60%)	5 (50%)	6 (60%)	6 (60%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Nose	(10)	(10)	(10)	(10)
Inflammation, chronic	8 (80%)	8 (80%)	7 (70%)	9 (90%)
Special Senses System				
None				
Urinary System				
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic, focal	4 (40%)	5 (50%)	4 (40%)	5 (50%)
2-Year Study				
Alimentary System				
Gallbladder	(44)	(40)	(43)	(48)
Dilatation		1 (3%)		1 (2%)
Intestine large, cecum	(47)	(44)	(45)	(50)
Edema			1 (2%)	
Hyperplasia, lymphoid	30 (64%)	18 (41%)	18 (40%)	17 (34%)
Intestine small, jejunum	(45)	(44)	(45)	(50)
Hyperplasia, lymphoid			1 (2%)	1 (2%)
Liver	(49)	(48)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Autolysis	1 (2%)			
Basophilic focus	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Clear cell focus		2 (4%)	2 (4%)	
Congestion	1 (2%)			
Eosinophilic focus	3 (6%)	3 (6%)	8 (16%)	25 (50%)
Fatty change	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Fatty change, focal			2 (4%)	
Hematopoietic cell proliferation	1 (2%)	1 (2%)	2 (4%)	
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid	2 (4%)	1 (2%)		
Necrosis, focal	5 (10%)		4 (8%)	10 (20%)
Mesentery	(6)		(1)	(2)
Fat, necrosis	5 (83%)			2 (100%)
Pancreas	(48)	(48)	(49)	(50)
Acinus, atrophy		1 (2%)	1 (2%)	2 (4%)
Duct, ectasia	2 (4%)	1 (2%)		2 (4%)
Stomach, forestomach	(47)	(49)	(49)	(50)
Abscess	1 (2%)			
Diverticulum			1 (2%)	
Ulcer	1 (2%)		1 (2%)	
Stomach, glandular	(48)	(46)	(48)	(50)
Edema		1 (2%)		
Erosion		2 (4%)		
Inflammation, chronic		1 (2%)	1 (2%)	
Inflammation, subacute				1 (2%)
Muscularis, hypertrophy	1 (2%)		1 (2%)	
Tongue	(3)			(1)
Angiectasis	3 (100%)			1 (100%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Cardiovascular System				
Heart	(48)	(49)	(50)	(50)
Artery, inflammation, chronic		1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(48)	(49)	(50)
Congestion	1 (2%)			
Cytoplasmic alteration, focal		2 (4%)		
Fibrosis				1 (2%)
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Hyperplasia, focal	1 (2%)			1 (2%)
Hypertrophy		1 (2%)	2 (4%)	
Capsule, hyperplasia	1 (2%)			
Adrenal medulla	(49)	(47)	(49)	(50)
Hyperplasia, focal	1 (2%)	1 (2%)		
Islets, pancreatic	(48)	(48)	(49)	(50)
Hyperplasia	6 (13%)	5 (10%)	9 (18%)	6 (12%)
Pituitary gland	(48)	(48)	(49)	(47)
Pars distalis, angiectasis	1 (2%)	1 (2%)		1 (2%)
Pars distalis, hyperplasia, focal	14 (29%)	10 (21%)	13 (27%)	10 (21%)
Thyroid gland	(49)	(48)	(49)	(49)
Inflammation, acute, focal				1 (2%)
Inflammation, chronic		1 (2%)		
Follicle, cyst			2 (4%)	1 (2%)
Follicular cell, hyperplasia, focal	4 (8%)	11 (23%)	8 (16%)	5 (10%)
General Body System				
None				
Genital System				
Clitoral gland	(42)	(41)	(44)	(46)
Abscess			1 (2%)	
Angiectasis				1 (2%)
Dilatation	2 (5%)	1 (2%)		
Pigmentation, hemosiderin			1 (2%)	
Ovary	(46)	(48)	(49)	(48)
Abscess			1 (2%)	
Angiectasis			1 (2%)	
Cyst	6 (13%)	9 (19%)	11 (22%)	8 (17%)
Uterus	(49)	(49)	(49)	(50)
Angiectasis	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Fibrosis, focal				1 (2%)
Hydrometra	4 (8%)	7 (14%)	6 (12%)	11 (22%)
Inflammation, suppurative	1 (2%)			2 (4%)
Thrombosis				1 (2%)
Endometrium, hyperplasia, cystic	44 (90%)	44 (90%)	40 (82%)	44 (88%)
Endometrium, metaplasia, squamous		1 (2%)	2 (4%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(49)	(49)	(48)	(50)
Angiectasis				1 (2%)
Hyperplasia, neutrophil	2 (4%)	6 (12%)	5 (10%)	2 (4%)
Myelofibrosis	22 (45%)	20 (41%)	21 (44%)	20 (40%)
Lymph node	(7)	(7)	(8)	(5)
Lumbar, hematopoietic cell proliferation	1 (14%)			
Lumbar, lymphatic, angiectasis			1 (13%)	
Mediastinal, hyperplasia, lymphoid	1 (14%)			
Mediastinal, infiltration cellular, mixed cell			1 (13%)	
Pancreatic, hyperplasia, lymphoid	1 (14%)		2 (25%)	
Renal, hematopoietic cell proliferation	1 (14%)			
Lymph node, mandibular	(48)	(45)	(49)	(49)
Hematopoietic cell proliferation	1 (2%)			
Necrosis			1 (2%)	
Lymphatic, angiectasis				1 (2%)
Lymph node, mesenteric	(45)	(47)	(47)	(47)
Congestion	1 (2%)			
Depletion lymphoid	1 (2%)			
Inflammation, chronic	1 (2%)			
Lymphatic, angiectasis		1 (2%)	3 (6%)	1 (2%)
Spleen	(48)	(48)	(49)	(50)
Congestion	1 (2%)		1 (2%)	2 (4%)
Depletion lymphoid	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation	8 (17%)	9 (19%)	12 (24%)	9 (18%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	4 (8%)	2 (4%)
Necrosis, focal		1 (2%)	1 (2%)	
Thymus	(47)	(47)	(49)	(49)
Angiectasis				1 (2%)
Depletion lymphoid	1 (2%)	2 (4%)	2 (4%)	
Hyperplasia, lymphoid	1 (2%)			1 (2%)
Integumentary System				
Mammary gland	(40)	(43)	(46)	(44)
Lactation	1 (3%)	2 (5%)	3 (7%)	2 (5%)
Skin	(49)	(49)	(50)	(50)
Inflammation, chronic				1 (2%)
Ulcer	1 (2%)			
Musculoskeletal System				
Bone	(49)	(49)	(50)	(50)
Hyperostosis		1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride (continued)

	0 ppm	50 ppm	250 ppm	500 ppm
2-Year Study (continued)				
Nervous System				
Brain	(49)	(49)	(50)	(50)
Compression	1 (2%)		1 (2%)	
Hemorrhage, focal		1 (2%)		
Mineralization	36 (73%)	33 (67%)	30 (60%)	32 (64%)
Artery, inflammation, chronic		1 (2%)		
Spinal cord		(1)		
Artery, inflammation, chronic		1 (100%)		
Respiratory System				
Lung	(48)	(49)	(50)	(50)
Congestion	1 (2%)	1 (2%)		
Hemorrhage, focal	2 (4%)	2 (4%)	1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)	
Thrombosis		1 (2%)		
Alveolar epithelium, hyperplasia				4 (8%)
Nose	(49)	(49)	(50)	(50)
Inflammation, chronic	46 (94%)	41 (84%)	44 (88%)	47 (94%)
Special Senses System				
Harderian gland	(2)	(1)	(4)	(5)
Hyperplasia	1 (50%)		1 (25%)	1 (20%)
Urinary System				
Kidney	(49)	(48)	(50)	(50)
Congestion		1 (2%)	1 (2%)	
Fatty change	2 (4%)			
Glomerulosclerosis	2 (4%)	2 (4%)		1 (2%)
Hemorrhage, focal	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	
Infarct	2 (4%)		2 (4%)	3 (6%)
Mineralization	1 (2%)			1 (2%)
Nephropathy			1 (2%)	1 (2%)
Renal tubule, degeneration, granular	1 (2%)		2 (4%)	
Renal tubule, necrosis		2 (4%)		
Renal tubule, regeneration	7 (14%)	3 (6%)	2 (4%)	3 (6%)
Urinary bladder	(43)	(40)	(44)	(50)
Inflammation, chronic, focal		1 (3%)		

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Methylphenidate hydrochloride was sent to two testing laboratories as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA97, TA98, TA100, TA1535, TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of methylphenidate hydrochloride. The high dose was limited to 5,000 μg/plate in the test performed at Microbiological Associates; slight toxicity was observed in the assays without S9 at 4,000 μg/plate. No toxicity was noted in the test performed at SRI, International, and 10,000 μg/plate was selected as the high dose. All trials were repeated.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

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

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for approximately 26 hours with methylphenidate hydrochloride in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing methylphenidate hydrochloride was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with methylphenidate hydrochloride, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no methylphenidate hydrochloride, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen in the trial performed without S9 at Litton Bionetics, Inc. (LBI), incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20%, or greater, at any single dose, was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.05$), in the absence of any responses reaching 20% above background, led to a call of equivocal. Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with methylphenidate hydrochloride for 10 to 11 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with methylphenidate hydrochloride and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 8 to 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: because cell cycle delay was anticipated, the incubation period was extended in the one trial performed without S9 at LBI.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. Where possible, 100 first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

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

RESULTS

Methylphenidate hydrochloride was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, TA1535, or TA1537 when tested at two laboratories with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Mortelmans *et al.*, 1986). A slight degree of toxicity was noted in the tests performed at Microbiological Associates, limiting the highest dose tested to 5,000 μg/plate, compared to the 10,000 μg/plate tested at SRI, International.

In cytogenetic tests with cultured CHO cells, apparently inconsistent results were obtained for induction of SCEs (Table E2) and Abs (Table E3) between two laboratories. However, closer examination of the data shows that the positive responses were recorded in tests that employed higher doses of methylphenidate hydrochloride. In the SCE test performed at Environmental Health Research and Testing (EHRT), negative results were obtained with and without S9. At LBI (data presented in Galloway *et al.*, 1987), a positive response was obtained at all three scorable doses in the test performed without S9. The cells in this trial were harvested 10 hours later than the normal harvest time of 26 hours to offset the severe cell cycle delay induced by treatment with methylphenidate hydrochloride. The doses that produced the positive response ranged from 702 to 900 μg/mL, much higher doses than those tested at EHRT. With S9, a weakly positive response observed at LBI in the first trial did not repeat in a second trial, and the SCE

test with S9 was judged to be negative. This latter result was in agreement with the SCE test with S9 performed at EHRT.

The Abs test performed at EHRT gave positive results without S9. Two trials were performed. No significant increases in Abs were observed in the first trial, but a second trial conducted with higher doses produced positive responses at the two highest doses (1,750 and 2,000 μg/mL). With S9, results of the first trial were again negative, while the second trial showed a strong increase in Abs at the highest scorable dose (1,500 μg/mL). However, because no increase in Abs was seen at this dose level in the first trial, the overall results of the test with S9 were considered to be equivocal. At LBI no increase in Abs was observed without S9 (highest dose, 1,250 μg/mL) but with S9, significant increases in Abs were observed at each of the three doses scored. These tests were not repeated.

Methylphenidate hydrochloride did not induce mutations in *S. typhimurium*, but did induce Abs and SCEs in mammalian cells *in vitro*. The NTP has evaluated these mutagenicity tests with respect to their predictive value for rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). A strong correlation was found to exist among the potential electrophilicity of a chemical (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rats and mice at single or multiple tissue sites (Ashby and Tennant, 1991). Although a positive result in the *Salmonella* test was shown to be a good predictor of carcinogenicity in rodents (89% of *Salmonella* mutagens were carcinogens in rats and/or mice), the negative predictivity was less precise. Approximately 50% of nonmutagens were also found to be noncarcinogens. Positive results in cultured CHO cell cytogenetic studies are less predictive than positive results in the *Salmonella* assay for rodent carcinogenicity: 64% of chemicals that induced SCEs and 73% of chemicals that induce Abs were positive in the rodent bioassay. It is also important to note that no combination of *in vitro* genetic toxicity tests improved upon the predictivity of the *Salmonella* assay.

TABLE E1
Mutagenicity of Methylphenidate Hydrochloride in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at SRI, International							
TA100	0	126 ± 1.0	122 ± 3.6	117 ± 4.7	124 ± 3.5	142 ± 3.8	132 ± 8.2
	100	115 ± 4.8	150 ± 1.5	140 ± 3.5	156 ± 10.7	149 ± 5.8	164 ± 9.4
	333	121 ± 5.6	144 ± 6.9	136 ± 6.4	167 ± 11.7	136 ± 14.1	169 ± 15.4
	1,000	127 ± 8.5	150 ± 7.8	126 ± 5.8	139 ± 14.2	149 ± 6.4	163 ± 4.4
	3,333	142 ± 5.7	167 ± 7.1	135 ± 5.4	167 ± 4.0	156 ± 2.7	181 ± 2.0
	10,000	120 ± 7.5	147 ± 8.1	134 ± 3.5	162 ± 22.7	160 ± 7.2	170 ± 15.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		493 ± 24.8	447 ± 7.2	2,193 ± 40.6	1,577 ± 17.7	1,082 ± 50.9	930 ± 108.2
TA1535	0	32 ± 3.0	23 ± 3.1	7 ± 0.6	8 ± 2.1	10 ± 2.7	6 ± 0.9
	100	34 ± 6.5	22 ± 5.0	15 ± 3.8	7 ± 0.9	12 ± 0.3	12 ± 3.2
	333	38 ± 1.2	25 ± 2.4	12 ± 2.0	8 ± 1.3	12 ± 2.0	8 ± 1.3
	1,000	33 ± 6.2	28 ± 5.0	16 ± 1.7	8 ± 2.5	10 ± 2.5	8 ± 0.9
	3,333	40 ± 1.9	29 ± 3.5	8 ± 2.2	6 ± 0.7	11 ± 1.5	8 ± 0.6
	10,000	41 ± 4.3	19 ± 3.7	11 ± 1.2	5 ± 1.2	12 ± 2.4	8 ± 0.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		531 ± 11.7	385 ± 7.1	426 ± 8.5	376 ± 36.1	193 ± 14.4	163 ± 6.6
TA1537	0	6 ± 1.5	5 ± 0.7	14 ± 0.3	7 ± 1.5	8 ± 2.0	7 ± 2.5
	100	7 ± 0.3	5 ± 0.3	8 ± 0.7	8 ± 2.9	12 ± 1.7	6 ± 1.5
	333	7 ± 1.3	4 ± 1.2	8 ± 0.6	8 ± 3.0	10 ± 1.3	7 ± 1.2
	1,000	6 ± 1.3	6 ± 1.5	7 ± 3.2	7 ± 2.3	10 ± 1.2	10 ± 2.2
	3,333	3 ± 0.6	5 ± 1.2	10 ± 2.5	6 ± 0.9	11 ± 2.8	9 ± 2.3
	10,000	11 ± 1.2	6 ± 0.7	13 ± 1.9	5 ± 1.0	11 ± 1.8	4 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		143 ± 22.8	135 ± 21.4	324 ± 13.2	129 ± 0.6	216 ± 23.7	185 ± 10.4
TA98	0	21 ± 1.5	17 ± 1.7	34 ± 1.0	31 ± 3.8	28 ± 4.3	26 ± 0.9
	100	24 ± 2.7	22 ± 4.4	36 ± 2.6	29 ± 4.4	37 ± 3.4	30 ± 1.2
	333	19 ± 1.2	17 ± 0.3	43 ± 2.6	33 ± 4.7	29 ± 2.0	33 ± 2.6
	1,000	25 ± 1.0	16 ± 1.0	35 ± 4.0	33 ± 5.2	37 ± 2.8	26 ± 3.5
	3,333	24 ± 3.5	18 ± 2.2	41 ± 3.4	28 ± 1.5	39 ± 1.7	30 ± 5.2
	10,000	25 ± 3.5	16 ± 1.2	43 ± 2.0	33 ± 3.0	36 ± 3.5	29 ± 6.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		737 ± 15.2	878 ± 45.2	1,772 ± 33.7	1,285 ± 87.0	983 ± 21.0	727 ± 31.3

TABLE E1
Mutagenicity of Methylphenidate Hydrochloride in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
Study performed at Microbiological Associates							
TA100	0	114 ± 5.8	87 ± 7.5	94 ± 3.7	99 ± 12.3	107 ± 13.4	96 ± 5.2
	100	113 ± 6.0	90 ± 3.2	87 ± 9.0	90 ± 3.3	108 ± 5.0	90 ± 7.9
	333	102 ± 5.9	85 ± 10.0	104 ± 9.0	79 ± 4.4	105 ± 2.0	87 ± 7.9
	1,000	111 ± 4.9	82 ± 7.0	89 ± 2.6	77 ± 6.4	108 ± 5.5	86 ± 8.0
	3,333	104 ± 6.4	105 ± 3.2	91 ± 5.5	87 ± 0.9	103 ± 3.8	95 ± 7.8
	4,000	105 ± 8.0[d]	85 ± 4.3				
	5,000			100 ± 7.9	81 ± 0.3	105 ± 7.3	98 ± 2.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		494 ± 29.8	236 ± 8.1	423 ± 19.7	250 ± 6.1	818 ± 29.3	477 ± 1.5
TA1535	0	25 ± 1.9	13 ± 0.0	14 ± 1.3	9 ± 0.7	7 ± 1.7	9 ± 0.9
	100	26 ± 5.1	11 ± 3.4	9 ± 0.9	10 ± 3.5	11 ± 1.5	9 ± 0.9
	333	23 ± 1.2	9 ± 0.6	11 ± 1.2	11 ± 0.7	7 ± 0.3	9 ± 0.9
	1,000	26 ± 5.3	10 ± 3.0	9 ± 1.9	8 ± 0.6	9 ± 1.2	9 ± 1.2
	3,333	30 ± 2.9	7 ± 2.6	7 ± 0.9	6 ± 2.0	10 ± 1.7	9 ± 1.3
	4,000	25 ± 2.4[d]	10 ± 1.5				
	5,000			10 ± 2.2	8 ± 2.6	11 ± 1.2	7 ± 0.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		253 ± 17.5	153 ± 6.4	52 ± 3.1	75 ± 3.8	187 ± 8.4	78 ± 2.4
TA97	0	106 ± 4.9	98 ± 2.9	125 ± 4.8	130 ± 2.7	115 ± 3.2	126 ± 12.0
	100	111 ± 5.2	97 ± 8.5	129 ± 2.9	122 ± 5.5	128 ± 2.9	116 ± 7.0
	333	95 ± 8.1	95 ± 2.8	122 ± 5.0	122 ± 2.5	114 ± 11.7	126 ± 2.1
	1,000	95 ± 4.2	102 ± 3.8	126 ± 4.0	130 ± 10.3	130 ± 13.3	157 ± 5.6
	3,333	96 ± 1.7	88 ± 4.0	122 ± 9.4	126 ± 11.8	161 ± 6.5	163 ± 5.8
	4,000	95 ± 4.7	83 ± 1.7[d]				
	5,000			131 ± 7.2	158 ± 3.0	124 ± 2.7	128 ± 4.6
Trial summary		Negative	Negative	Negative	Negative	Equivocal	Equivocal
Positive control		333 ± 8.5	217 ± 17.1	228 ± 13.8	416 ± 21.4	1,375 ± 54.2	420 ± 10.4
TA98	0	16 ± 3.5	19 ± 2.7	24 ± 3.5	31 ± 2.7	28 ± 0.6	34 ± 1.8
	100	16 ± 2.7	23 ± 1.3	22 ± 1.9	37 ± 1.2	34 ± 3.3	43 ± 3.0
	333	11 ± 0.9	27 ± 1.3	30 ± 2.6	33 ± 4.6	27 ± 2.0	35 ± 6.7
	1,000	13 ± 1.5	25 ± 2.8	25 ± 3.9	32 ± 1.7	23 ± 1.5	36 ± 1.2
	3,333	18 ± 0.7	19 ± 1.0	27 ± 3.7	38 ± 2.6	27 ± 2.1	40 ± 6.4
	4,000	20 ± 1.2	28 ± 2.3				
	5,000			28 ± 4.2	33 ± 4.4	32 ± 4.0	32 ± 2.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		159 ± 7.9	244 ± 5.8	156 ± 8.6	74 ± 1.3	280 ± 4.1	116 ± 6.1

[a] The detailed protocol and these data are presented in Mortelmans *et al.* (1986). 0 μg/plate dose is the solvent control.
[b] Revertants are presented as mean ± the 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 tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537 and TA97.
[d] Slight toxicity

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Methylphenidate Hydrochloride[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome %[b]
Study performed at Environmental Health Research & Testing								
-S9								
Summary: Negative								
Medium		50	1,023	351	0.34	7.0	26.5	
Mitomycin-C	0.003	50	1,041	1,183	1.13	23.7	26.5	231.22
	0.005	50	1,043	1,254	1.20	25.1	26.5	250.42
Methylphenidate hydrochloride								
	5	50	1,033	377	0.36	7.5	26.5	6.37
	16	50	1,035	417	0.40	8.3	26.5	17.43
	50	50	1,035	373	0.36	7.5	26.5	5.04
	160	50	1,046	416	0.39	8.3	26.5	15.91
	500	0						
	1,000	0						
								P=0.041[c]
+S9								
Trial 1								
Summary: Weakly positive								
Medium		50	1,044	390	0.37	7.8	26.5	
Cyclophosphamide	1.5	50	1,039	1,235	1.18	24.7	26.5	218.19
Methylphenidate hydrochloride								
	50	50	1,041	368	0.35	7.4	26.5	-5.37
	160	50	1,047	422	0.40	8.4	26.5	7.89
	500	50	1,040	368	0.35	7.4	26.5	-5.28
	1000	50	1,043	351	0.33	7.0	26.5	-9.92
	1,600	50	1,043	502	0.48	10.0	26.5	28.84*
	2,000	0						
					P=0.015			
Trial 2								
Summary: Negative								
Medium		50	1,042	427	0.40	8.5	26.0	
Cyclophosphamide	2	50	1,044	2,001	1.91	40.0	26.0	367.73
Methylphenidate hydrochloride								
	1,000	50	1,031	414	0.40	8.3	26.0	-2.01
	1,250	50	1,043	411	0.39	8.2	26.0	-3.84
	1,500	50	1,041	507	0.48	10.1	26.0	18.85
	1,750	50	1,042	496	0.47	9.9	26.0	16.16
	2,000	0					26.0	
					P<0.001			

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Methylphenidate Hydrochloride (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome %
Study performed at Litton Bionetics, Inc.								
-S9								
Summary: Positive								
Distilled water		50	1,034	388	0.37	7.8	26.0	
Mitomycin-C	0.001	50	1,023	644	0.62	12.9	26.0	67.76
	0.010	5	105	211	2.00	42.2	26.0	435.53
Methylphenidate hydrochloride								
	702	50	1,013	464	0.45	9.3	36.6[d]	22.07*
	800	50	1,010	505	0.50	10.1	36.6[d]	33.25*
	900	50	1,016	575	0.56	11.5	36.6[d]	50.82*
	1,000	0					36.6	
					P<0.001			
+S9								
Trial 1								
Summary: Weakly positive								
Distilled water		50	1,031	391	0.37	7.8	25.7	
Cyclophosphamide	0.3	50	1,025	474	0.46	9.5	25.7	21.94
	2.0	5	104	119	1.14	23.8	25.7	201.72
Methylphenidate hydrochloride								
	1,400	50	1,035	448	0.43	9.0	25.7	14.14
	1,600	50	1,041	470	0.45	9.4	25.7	19.05
	2,000	50	1,029	474	0.46	9.5	25.7	21.46*
					P=0.002			
Trial 2								
Summary: Negative								
Distilled water		50	1,019	522	0.51	10.4	25.3	
Cyclophosphamide	0.3	50	1,008	678	0.67	13.6	25.3	31.30
	2.0	5	104	250	2.40	50.0	25.3	369.26
Methylphenidate hydrochloride								
	1,500	50	1,020	538	0.52	10.8	25.3	2.97
	1,750	50	1,015	583	0.57	11.7	25.3	12.13
	2,000	50	1,020	594	0.58	11.9	25.3	13.68[e]
	2,500	0						
					P=0.006			

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Methylphenidate Hydrochloride (continued)

* ($P<0.01$)
[a] SCE=sister chromatid exchange; BrdU=bromodeoxyuridine. A detailed description of the protocol and the data for the Litton Bionetics, Inc., study are presented in Galloway *et al.* (1987).
[b] SCEs/chromosome of culture exposed to methylphenidate hydrochloride relative to those of culture exposed to solvent.
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose.
[d] Because methylphenidate hydrochloride induced a delay in the cell division cycle, harvest time was extended to maximize the proportion of second-division cells available for analysis.
[e] Confluence reduced by approximately 80%; evidence of severe toxicity.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Methylphenidate Hydrochloride[a]

-S9					+S9				
Dose μg/mL	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	Dose μg/mL	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Study performed at Environmental Health Research and Testing									
Trial 1 - Harvest time: 12.5 hours					**Trial 1** - Harvest time: 12.5 hours				
Summary: Negative					Summary: Negative				
Medium					Medium				
	100	3	0.03	3.0		100	1	0.01	1.0
Mitomycin-C					Cyclophosphamide				
0.5	100	103	1.03	64.0	50	100	123	1.23	65.0
Methylphenidate hydrochloride					Methylphenidate hydrochloride				
16	100	1	0.01	1.0	16	100	3	0.03	3.0
50	100	4	0.04	4.0	50	100	0	0.00	0.0
160	100	1	0.01	1.0	160	100	2	0.02	2.0
500	100	2	0.02	2.0	500	100	2	0.02	2.0
1,600	100	6	0.06	6.0	1,600	100	2	0.02	2.0
5,000	0				5,000	0			
				P=0.140[b]					P=0.353
Trial 2 - Harvest time: 12.0 hours					**Trial 2** - Harvest time: 12.0 hours				
Summary: Positive					Summary: Weakly positive				
Medium					Medium				
	100	0	0.00	0.0		100	4	0.04	4.0
Mitomycin-C					Cyclophosphamide				
0.5	100	51	0.51	38.0	50	100	57	0.57	41.0
Methylphenidate hydrochloride					Methylphenidate hydrochloride				
1,500	100	1	0.01	1.0	1,000	100	5	0.05	5.0
1,750	100	16	0.16	16.0*	1,250	100	8	0.08	8.0
2,000	100	16	0.16	15.0*	1,500	100	27	0.27	20.0*
					1,750	0			
				P<0.001					P<0.001

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Methylphenidate Hydrochloride (continued)

-S9					+S9				
Dose µg/mL	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	Dose µg/mL	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Study performed at Litton Bionetics, Inc.									
Harvest time: 21.0 hours[c]					Harvest time: 10.5 hours				
Summary: Negative					Summary: Positive				
Distilled water					Distilled water				
	100	1	0.01	1.0		100	0	0.00	0.0
Mitomycin-C					Cyclophosphamide				
0.062	50	9	0.18	14.0	25	50	11	0.22	18.0
Methylphenidate hydrochloride					Methylphenidate hydrochloride				
750	100	2	0.02	1.0	1,000	100	11	0.11	8.0*
1,000	84	4	0.05	4.0	1,250	100	11	0.11	9.0*
1,250	100	6	0.06	5.0	1,500	100	8	0.08	8.0*
1,500	0				1,750	0			
				P=0.020					P=0.010

* $P<0.05$

[a] Abs=aberrations. A detailed presentation of the protocol and the data from the Litton Bionetics, Inc., study are presented in Galloway *et al.* (1987).

[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose.

[c] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphase cells at harvest.

APPENDIX F
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Day Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	16 ppm	62 ppm	250 ppm	1,000 ppm	4,000 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	216 ± 4	215 ± 4	216 ± 4	212 ± 2	211 ± 3	196 ± 4**
Brain						
Absolute	1.771 ± 0.022	1.804 ± 0.024	1.791 ± 0.035	1.821 ± 0.014	1.828 ± 0.035	1.770 ± 0.049
Relative	8.22 ± 0.23	8.42 ± 0.16	8.30 ± 0.25	8.60 ± 0.12	8.66 ± 0.15	9.01 ± 0.15**
Heart						
Absolute	0.777 ± 0.024	0.724 ± 0.020	0.759 ± 0.010	0.740 ± 0.016	0.701 ± 0.014*	0.714 ± 0.036*
Relative	3.60 ± 0.06	3.38 ± 0.06	3.51 ± 0.04	3.50 ± 0.09	3.32 ± 0.06	3.63 ± 0.15
R. Kidney						
Absolute	0.803 ± 0.022	0.793 ± 0.025	0.839 ± 0.012	0.783 ± 0.027	0.789 ± 0.028	0.832 ± 0.023[b]
Relative	3.72 ± 0.08	3.69 ± 0.08	3.89 ± 0.06	3.70 ± 0.12	3.74 ± 0.08	4.22 ± 0.13**[b]
Liver						
Absolute	6.920 ± 0.154	6.860 ± 0.256	7.048 ± 0.244	6.658 ± 0.111	6.929 ± 0.203	7.887 ± 0.237*
Relative	32.06 ± 0.39	31.93 ± 0.64	32.59 ± 0.53	31.43 ± 0.37	32.82 ± 0.59	40.16 ± 0.87**
Lungs						
Absolute	1.140 ± 0.042	1.181 ± 0.029	1.233 ± 0.055	1.179 ± 0.032	1.268 ± 0.066	1.086 ± 0.023
Relative	5.28 ± 0.16	5.51 ± 0.07	5.70 ± 0.20	5.57 ± 0.16	6.00 ± 0.25	5.54 ± 0.18
R. Testis						
Absolute	1.242 ± 0.018	1.186 ± 0.011	1.177 ± 0.029	1.198 ± 0.022	1.203 ± 0.031	1.186 ± 0.021
Relative	5.76 ± 0.08	5.53 ± 0.07	5.45 ± 0.16	5.66 ± 0.10	5.70 ± 0.15	6.04 ± 0.14
Thymus						
Absolute	0.422 ± 0.022	0.411 ± 0.045	0.407 ± 0.027	0.429 ± 0.021	0.367 ± 0.028	0.439 ± 0.043[b]
Relative	1.95 ± 0.07	1.91 ± 0.18	1.89 ± 0.15	2.03 ± 0.11	1.74 ± 0.12	2.21 ± 0.22[b]
Female						
n	5	5	5	5	5	5
Necropsy body wt	143 ± 2	144 ± 2	143 ± 1	136 ± 3	142 ± 2	131 ± 3**
Brain						
Absolute	1.723 ± 0.024	1.675 ± 0.014	1.712 ± 0.025	1.704 ± 0.018	1.744 ± 0.014	1.725 ± 0.034
Relative	12.03 ± 0.27	11.66 ± 0.24	12.01 ± 0.18	12.57 ± 0.29	12.31 ± 0.06	13.20 ± 0.27**
Heart						
Absolute	0.535 ± 0.014	0.515 ± 0.009	0.559 ± 0.034	0.499 ± 0.021	0.530 ± 0.009	0.492 ± 0.018
Relative	3.73 ± 0.10	3.59 ± 0.11	3.92 ± 0.21	3.67 ± 0.15	3.74 ± 0.03	3.76 ± 0.16
R. Kidney						
Absolute	0.575 ± 0.014	0.563 ± 0.014	0.565 ± 0.014	0.524 ± 0.007*	0.569 ± 0.011	0.567 ± 0.016
Relative	4.01 ± 0.08	3.91 ± 0.09	3.96 ± 0.08	3.86 ± 0.03	4.02 ± 0.09	4.34 ± 0.13
Liver						
Absolute	4.603 ± 0.101	4.452 ± 0.061	4.479 ± 0.190	4.241 ± 0.115	4.698 ± 0.096	5.112 ± 0.177*
Relative	32.13 ± 0.64	30.95 ± 0.25	31.39 ± 1.09	31.22 ± 0.40	33.15 ± 0.56	39.05 ± 0.95**
Lungs						
Absolute	0.972 ± 0.062	0.942 ± 0.034	1.002 ± 0.029	0.929 ± 0.032	0.935 ± 0.029	0.954 ± 0.029
Relative	6.76 ± 0.33	6.54 ± 0.13	7.03 ± 0.21	6.84 ± 0.17	6.60 ± 0.16	7.30 ± 0.21
Thymus						
Absolute	0.387 ± 0.018	0.378 ± 0.026	0.386 ± 0.024	0.347 ± 0.012	0.392 ± 0.018	0.358 ± 0.006[b]
Relative	2.70 ± 0.15	2.63 ± 0.17	2.70 ± 0.15	2.56 ± 0.11	2.78 ± 0.16	2.75 ± 0.11[b]

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=4

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	125 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm
Male						
n	10	9	9	10	10	10
Necropsy body wt	366 ± 7	361 ± 8	367 ± 9	348 ± 7	351 ± 6	347 ± 6
Brain						
Absolute	1.989 ± 0.018	1.999 ± 0.019	2.015 ± 0.018	2.062 ± 0.009*	2.043 ± 0.019*	2.025 ± 0.009*
Relative	5.45 ± 0.11	5.56 ± 0.10	5.52 ± 0.12	5.95 ± 0.13**	5.84 ± 0.11**	5.86 ± 0.08**
Heart						
Absolute	1.092 ± 0.030	1.101 ± 0.025	1.098 ± 0.030	1.078 ± 0.026	1.062 ± 0.021	1.033 ± 0.029
Relative	2.98 ± 0.05	3.05 ± 0.03	3.00 ± 0.05	3.10 ± 0.06	3.03 ± 0.05	2.98 ± 0.05
R. Kidney						
Absolute	1.234 ± 0.036	1.211 ± 0.030	1.241 ± 0.024	1.210 ± 0.027	1.302 ± 0.026	1.316 ± 0.030
Relative	3.37 ± 0.06	3.36 ± 0.04	3.39 ± 0.05	3.49 ± 0.12	3.71 ± 0.04**	3.80 ± 0.07**
Liver						
Absolute	11.962 ± 0.330	12.173 ± 0.296	12.339 ± 0.341	11.943 ± 0.252	12.916 ± 0.386	14.010 ± 0.400**
Relative	32.64 ± 0.62	33.76 ± 0.38	33.65 ± 0.29	34.39 ± 0.88	36.76 ± 0.65**	40.44 ± 1.06**
Lungs						
Absolute	1.718 ± 0.040	1.788 ± 0.073	1.830 ± 0.040	1.735 ± 0.046	1.726 ± 0.064	1.903 ± 0.190
Relative	4.69 ± 0.10	4.96 ± 0.18	5.01 ± 0.15	4.99 ± 0.12	4.91 ± 0.14	5.52 ± 0.59
L. Testis						
Absolute	1.531 ± 0.023	1.516 ± 0.025[b]	1.538 ± 0.031	1.480 ± 0.022	1.516 ± 0.028	1.516 ± 0.025
Relative	4.18 ± 0.05	4.23 ± 0.05[b]	4.20 ± 0.08	4.26 ± 0.07	4.32 ± 0.07	4.38 ± 0.05*
R. Testis						
Absolute	1.482 ± 0.026	1.498 ± 0.054[b]	–[c]	1.422 ± 0.016	–	1.452 ± 0.019
Relative	4.05 ± 0.06	4.12 ± 0.11[b]		4.10 ± 0.06		4.19 ± 0.05
Thymus						
Absolute	0.338 ± 0.022	0.323 ± 0.021	0.340 ± 0.023	0.297 ± 0.012	0.314 ± 0.014	0.327 ± 0.017
Relative	0.92 ± 0.06	0.90 ± 0.06	0.93 ± 0.06	0.85 ± 0.04	0.89 ± 0.04	0.94 ± 0.04
Female						
n	10	7	10	10	10	10
Necropsy body wt	215 ± 4	204 ± 2	204 ± 4	209 ± 3	204 ± 4	207 ± 3
Brain						
Absolute	1.880 ± 0.018	1.836 ± 0.017	1.864 ± 0.013	1.899 ± 0.017	1.908 ± 0.028	1.940 ± 0.024
Relative	8.76 ± 0.17	9.01 ± 0.07	9.15 ± 0.16	9.10 ± 0.08	9.40 ± 0.19**	9.40 ± 0.19**
Heart						
Absolute	0.730 ± 0.010	0.691 ± 0.014	0.688 ± 0.014	0.691 ± 0.015	0.672 ± 0.016*	0.689 ± 0.015*
Relative	3.40 ± 0.06	3.39 ± 0.07	3.37 ± 0.04	3.31 ± 0.06	3.30 ± 0.07	3.33 ± 0.05
R. Kidney						
Absolute	0.742 ± 0.014	0.675 ± 0.014	0.708 ± 0.007	0.734 ± 0.012	0.750 ± 0.025	0.770 ± 0.017
Relative	3.45 ± 0.05	3.31 ± 0.05	3.47 ± 0.05	3.52 ± 0.04	3.68 ± 0.07**	3.72 ± 0.05**
Liver						
Absolute	6.098 ± 0.079	5.917 ± 0.142	5.916 ± 0.147	6.197 ± 0.117	6.347 ± 0.198	7.064 ± 0.154**
Relative	28.39 ± 0.41	29.01 ± 0.58	28.99 ± 0.64	29.67 ± 0.31	31.13 ± 0.50**	34.16 ± 0.41**
Lungs						
Absolute	1.255 ± 0.042	1.189 ± 0.031	1.241 ± 0.032	1.221 ± 0.031	1.199 ± 0.026	1.255 ± 0.019
Relative	5.84 ± 0.17	5.83 ± 0.12	6.08 ± 0.11	5.85 ± 0.12	5.89 ± 0.09	6.08 ± 0.12
Thymus						
Absolute	0.277 ± 0.013	0.260 ± 0.011	0.262 ± 0.008	0.271 ± 0.018	0.282 ± 0.017	0.291 ± 0.016
Relative	1.29 ± 0.05	1.28 ± 0.06	1.29 ± 0.04	1.29 ± 0.07	1.38 ± 0.06	1.41 ± 0.07

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=8
[c] Organ not examined to allow SMVCE procedures to be performed

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	100 ppm	500 ppm	1,000 ppm
Male				
n	10	10	10	9
Necropsy body wt	410 ± 14	406 ± 9	388 ± 11	388 ± 9
Brain				
Absolute	2.074 ± 0.029	2.029 ± 0.039	2.045 ± 0.027	2.076 ± 0.019
Relative	5.11 ± 0.18	5.03 ± 0.18	5.30 ± 0.11	5.37 ± 0.14
R. Kidney				
Absolute	1.465 ± 0.045	1.442 ± 0.044	1.530 ± 0.057	1.500 ± 0.048
Relative	3.59 ± 0.11	3.55 ± 0.11	3.94 ± 0.08*	3.87 ± 0.10*
Liver				
Absolute	15.558 ± 0.548	15.723 ± 0.555	15.341 ± 0.720	16.348 ± 0.565
Relative	38.01 ± 0.67	38.76 ± 1.32	39.49 ± 1.39	42.09 ± 0.90*
R. Testis				
Absolute	1.451 ± 0.031	1.444 ± 0.038	1.448 ± 0.038	1.490 ± 0.028
Relative	3.56 ± 0.08	3.56 ± 0.06	3.74 ± 0.09	3.85 ± 0.08*
Female				
n	10	10	10	10
Necropsy body wt	237 ± 5	227 ± 4	212 ± 3**	214 ± 3**
Brain				
Absolute	1.827 ± 0.031	1.880 ± 0.023	1.825 ± 0.037	1.926 ± 0.018*
Relative	7.75 ± 0.19	8.29 ± 0.17*	8.64 ± 0.21**	9.01 ± 0.11**
R. Kidney				
Absolute	0.843 ± 0.023	0.835 ± 0.007	0.778 ± 0.019	0.803 ± 0.028
Relative	3.58 ± 0.11	3.68 ± 0.05	3.68 ± 0.08	3.75 ± 0.10
Liver				
Absolute	8.066 ± 0.225	7.749 ± 0.272	6.903 ± 0.168**	7.291 ± 0.061**
Relative	34.19 ± 0.95	34.10 ± 1.09	32.66 ± 0.81	34.12 ± 0.48

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

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	100 ppm	500 ppm	1,000 ppm
Male				
n	10	10	10	10
Necropsy body wt	407 ± 17	411 ± 12	399 ± 14	377 ± 6
Brain				
Absolute	2.038 ± 0.025	2.040 ± 0.030	2.095 ± 0.017	2.081 ± 0.015
Relative	5.08 ± 0.22	4.99 ± 0.14	5.31 ± 0.18	5.54 ± 0.09
R. Kidney				
Absolute	1.541 ± 0.048	1.652 ± 0.063	1.610 ± 0.062	1.610 ± 0.027
Relative	3.82 ± 0.15	4.01 ± 0.06	4.05 ± 0.13	4.29 ± 0.10**
Liver				
Absolute	15.355 ± 0.683	16.426 ± 0.646	16.640 ± 0.747	15.784 ± 0.261
Relative	37.79 ± 1.13	40.01 ± 1.31	41.69 ± 1.04*	41.96 ± 0.60**
R. Testis				
Absolute	1.511 ± 0.068	1.855 ± 0.159	1.458 ± 0.067	1.806 ± 0.219
Relative	3.73 ± 0.15	4.60 ± 0.50	3.68 ± 0.18	4.78 ± 0.58
Female				
n	10	10	10	10
Necropsy body wt	288 ± 12	278 ± 5	242 ± 6**	217 ± 3**
Brain				
Absolute	1.850 ± 0.018	1.851 ± 0.019	1.840 ± 0.043	1.871 ± 0.029
Relative	6.52 ± 0.21	6.67 ± 0.12	7.61 ± 0.19**	8.63 ± 0.18**
R. Kidney				
Absolute	0.991 ± 0.031	0.964 ± 0.027	0.899 ± 0.039	0.826 ± 0.032**
Relative	3.46 ± 0.07	3.47 ± 0.08	3.71 ± 0.14	3.81 ± 0.13*
Liver				
Absolute	9.483 ± 0.437	9.681 ± 0.226	8.525 ± 0.281*	7.611 ± 0.192**
Relative	32.98 ± 0.52	34.84 ± 0.80	35.15 ± 0.65*	35.10 ± 0.84*

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

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	16 ppm	62 ppm	250 ppm	1,000 ppm	4,000 ppm
Male						
n	5	5	5	5	5	2
Necropsy body wt	24.2 ± 0.5	26.2 ± 0.9	25.8 ± 0.5	24.4 ± 0.3	23.9 ± 0.6	24.1 ± 0.4
Brain						
Absolute	0.466 ± 0.006	0.471 ± 0.003	0.470 ± 0.005	0.462 ± 0.006	0.454 ± 0.009	0.485 ± 0.004
Relative	19.28 ± 0.34	18.08 ± 0.57	18.25 ± 0.33	18.96 ± 0.38	19.04 ± 0.57	20.17 ± 0.46
Heart						
Absolute	0.131 ± 0.007	0.142 ± 0.011	0.128 ± 0.004	0.122 ± 0.006	0.128 ± 0.010	0.128 ± 0.006
Relative	5.42 ± 0.26	5.39 ± 0.29	4.99 ± 0.15	5.03 ± 0.29	5.34 ± 0.39	5.30 ± 0.15
R. Kidney						
Absolute	0.194 ± 0.004	0.211 ± 0.007*	0.208 ± 0.003	0.198 ± 0.004	0.197 ± 0.003	0.207 ± 0.000
Relative	8.03 ± 0.22	8.06 ± 0.17	8.08 ± 0.15	8.13 ± 0.14	8.25 ± 0.17	8.61 ± 0.13
Liver						
Absolute	0.884 ± 0.018	1.023 ± 0.034**	1.040 ± 0.033**	1.007 ± 0.015**	1.095 ± 0.025**	1.851 ± 0.024**
Relative	36.53 ± 0.38	39.12 ± 0.50**	40.34 ± 0.56**	41.36 ± 0.39**	45.87 ± 0.60**	77.00 ± 2.12**
Lungs						
Absolute	0.190 ± 0.003	0.201 ± 0.009	0.202 ± 0.008	0.216 ± 0.007	0.203 ± 0.012[b]	0.216 ± 0.026
Relative	7.85 ± 0.20	7.69 ± 0.15	7.85 ± 0.28	8.88 ± 0.30	8.56 ± 0.73[b]	8.95 ± 0.93
R. Testis						
Absolute	0.103 ± 0.002	0.104 ± 0.003	0.101 ± 0.001	0.100 ± 0.004	0.105 ± 0.003	0.105 ± 0.005
Relative	4.27 ± 0.09	3.97 ± 0.13	3.92 ± 0.10	4.10 ± 0.16	4.41 ± 0.13	4.36 ± 0.14
Thymus						
Absolute	0.048 ± 0.006	0.051 ± 0.004	0.043 ± 0.004	0.048 ± 0.004	0.042 ± 0.004	0.037 ± 0.005
Relative	2.01 ± 0.29	1.97 ± 0.15	1.69 ± 0.18	1.97 ± 0.17	1.74 ± 0.17	1.52 ± 0.21
Female						
n	5	5	5	5	5	5
Necropsy body wt	20.1 ± 0.3	19.6 ± 0.7	18.9 ± 0.2	19.6 ± 0.5	19.0 ± 0.2	18.4 ± 0.2**
Brain						
Absolute	0.444 ± 0.017	0.456 ± 0.006	0.447 ± 0.011	0.462 ± 0.009	0.460 ± 0.008	0.407 ± 0.039
Relative	22.11 ± 0.59	23.32 ± 0.54	23.65 ± 0.51	23.64 ± 0.59	24.28 ± 0.28	22.05 ± 2.04
Heart						
Absolute	0.109 ± 0.005	0.104 ± 0.004	0.105 ± 0.001	0.099 ± 0.005	0.110 ± 0.009	0.118 ± 0.009
Relative	5.42 ± 0.28	5.30 ± 0.22	5.53 ± 0.05	5.06 ± 0.16	5.84 ± 0.54	6.39 ± 0.49
R. Kidney						
Absolute	0.146 ± 0.008	0.151 ± 0.004	0.143 ± 0.002	0.146 ± 0.006	0.153 ± 0.005	0.128 ± 0.013
Relative	7.28 ± 0.32	7.71 ± 0.17	7.58 ± 0.06	7.45 ± 0.15	8.06 ± 0.25	6.97 ± 0.69
Liver						
Absolute	0.846 ± 0.042	0.818 ± 0.036	0.742 ± 0.014	0.812 ± 0.058	0.887 ± 0.020	1.344 ± 0.030**
Relative	42.10 ± 1.74	41.67 ± 1.11	39.29 ± 0.75	41.30 ± 1.93	46.77 ± 0.91*	72.96 ± 1.26**
Lungs						
Absolute	0.181 ± 0.005	0.194 ± 0.009	0.182 ± 0.007	0.194 ± 0.014	0.183 ± 0.007	0.183 ± 0.014
Relative	8.99 ± 0.15	9.93 ± 0.65	9.64 ± 0.35	9.87 ± 0.52	9.67 ± 0.32	9.94 ± 0.70
Thymus						
Absolute	0.071 ± 0.003	0.072 ± 0.002	0.063 ± 0.003	0.066 ± 0.004	0.056 ± 0.005*	0.045 ± 0.006**
Relative	3.52 ± 0.13	3.67 ± 0.12	3.31 ± 0.15	3.37 ± 0.17	2.97 ± 0.28	2.45 ± 0.32**

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=4

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	125 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm
Male						
n	9	10	10	10	9	10
Necropsy body wt	36.1 ± 0.5	33.6 ± 0.6*	32.3 ± 1.3**	31.0 ± 1.3**	31.6 ± 0.4**	28.50 ± 0.70**
Brain						
Absolute	0.465 ± 0.002	0.478 ± 0.006	0.474 ± 0.004	0.471 ± 0.007	0.481 ± 0.007	0.498 ± 0.010**
Relative	12.89 ± 0.17	14.30 ± 0.34*	14.90 ± 0.71**	15.38 ± 0.55**	15.21 ± 0.29**	17.55 ± 0.48**
Heart						
Absolute	0.177 ± 0.006	0.170 ± 0.005	0.165 ± 0.006	0.174 ± 0.008	0.160 ± 0.002*	0.153 ± 0.002**
Relative	4.91 ± 0.16	5.06 ± 0.16	5.12 ± 0.08	5.62 ± 0.15*	5.04 ± 0.06*	5.42 ± 0.17*
R. Kidney						
Absolute	0.315 ± 0.005	0.310 ± 0.005	0.293 ± 0.010	0.297 ± 0.013	0.314 ± 0.006	0.301 ± 0.010
Relative	8.73 ± 0.13	9.24 ± 0.10	9.14 ± 0.30	9.60 ± 0.16*	9.94 ± 0.25**	10.62 ± 0.52**
Liver						
Absolute	1.510 ± 0.038	1.567 ± 0.035	1.580 ± 0.092	1.502 ± 0.094	1.760 ± 0.038*	1.952 ± 0.060**
Relative	41.79 ± 0.96	46.70 ± 0.90*	48.54 ± 1.36**	48.01 ± 1.51**	55.64 ± 1.19**	68.88 ± 2.81**
Lungs						
Absolute	0.244 ± 0.007	0.223 ± 0.005	0.227 ± 0.010	0.234 ± 0.013	0.232 ± 0.005	0.221 ± 0.006
Relative	6.76 ± 0.17	6.66 ± 0.14	7.03 ± 0.20	7.56 ± 0.24*	7.34 ± 0.13*	7.83 ± 0.35**
L. Testis						
Absolute	0.118 ± 0.002	0.119 ± 0.002	0.119 ± 0.003	0.115 ± 0.003	0.116 ± 0.002	0.116 ± 0.003
Relative	3.27 ± 0.06	3.56 ± 0.05*	3.71 ± 0.11**	3.77 ± 0.14**	3.66 ± 0.06**	4.10 ± 0.13**
R. Testis						
Absolute	0.130 ± 0.003	0.129 ± 0.002	–[b]	0.116 ± 0.002**	–	0.115 ± 0.003**
Relative	3.61 ± 0.07	3.84 ± 0.09		3.79 ± 0.18		4.05 ± 0.12*
Thymus						
Absolute	0.043 ± 0.004	0.040 ± 0.003	0.040 ± 0.005	0.040 ± 0.004	0.045 ± 0.002	0.038 ± 0.003
Relative	1.21 ± 0.12	1.18 ± 0.09	1.23 ± 0.15	1.25 ± 0.11	1.43 ± 0.07	1.35 ± 0.12
Female						
n	10	10	10	10	10	10
Necropsy body wt	25.5 ± 0.9	26.7 ± 0.4	25.7 ± 0.5	26.4 ± 0.5	26.4 ± 0.5	24.8 ± 0.3
Brain						
Absolute	0.483 ± 0.008	0.479 ± 0.008	0.481 ± 0.009	0.483 ± 0.007	0.492 ± 0.006	0.489 ± 0.007
Relative	19.10 ± 0.59	18.03 ± 0.48	18.81 ± 0.47	18.37 ± 0.42	18.69 ± 0.42	19.79 ± 0.30
Heart						
Absolute	0.134 ± 0.004	0.134 ± 0.003	0.129 ± 0.003	0.128 ± 0.003	0.132 ± 0.003	0.140 ± 0.003
Relative	5.29 ± 0.21	5.02 ± 0.08	5.05 ± 0.12	4.84 ± 0.10	4.99 ± 0.13	5.66 ± 0.08
R. Kidney						
Absolute	0.185 ± 0.004	0.190 ± 0.005	0.185 ± 0.004	0.183 ± 0.004	0.187 ± 0.004	0.191 ± 0.006
Relative	7.30 ± 0.16	7.13 ± 0.21	7.21 ± 0.07	6.92 ± 0.12	7.07 ± 0.16	7.71 ± 0.16
Liver						
Absolute	1.052 ± 0.026	1.144 ± 0.012*	1.156 ± 0.024*	1.117 ± 0.026*	1.258 ± 0.032**	1.385 ± 0.030**
Relative	41.49 ± 1.13	42.94 ± 0.60	45.08 ± 0.77	42.37 ± 0.72	47.59 ± 0.84**	55.96 ± 0.83**
Lungs						
Absolute	0.207 ± 0.006	0.226 ± 0.012	0.218 ± 0.015[c]	0.216 ± 0.007	0.218 ± 0.009	0.235 ± 0.009
Relative	8.16 ± 0.25	8.50 ± 0.51	8.55 ± 0.64[c]	8.19 ± 0.27	8.25 ± 0.32	9.52 ± 0.35*
Thymus						
Absolute	0.044 ± 0.002	0.051 ± 0.002	0.051 ± 0.003	0.051 ± 0.003	0.050 ± 0.004	0.045 ± 0.001
Relative	1.74 ± 0.07	1.93 ± 0.09	1.99 ± 0.09	1.94 ± 0.10	1.89 ± 0.16	1.81 ± 0.06

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] Organ not examined to allow SMVCE procedures to be performed
[c] n=9

TABLE F7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	50 ppm	250 ppm	500 ppm
Male				
n	10	10	10	10
Necropsy body wt	47.0 ± 1.2	46.3 ± 0.6	42.3 ± 1.5*	41.0 ± 1.7**
Brain				
Absolute	0.452 ± 0.008	0.452 ± 0.005	0.457 ± 0.004	0.447 ± 0.006
Relative	9.68 ± 0.33	9.79 ± 0.16	10.93 ± 0.42*	11.03 ± 0.41**
R. Kidney				
Absolute	0.342 ± 0.012	0.327 ± 0.006	0.327 ± 0.010	0.326 ± 0.010
Relative	7.28 ± 0.13	7.07 ± 0.09	7.77 ± 0.21	7.99 ± 0.20**
Liver				
Absolute	2.054 ± 0.143	1.980 ± 0.081	1.844 ± 0.070	1.996 ± 0.131
Relative	43.35 ± 2.07	42.68 ± 1.22	43.53 ± 0.44	48.40 ± 1.54*
R. Testis				
Absolute	0.122 ± 0.003	0.121 ± 0.004	0.117 ± 0.003	0.116 ± 0.003
Relative	2.60 ± 0.05	2.62 ± 0.06	2.78 ± 0.09	2.86 ± 0.09*
Female				
n	10	9	10	10
Necropsy body wt	42.2 ± 1.7	38.1 ± 1.6	38.6 ± 1.6	39.8 ± 1.6
Brain				
Absolute	0.463 ± 0.004	0.465 ± 0.009	0.472 ± 0.007	0.468 ± 0.005
Relative	11.13 ± 0.45	12.43 ± 0.66	12.40 ± 0.51	11.93 ± 0.43
R. Kidney				
Absolute	0.213 ± 0.005	0.216 ± 0.005	0.217 ± 0.007	0.215 ± 0.006
Relative	5.08 ± 0.15	5.75 ± 0.26	5.66 ± 0.18	5.47 ± 0.20
Liver				
Absolute	1.594 ± 0.042	1.599 ± 0.040	1.644 ± 0.037	1.712 ± 0.056
Relative	38.02 ± 1.00	42.34 ± 1.18*	42.99 ± 1.40**	43.33 ± 1.19**

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

TABLE F8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Methylphenidate[a]

	0 ppm	50 ppm	250 ppm	500 ppm
Male				
n	10	10	10	9
Necropsy body wt	43.7 ± 1.2	44.6 ± 1.8	42.7 ± 1.2	41.0 ± 1.8
Brain				
Absolute	0.453 ± 0.005	0.445 ± 0.007	0.453 ± 0.009	0.438 ± 0.008
Relative	10.44 ± 0.30	10.08 ± 0.31	10.64 ± 0.22	10.79 ± 0.38
R. Kidney				
Absolute	0.352 ± 0.009	0.364 ± 0.021	0.358 ± 0.009	0.349 ± 0.013
Relative	8.11 ± 0.28	8.14 ± 0.31	8.42 ± 0.26	8.55 ± 0.18
Liver				
Absolute	1.877 ± 0.076	2.236 ± 0.164	2.116 ± 0.089	2.048 ± 0.090
Relative	42.94 ± 1.17	49.67 ± 1.85**	49.48 ± 1.12**	50.27 ± 1.96**
R. Testis				
Absolute	0.117 ± 0.002	0.114 ± 0.004	0.118 ± 0.005[b]	0.116 ± 0.004
Relative	2.70 ± 0.10	2.58 ± 0.11	2.74 ± 0.12[b]	2.85 ± 0.11
Female				
n	10	10	10	9
Necropsy body wt	39.9 ± 1.3	41.9 ± 1.6	39.6 ± 2.6	43.5 ± 1.3
Brain				
Absolute	0.463 ± 0.007	0.468 ± 0.005	0.456 ± 0.005	0.466 ± 0.007
Relative	11.71 ± 0.43	11.32 ± 0.43	12.08 ± 1.01	10.77 ± 0.33
R. Kidney				
Absolute	0.224 ± 0.008	0.243 ± 0.010	0.224 ± 0.006	0.239 ± 0.007
Relative	5.65 ± 0.19	5.85 ± 0.28	5.83 ± 0.31	5.51 ± 0.16
Liver				
Absolute	1.531 ± 0.048	1.721 ± 0.053*	1.695 ± 0.061*	1.903 ± 0.069**
Relative	38.53 ± 1.09	41.58 ± 1.89	43.84 ± 1.98*	43.75 ± 1.00*

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

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Clinical Chemistry Data for Rats in the 14-Day Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	16 ppm	62 ppm	250 ppm	1,000 ppm	4,000 ppm
Male						
n	5	5	5	5	5	5
Urea nitrogen (mg/dL)	17.9 ± 0.3	19.9 ± 0.7*	19.4 ± 0.7	19.3 ± 0.4	21.0 ± 0.5**	24.4 ± 1.1**
Creatinine (mg/dL)	0.90 ± 0.00	0.80 ± 0.03*	0.74 ± 0.02**	0.80 ± 0.03**	0.68 ± 0.02**	0.64 ± 0.04**
Alanine aminotransferase (IU/L)	31 ± 2	27 ± 2	30 ± 2	27 ± 2	28 ± 1	29 ± 2
Aspartate aminotransferase (IU/L)	116 ± 14	101 ± 10	116 ± 17	91 ± 4	98 ± 4	75 ± 2**
Sorbitol dehydrogenase (IU/L)	8.1 ± 0.7	5.5 ± 0.6	8.2 ± 1.0	7.0 ± 1.3	6.3 ± 0.7	6.5 ± 0.9
Female						
n	5	5	5	5	5	5
Urea nitrogen (mg/dL)	18.8 ± 0.4	18.9 ± 1.1	22.6 ± 0.8**	22.2 ± 0.7**	23.9 ± 0.6**	26.7 ± 1.4**
Creatinine (mg/dL)	0.70 ± 0.03	0.80 ± 0.06	0.72 ± 0.06	0.72 ± 0.02	0.62 ± 0.05	0.58 ± 0.06
Alanine aminotransferase (IU/L)	25 ± 3	25 ± 2	26 ± 2	28 ± 2	24 ± 1	31 ± 3
Aspartate aminotransferase (IU/L)	78 ± 8	82 ± 9	85 ± 8	89 ± 13	72 ± 4	77 ± 8
Sorbitol dehydrogenase (IU/L)	7.9 ± 1.0	7.1 ± 0.4	5.5 ± 0.2*	6.9 ± 0.7	7.1 ± 0.5	6.1 ± 0.3[b]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=4

TABLE G2
Hematology and Clinical Chemistry Data for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	100 ppm	500 ppm	1,000 ppm
Male				
n	7	10	9	9
Hematology				
Hematocrit (%)	44.7 ± 0.9	43.9 ± 0.4	43.2 ± 0.6	43.3 ± 0.7
Hemoglobin (g/dL)	16.2 ± 0.2	16.6 ± 0.2	16.3 ± 0.2	16.1 ± 0.4
Erythrocytes (10^6/μL)	8.77 ± 0.12	8.76 ± 0.13	8.73 ± 0.11	8.60 ± 0.20
Mean cell volume (fL)	50.9 ± 0.4	50.1 ± 0.5	49.6 ± 0.8	50.3 ± 0.4
Mean cell hemoglobin (pg)	18.5 ± 0.4	18.9 ± 0.2	18.7 ± 0.2	18.7 ± 0.3
Mean cell hemoglobin concentration (g/dL)	36.4 ± 1.1	37.8 ± 0.3	37.7 ± 0.2	37.1 ± 0.6
Reticulocytes (10^6/μL)	0.3 ± 0.1	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0[b]
Leukocytes (10^3/μL)	6.79 ± 0.35	7.81 ± 0.24*	8.16 ± 0.42*	9.13 ± 0.66**
Segmented neutrophils (10^3/μL)	1.89 ± 0.29	1.77 ± 0.19	2.61 ± 0.33	2.04 ± 0.25
Lymphocytes (10^3/μL)	4.68 ± 0.28	5.74 ± 0.27*	5.21 ± 0.19	6.71 ± 0.59**
Monocytes (10^3/μL)	0.13 ± 0.03	0.24 ± 0.03*	0.21 ± 0.04	0.29 ± 0.04*
Eosinophils (10^3/μL)	0.09 ± 0.03	0.07 ± 0.03	0.12 ± 0.04	0.09 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.019 ± 0.019	0.000 ± 0.000	0.000 ± 0.000	0.009 ± 0.009
Clinical Chemistry				
γ-glutamyltransferase (IU/L)	1.8 ± 0.4[c]	2.2 ± 0.5	1.8 ± 0.4[c]	2.2 ± 0.5
Urea nitrogen (mg/dL)	21.1 ± 0.6[c]	22.1 ± 0.9	19.9 ± 0.7[c]	20.9 ± 0.5
Creatinine (mg/dL)	0.58 ± 0.02[c]	0.54 ± 0.03	0.58 ± 0.02[c]	0.60 ± 0.03
Alanine aminotransferase (IU/L)	80 ± 3[d]	76 ± 6	64 ± 3*[c]	59 ± 4**
Aspartate aminotransferase (IU/L)	119 ± 9	103 ± 6	108 ± 6[c]	92 ± 5*
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	42.3 ± 0.5	42.6 ± 0.3	41.9 ± 0.3	42.4 ± 1.0
Hemoglobin (g/dL)	15.6 ± 0.1	15.5 ± 0.1	15.7 ± 0.1	15.4 ± 0.2
Erythrocytes (10^6/μL)	7.83 ± 0.11	7.86 ± 0.04	7.78 ± 0.06	7.90 ± 0.20
Mean cell volume (fL)	54.1 ± 0.4	54.1 ± 0.5	54.0 ± 0.3	53.8 ± 0.6
Mean cell hemoglobin (pg)	19.9 ± 0.3	19.7 ± 0.2	20.2 ± 0.2	19.5 ± 0.4
Mean cell hemoglobin concentration (g/dL)	36.9 ± 0.4	36.3 ± 0.2	37.4 ± 0.3	36.3 ± 0.6
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.1 ± 0.0
Leukocytes (10^3/μL)	5.60 ± 0.27	5.86 ± 0.29	6.83 ± 0.38*	8.23 ± 0.34**[d]
Segmented neutrophils (10^3/μL)	0.90 ± 0.08	1.19 ± 0.17	1.44 ± 0.21**	1.42 ± 0.26*
Lymphocytes (10^3/μL)	4.45 ± 0.26	4.34 ± 0.19	4.90 ± 0.22	6.18 ± 0.15**[d]
Monocytes (10^3/μL)	0.20 ± 0.04	0.27 ± 0.03*	0.39 ± 0.06**	0.41 ± 0.07**
Eosinophils (10^3/μL)	0.05 ± 0.01	0.07 ± 0.02	0.09 ± 0.02	0.06 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.024 ± 0.013	0.007 ± 0.007	0.000 ± 0.000	0.000 ± 0.000*
Clinical Chemistry				
γ-glutamyltransferase (IU/L)	0.6 ± 0.2	0.7 ± 0.2	0.5 ± 0.2	0.9 ± 0.2
Urea nitrogen (mg/dL)	20.4 ± 1.2	20.2 ± 1.0	19.9 ± 1.0	21.5 ± 1.1
Creatinine (mg/dL)	0.49 ± 0.02	0.54 ± 0.03	0.55 ± 0.03	0.59 ± 0.03*
Alanine aminotransferase (IU/L)	64 ± 9	53 ± 4	49 ± 1	50 ± 2
Aspartate aminotransferase (IU/L)	74 ± 6	68 ± 6	67 ± 3	67 ± 6

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=8 [c] n=10 [d] n=9

TABLE G3
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	100 ppm	500 ppm	1,000 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	43.5 ± 0.9	42.9 ± 0.7	45.2 ± 1.4	44.7 ± 0.8
Hemoglobin (g/dL)	15.8 ± 0.4	15.5 ± 0.3	16.7 ± 0.5	16.5 ± 0.3
Erythrocytes (10^6/μL)	8.56 ± 0.22	8.44 ± 0.16	9.03 ± 0.29	8.87 ± 0.17
Mean cell volume (fL)	51.0 ± 0.4	50.9 ± 0.5	50.1 ± 0.7	50.5 ± 0.5
Mean cell hemoglobin (pg)	18.5 ± 0.2	18.4 ± 0.2	18.5 ± 0.2	18.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	36.3 ± 0.3	36.2 ± 0.3	36.9 ± 0.3	36.6 ± 0.2
Reticulocytes (10^6/μL)	0.3 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	6.43 ± 0.52	7.72 ± 0.47	7.23 ± 0.48	7.57 ± 0.93
Segmented neutrophils (10^3/μL)	2.11 ± 0.28	2.14 ± 0.23	1.79 ± 0.26	1.71 ± 0.26[b]
Lymphocytes (10^3/μL)	3.56 ± 0.41	4.70 ± 0.41	4.56 ± 0.40	4.23 ± 0.35
Monocytes (10^3/μL)	0.60 ± 0.07	0.70 ± 0.10	0.70 ± 0.07	0.59 ± 0.09
Eosinophils (10^3/μL)	0.05 ± 0.02	0.05 ± 0.02	0.05 ± 0.02	0.13 ± 0.04
Nucleated erythrocytes (10^3/μL)	0.04 ± 0.03	0.07 ± 0.03	0.01 ± 0.01	0.00 ± 0.00
Clinical Chemistry				
γ-glutamyltransferase (IU/L)	2.1 ± 0.5	2.3 ± 0.5	2.6 ± 0.7	1.5 ± 0.5
Urea nitrogen (mg/dL)	19.5 ± 0.7	19.9 ± 0.6	19.8 ± 0.7	19.4 ± 0.9
Creatinine (mg/dL)	0.40 ± 0.03	0.38 ± 0.02	0.38 ± 0.03	0.38 ± 0.02
Alanine aminotransferase (IU/L)	83 ± 5	65 ± 3**	66 ± 5**	66 ± 8**
Aspartate aminotransferase (IU/L)	91 ± 6	85 ± 6	86 ± 8	92 ± 9
Female				
n	9	10	9	10
Hematology				
Hematocrit (%)	43.0 ± 0.4	43.8 ± 0.4	43.4 ± 1.4	42.6 ± 0.6
Hemoglobin (g/dL)	15.6 ± 0.2	15.6 ± 0.1	15.6 ± 0.3	15.3 ± 0.2
Erythrocytes (10^6/μL)	7.83 ± 0.11	7.99 ± 0.10	7.94 ± 0.19	7.85 ± 0.13
Mean cell volume (fL)	55.0 ± 0.5	54.9 ± 0.6	54.9 ± 0.5	54.1 ± 0.4
Mean cell hemoglobin (pg)	20.0 ± 0.2	19.6 ± 0.1	19.7 ± 0.2	19.5 ± 0.2*
Mean cell hemoglobin concentration (g/dL)	36.3 ± 0.2	35.7 ± 0.3	36.0 ± 0.4	35.9 ± 0.2
Reticulocytes (10^6/μL)	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	5.21 ± 0.43	4.98 ± 0.25	4.63 ± 0.35	5.94 ± 0.70
Segmented neutrophils (10^3/μL)	1.41 ± 0.16	1.09 ± 0.10	1.13 ± 0.08	1.47 ± 0.31
Lymphocytes (10^3/μL)	3.08 ± 0.28	3.21 ± 0.18	2.91 ± 0.28	3.61 ± 0.34
Monocytes (10^3/μL)	0.53 ± 0.10	0.48 ± 0.05	0.47 ± 0.05	0.62 ± 0.10
Eosinophils (10^3/μL)	0.07 ± 0.03	0.05 ± 0.02	0.05 ± 0.01	0.06 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.05 ± 0.02	0.05 ± 0.02	0.02 ± 0.01	0.02 ± 0.01
Clinical Chemistry				
γ-glutamyltransferase (IU/L)	1.8 ± 0.4[c]	2.9 ± 0.9	1.7 ± 0.5[c]	2.3 ± 0.6
Urea nitrogen (mg/dL)	19.5 ± 0.8[c]	19.3 ± 0.8	20.8 ± 0.9[c]	22.2 ± 0.7*
Creatinine (mg/dL)	0.37 ± 0.03[c]	0.30 ± 0.03	0.36 ± 0.03[c]	0.37 ± 0.03
Alanine aminotransferase (IU/L)	53 ± 2[c]	56 ± 1	58 ± 5[c]	53 ± 3
Aspartate aminotransferase (IU/L)	67 ± 3[c]	63 ± 2	67 ± 5[c]	76 ± 5

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9 [c] n=10

TABLE G4
Clinical Chemistry Data for Mice in the 14-Day Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	16 ppm	62 ppm	250 ppm	1,000 ppm	4,000 ppm
Male						
n	5	5	5	5	5	2
Urea nitrogen (mg/dL)	27.0 ± 1.4	24.8 ± 1.4	21.9 ± 1.5	22.7 ± 1.2	24.0 ± 1.0	23.1 ± 2.3
Creatinine (mg/dL)	0.35 ± 0.09[b]	0.46 ± 0.04	0.48 ± 0.05	0.44 ± 0.07	0.60 ± 0.03	0.35 ± 0.05
Alanine aminotransferase (IU/L)	28 ± 6	35 ± 11	20 ± 2	24 ± 6	22 ± 4	73 ± 22
Aspartate aminotransferase (IU/L)	166 ± 41	161 ± 41	99 ± 16	105 ± 35	99 ± 8	203 ± 45
Sorbitol dehydrogenase (IU/L)	20 ± 1[c]	18 ± 2	20 ± 1[c]	21 ± 3[c]	16 ± 1	41 ± 9
Female						
n	5	5	5	5	5	5
Urea nitrogen (mg/dL)	20.9 ± 1.1	17.9 ± 0.7	19.7 ± 1.4	20.5 ± 0.8	20.4 ± 0.7	23.4 ± 1.3
Creatinine (mg/dL)	0.50 ± 0.03	0.54 ± 0.09	0.44 ± 0.05	0.46 ± 0.05	0.50 ± 0.00[b]	0.44 ± 0.05
Alanine aminotransferase (IU/L)	22 ± 3	23 ± 7	17 ± 1	29 ± 3	17 ± 4	26 ± 2
Aspartate aminotransferase (IU/L)	112 ± 15	100 ± 8	116 ± 9	123 ± 17	91 ± 21	106 ± 19
Sorbitol dehydrogenase (IU/L)	10 ± 1[d]	14 ± 0[d]	10 ± 2[b]	12 ± 3[c]	11 ± 2[c]	16 ± 2[b]

[a] Mean ± standard error
[b] n=4
[c] n=3
[d] n=2

TABLE G5
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	50 ppm	250 ppm	500 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	44.5 ± 0.4	45.0 ± 0.8	44.9 ± 0.7	44.4 ± 0.3
Hemoglobin (g/dL)	15.4 ± 0.2	15.7 ± 0.3	15.9 ± 0.3	15.4 ± 0.1
Erythrocytes (10^6/μL)	9.27 ± 0.09	9.36 ± 0.19	9.40 ± 0.17	9.14 ± 0.09
Mean cell volume (fL)	47.9 ± 0.2	48.2 ± 0.1	48.1 ± 0.4	48.6 ± 0.2*
Mean cell hemoglobin (pg)	16.6 ± 0.1	16.8 ± 0.1	16.9 ± 0.2	16.8 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.6 ± 0.2	34.9 ± 0.2	35.5 ± 0.4	34.6 ± 0.2
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes (10^3/μL)	3.52 ± 0.31	2.63 ± 0.28	2.94 ± 0.31	3.12 ± 0.40
Segmented neutrophils (10^3/μL)	1.36 ± 0.19	0.72 ± 0.14*	1.18 ± 0.19	1.21 ± 0.13
Lymphocytes (10^3/μL)	2.02 ± 0.18	1.83 ± 0.23	1.70 ± 0.28	1.81 ± 0.38
Monocytes (10^3/μL)	0.10 ± 0.03	0.05 ± 0.02	0.03 ± 0.01*	0.03 ± 0.01*
Eosinophils (10^3/μL)	0.01 ± 0.01	0.03 ± 0.01	0.01 ± 0.01	0.04 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
γ-glutamyltransferase (IU/L)	0.9 ± 0.4	2.4 ± 0.7[b]	1.2 ± 0.5	2.4 ± 0.2
Urea nitrogen (mg/dL)	19.4 ± 1.9	19.7 ± 2.8	16.4 ± 1.9	19.8 ± 2.4
Creatinine (mg/dL)	0.37 ± 0.04[b]	0.37 ± 0.03	0.36 ± 0.02	0.38 ± 0.03[b]
Alanine aminotransferase (IU/L)	328 ± 55[b]	314 ± 61	234 ± 39	240 ± 42
Aspartate aminotransferase (IU/L)	221 ± 33[b]	281 ± 66	202 ± 28	211 ± 35
Female				
n	10	9	9	10
Hematology				
Hematocrit (%)	44.9 ± 0.5	45.1 ± 0.7	45.2 ± 0.8	45.2 ± 0.5
Hemoglobin (g/dL)	16.1 ± 0.2	16.3 ± 0.3	16.3 ± 0.4	16.0 ± 0.2
Erythrocytes (10^6/μL)	9.31 ± 0.13	9.35 ± 0.15	9.38 ± 0.20	9.33 ± 0.11
Mean cell volume (fL)	48.1 ± 0.4	48.3 ± 0.5	48.2 ± 0.4	48.6 ± 0.3
Mean cell hemoglobin (pg)	17.3 ± 0.2	17.4 ± 0.2	17.4 ± 0.2	17.1 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.8 ± 0.3	36.1 ± 0.5	36.0 ± 0.5	35.3 ± 0.3
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes (10^3/μL)	3.30 ± 0.23	4.08 ± 0.33	3.61 ± 0.32	3.34 ± 0.41
Segmented neutrophils (10^3/μL)	0.86 ± 0.08	1.31 ± 0.16	1.09 ± 0.13	1.13 ± 0.19
Lymphocytes (10^3/μL)	2.37 ± 0.17	2.68 ± 0.19	2.41 ± 0.29	2.11 ± 0.27
Monocytes (10^3/μL)	0.03 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.02
Eosinophils (10^3/μL)	0.04 ± 0.02	0.06 ± 0.03	0.08 ± 0.02	0.06 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
γ-glutamyltransferase (IU/L)	3.4 ± 2.6	1.6 ± 1.6	0.9 ± 0.9[c]	0.0 ± 0.0
Urea nitrogen (mg/dL)	25.9 ± 2.1	23.4 ± 2.4	20.5 ± 1.7[c]	18.0 ± 1.4*
Creatinine (mg/dL)	0.32 ± 0.04[b]	0.30 ± 0.03	0.34 ± 0.03[d]	0.34 ± 0.04
Alanine aminotransferase (IU/L)	175 ± 35	105 ± 17	86 ± 11[d]	112 ± 14[b]
Aspartate aminotransferase (IU/L)	199 ± 40	134 ± 15	211 ± 47[c]	126 ± 10[b]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] n=9 [c] n=10 [d] n=8

TABLE G6
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	50 ppm	250 ppm	500 ppm
Male				
n	10	10	10	9
Hematology				
Hematocrit (%)	42.7 ± 0.9	44.3 ± 0.4	44.0 ± 1.1	44.6 ± 1.1
Hemoglobin (g/dL)	15.5 ± 0.3	15.8 ± 0.2	15.5 ± 0.1	16.0 ± 0.2
Erythrocytes (10^6/μL)	8.95 ± 0.23	9.30 ± 0.05	9.19 ± 0.18	9.36 ± 0.16
Mean cell volume (fL)	47.9 ± 0.8	47.8 ± 0.3	47.8 ± 0.4	47.7 ± 0.5
Mean cell hemoglobin (pg)	17.4 ± 0.3	17.0 ± 0.2	16.9 ± 0.2	17.1 ± 0.3
Mean cell hemoglobin concentration (g/dL)	36.3 ± 0.3	35.7 ± 0.5	35.4 ± 0.6	36.0 ± 0.8
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	4.13 ± 0.22	5.02 ± 0.42	4.23 ± 0.18	4.42 ± 0.33
Segmented neutrophils (10^3/μL)	0.94 ± 0.13	0.91 ± 0.07	0.91 ± 0.11	0.86 ± 0.13
Lymphocytes (10^3/μL)	3.05 ± 0.17	3.98 ± 0.37	3.17 ± 0.15	3.45 ± 0.28
Monocytes (10^3/μL)	0.10 ± 0.02	0.08 ± 0.03	0.09 ± 0.02	0.08 ± 0.02
Eosinophils (10^3/μL)	0.04 ± 0.01	0.05 ± 0.02	0.06 ± 0.01	0.03 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Clinical Chemistry				
γ-glutamyltransferase (IU/L)	1.1 ± 0.7[b]	0.2 ± 0.1	0.6 ± 0.3	0.6 ± 0.4
Urea nitrogen (mg/dL)	24.4 ± 1.1[c]	25.8 ± 0.8	24.0 ± 0.9	24.9 ± 0.9[c]
Creatinine (mg/dL)	0.34 ± 0.05[d]	0.36 ± 0.04	0.33 ± 0.06[c]	0.46 ± 0.12[d]
Alanine aminotransferase (IU/L)	185 ± 24[b]	189 ± 28	164 ± 16[b]	252 ± 48[e]
Aspartate aminotransferase (IU/L)	141 ± 20[b]	134 ± 16	111 ± 11[b]	165 ± 37[e]
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	44.8 ± 0.8	44.4 ± 0.7	43.4 ± 0.5	45.3 ± 1.0
Hemoglobin (g/dL)	16.0 ± 0.3	16.0 ± 0.2	16.2 ± 0.2	16.1 ± 0.2
Erythrocytes (10^6/μL)	9.39 ± 0.13	9.33 ± 0.13	9.17 ± 0.15	9.54 ± 0.18
Mean cell volume (fL)	47.8 ± 0.8	47.6 ± 0.3	47.3 ± 0.4	47.5 ± 0.6
Mean cell hemoglobin (pg)	17.0 ± 0.3	17.1 ± 0.2	17.7 ± 0.4	16.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.8 ± 1.0	36.0 ± 0.5	37.4 ± 0.6	35.7 ± 0.6
Reticulocytes (10^6/μL)	0.3 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.3 ± 0.0
Leukocytes (10^3/μL)	4.19 ± 0.46	3.72 ± 0.32	3.77 ± 0.42	4.42 ± 0.50
Segmented neutrophils (10^3/μL)	0.86 ± 0.15	0.68 ± 0.08	0.70 ± 0.10	0.71 ± 0.07
Lymphocytes (10^3/μL)	3.16 ± 0.37	2.86 ± 0.27	2.94 ± 0.38	3.55 ± 0.44
Monocytes (10^3/μL)	0.10 ± 0.02	0.14 ± 0.04	0.08 ± 0.02	0.10 ± 0.02
Eosinophils (10^3/μL)	0.06 ± 0.02	0.04 ± 0.02	0.05 ± 0.01	0.06 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
γ-glutamyltransferase (IU/L)	1.2 ± 1.1	0.9 ± 0.6	0.0 ± 0.0[b]	0.0 ± 0.0
Urea nitrogen (mg/dL)	21.5 ± 2.0	23.1 ± 1.8	22.7 ± 1.2[b]	25.7 ± 1.6
Creatinine (mg/dL)	0.29 ± 0.04[b]	0.30 ± 0.04[b]	0.31 ± 0.04[b]	0.26 ± 0.04
Alanine aminotransferase (IU/L)	85 ± 21	129 ± 28	98 ± 27	56 ± 9
Aspartate aminotransferase (IU/L)	174 ± 37	125 ± 11	141 ± 24[b]	96 ± 11

[a] Mean ± standard error
[b] n=9 [c] n=7 [d] n=5 [e] n=8

APPENDIX H
SPECIAL STUDIES

SPECIAL STUDIES

METHODS

Nose-to-Rump Length in the 13-Week Studies

For the 13-week studies, nose-to-rump length measurements were taken on all rats prior to study initiation, and on all surviving rats at approximately 4, 8, and 13 weeks into the study.

A stationary bar was positioned at the 0.5 centimeter mark of a rule, the rat's teeth were engaged to the bar, and the tail was pulled. The nose-to-rump length at the base of the tail was recorded to the nearest one-half centimeter.

Bone Length and Density in the 13-Week Studies

Both femurs of all surviving rats were removed at terminal sacrifice. The right femur was used to determine bone length; the left femur was used to determine bone density. Prior to measurement of bone length or density, the femurs were manually cleared of extraneous tissue.

Bone length was measured to the nearest millimeter as the shortest distance between opposing epiphyses.

Prior to measurement of bone density, left femurs were rehydrated in 0.85% sodium chloride at room temperature for 1 hour. The bones were then rinsed and suspended in distilled water by a stainless steel wire. While suspended, the weights of the bones were measured to the nearest 0.001 gram with a Mettler Balance (Mettler Instrument Corporation). The bones were then blotted dry, suspended in air from the same stainless steel wires, and measured again. Bone density was calculated using a standard temperature and pressure method, where the density of the bone (g/mL) is the weight of the bone in air divided by the difference between weight of the bone in air and weight of the bone in water.

TABLE H1
Nose-to-Rump Length in Rats in the 13-Week Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	125 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm
n	10	10	10	10	10	10
Male						
Study initiation	15.40 ± 0.16	15.25 ± 0.13	15.40 ± 0.15	15.45 ± 0.16	15.30 ± 0.17	15.45 ± 0.14
4 Weeks	20.55 ± 0.19	20.45 ± 0.09	20.75 ± 0.19	20.45 ± 0.20	20.60 ± 0.18	20.05 ± 0.14
8 Weeks	22.55 ± 0.12	22.44 ± 0.18[b]	22.70 ± 0.19	22.35 ± 0.11	22.40 ± 0.10	22.20 ± 0.13
13 Weeks	23.75 ± 0.20	23.50 ± 0.19[b]	23.44 ± 0.21[b]	23.50 ± 0.20	23.60 ± 0.15	23.10 ± 0.15
Female						
Study initiation	14.65 ± 0.11	14.55 ± 0.09	14.50 ± 0.11	14.80 ± 0.11	14.75 ± 0.08	14.60 ± 0.12
4 Weeks	18.65 ± 0.11	18.75 ± 0.13	18.65 ± 0.11	18.80 ± 0.19	18.65 ± 0.13	18.55 ± 0.14
8 Weeks	21.35 ± 0.13	21.35 ± 0.18	21.30 ± 0.13	21.60 ± 0.19	21.65 ± 0.17	21.40 ± 0.12
13 Weeks	21.45 ± 0.09	21.43 ± 0.13[c]	21.40 ± 0.10	21.70 ± 0.15	21.75 ± 0.17	21.65 ± 0.08

[a] Data are presented as mean ± standard error. Nose-to-rump lengths are measured in centimeters. Differences from the control are not significant by Williams' or Dunnett's test.
[b] n=9
[c] n=7

TABLE H2
Bone Length and Bone Density in Rats in the 13-Week Feed Study of Methylphenidate Hydrochloride[a]

	0 ppm	125 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm
n	10	10	10	10	10	10
Male						
Bone length	38.50 ± 0.27	38.25 ± 0.70[b]	38.63 ± 0.32[b]	38.70 ± 0.33	39.60 ± 0.31*	39.20 ± 0.44
Bone density	1.32 ± 0.01	1.32 ± 0.01[c]	1.29 ± 0.02[c]	1.31 ± 0.01	1.34 ± 0.01	1.30 ± 0.02
Female						
Bone length	35.50 ± 0.50	33.57 ± 0.95	35.20 ± 0.51	35.50 ± 0.56	35.60 ± 0.54	35.50 ± 0.62
Bone density	1.32 ± 0.02	1.30 ± 0.01[d]	1.30 ± 0.01	1.29 ± 0.01	1.31 ± 0.01	1.29 ± 0.02

* Significantly different (P=0.05) from the control by Shirley's test
[a] Data are presented as mean ± standard error. Bone density is measured in grams per cubic centimeter; bone length is measured in millimeters.
[b] n=8
[c] n=9
[d] n=7

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS STUDIES

PROCUREMENT AND CHARACTERIZATION OF METHYLPHENIDATE HYDROCHLORIDE

United States Pharmacopeia (USP) grade methylphenidate hydrochloride (*threo* racemate) was supplied by Ciba-Geigy Corporation (Summit, NJ) in two lots. Lot M1088 was used throughout the 14-day and 13-week studies. Lot CMS86-166-001 was used throughout the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the methylphenidate hydrochloride studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a white, fine crystalline solid, were identified as methylphenidate hydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the structure and the infrared and ultraviolet spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of methylphenidate hydrochloride. The infrared and nuclear magnetic resonance spectra are presented in Figures I1 and I2. No optical activity was detected.

The purity of each lot was determined by elemental analyses, Karl Fischer water analysis, titration of the amine group, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). Titration of the amine group was performed by dissolving samples of methylphenidate hydrochloride in glacial acetic acid and adding mercuric acetate test solution. The sample solutions were then titrated with 0.1 N perchloric acid and monitored potentiometrically using a micro combination pH/mV electrode filled with aqueous 4 M potassium chloride electrolyte. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates using two solvent systems: 1) chloroform:methanol:concentrated ammonium hydroxide (95:5:0.5) and 2) *n*-butanol:water:glacial acetic acid (66:17:17). Nicotinamide was used as a reference standard. Plates were examined under shortwave (254 nm) ultraviolet light and after spraying with Dragendorff's reagent, followed by 1 N sulfuric acid. To confirm conformance with USP purity specifications, for two impurities, the *erythro* (*d,l*) isomer (<1%) and α-phenyl-2-piperidineacetic acid hydrochloride (<0.6%), USP thin-layer chromatography methods were used. To determine the level of the *erythro* (*d,l*) isomer, TLC was performed using system 1 with a solvent ratio of 95:5:0.5. Methylphenidate hydrochloride *erythro* isomer (USP grade) was used as a reference standard. Plates were examined under ordinary light after being air-dried and sprayed with Dragendorff's reagent, followed by 1 N sulfuric acid. To determine the level of α-phenyl-2-piperidineacetic acid hydrochloride, TLC was performed on Silica Gel 60 F-254 plates using a solvent system of chloroform:methanol:glacial acetic acid (65:25:5). The reference standard used was α-phenyl-2-piperidineacetic acid hydrochloride (USP grade). Plates were examined under 254 nm ultraviolet light after being air-dried and exposed overnight to longwave (366 nm) ultraviolet light. HPLC was performed with a Waters μBondapak C_{18} column using ultraviolet detection (205 nm) and a solvent system of 0.02 M aqueous potassium dihydrogen phosphate:acetonitrile (82:18). The flow rate was 1.0 mL/minute. A concomitant analysis of lot M1088 with lot CMS86-166-001 was performed using the HPLC system previously described, except a solvent system of 0.02 M aqueous potassium dihydrogen phosphate:acetonitrile (70:30) was used.

For lot M1088, elemental analyses of the chemical for carbon, hydrogen, nitrogen, and chlorine were in agreement with the theoretical values for methylphenidate hydrochloride. Karl Fischer water analysis indicated 0.05 ± 0.01% water. Titration of the amine group indicated a purity of 100.0 ± 0.6%. Thin-layer chromatography by system 1 indicated a major spot and one trace impurity, and system 2 indicated a major spot. United States Pharmacopeia purity TLC indicated no *erythro* isomer was present and 0.2% α-phenyl-2-piperidineacetic acid hydrochloride content. HPLC revealed a major peak and no impurities with areas greater than 0.1% of the major peak area. A major peak comparison with a USP standard

solution indicated that the bulk chemical had a purity of 99.4 ± 0.7% relative to the USP standard. The overall purity was determined to be greater than 99% and was consistent with USP purity specifications.

For lot CMS86-166-001, elemental analyses of the chemical for hydrogen, nitrogen, and chlorine were in agreement with the theoretical values for methylphenidate hydrochloride. The elemental analysis for carbon was slightly high. Karl Fischer water analysis indicated 0.086 ± 0.004% water. Titration of the amine group indicated a purity of 100.5 ± 0.3%. Thin-layer chromatography by both systems indicated a major spot. United States Pharmacopeia purity TLC indicated that neither the *erythro* isomer nor α-phenyl-2-piperidineacetic acid hydrochloride was present at a level above USP purity specifications. HPLC indicated a major peak and no impurities with areas greater than 0.1% of the major peak area. Based on the results of the concomitant analysis, lot CMS86-166-001 had a purity of 100.0 ± 1.5% relative to lot M1088. The overall purity of lot CMS86-166-001 was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory. HPLC was performed using the system described for the purity analysis, except a solvent ratio of 70:30 was used. These studies indicated that methylphenidate hydrochloride was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at 20° to 24° C in plastic bags inside metal pails which were placed in a ventilated cabinet. Stability was monitored during the 2-year studies using HPLC and titration of the amine group. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared weekly by mixing methylphenidate hydrochloride with feed (Table I1). Mixtures were made by preparing a methylphenidate hydrochloride/feed premix by hand, which was then blended with feed in a Patterson-Kelly twin-shell blender for 15 minutes using an intensifier bar for the initial five minutes. Formulations were stored in double plastic bags at 4° C for up to 2 weeks.

Homogeneity studies of a mixture of 200 ppm methylphenidate hydrochloride in feed were performed by the analytical chemistry laboratory. Aliquots were extracted with acetonitrile containing 0.85% concentrated hydrochloric acid and centrifuged. Aliquots of the extract were mixed with an internal standard, acetophenone in acetonitrile (0.1 mg/mL), then diluted with 0.020 M aqueous potassium dihydrogen phosphate. HPLC was performed with a Waters μBondapak C_{18} column using ultraviolet detection (205 nm) and a solvent system of 0.02 M aqueous potassium dihydrogen phosphate:acetonitrile (68:32). The flow rate was 1.0 mL/minute. Stability studies of the 200 ppm formulation were also performed using HPLC. Homogeneity was confirmed and the stability of the dose formulation was confirmed for at least 3 weeks at 5° C when stored in the dark, and for up to 7 days when exposed to air and light (simulated animal cage conditions).

Periodic analyses of the dose formulations of methylphenidate hydrochloride were conducted at the study laboratory and analytical chemistry laboratory using HPLC. During the 14-day studies, only the initial formulation was analyzed (Table I2); all were within 10% of the target concentration. For the 13-week studies, dose formulations were analyzed at the beginning, midpoint, and end of the studies (Table I3); 90% (18/20) were within 10% of the target concentration. During the 2-year studies, the dose formulations were analyzed initially and then every 6 to 10 weeks (Table I4). Of the dose formulations analyzed during the 2-year studies, 88% (146/167) were within 10% of the target concentration, with no mixture differing by more than 21% from the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I5).

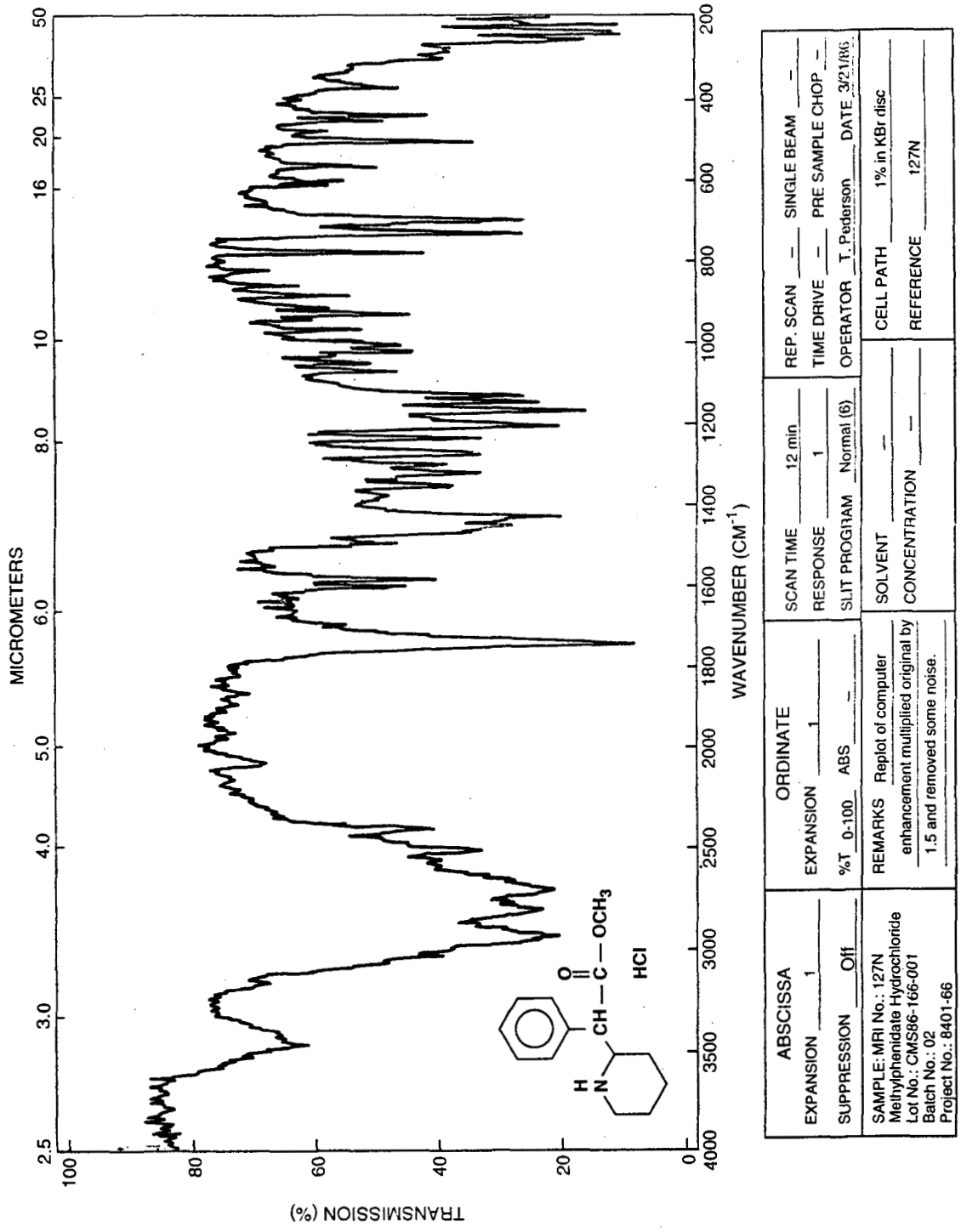

FIGURE I1
Infrared Absorption Spectrum of Methylphenidate Hydrochloride

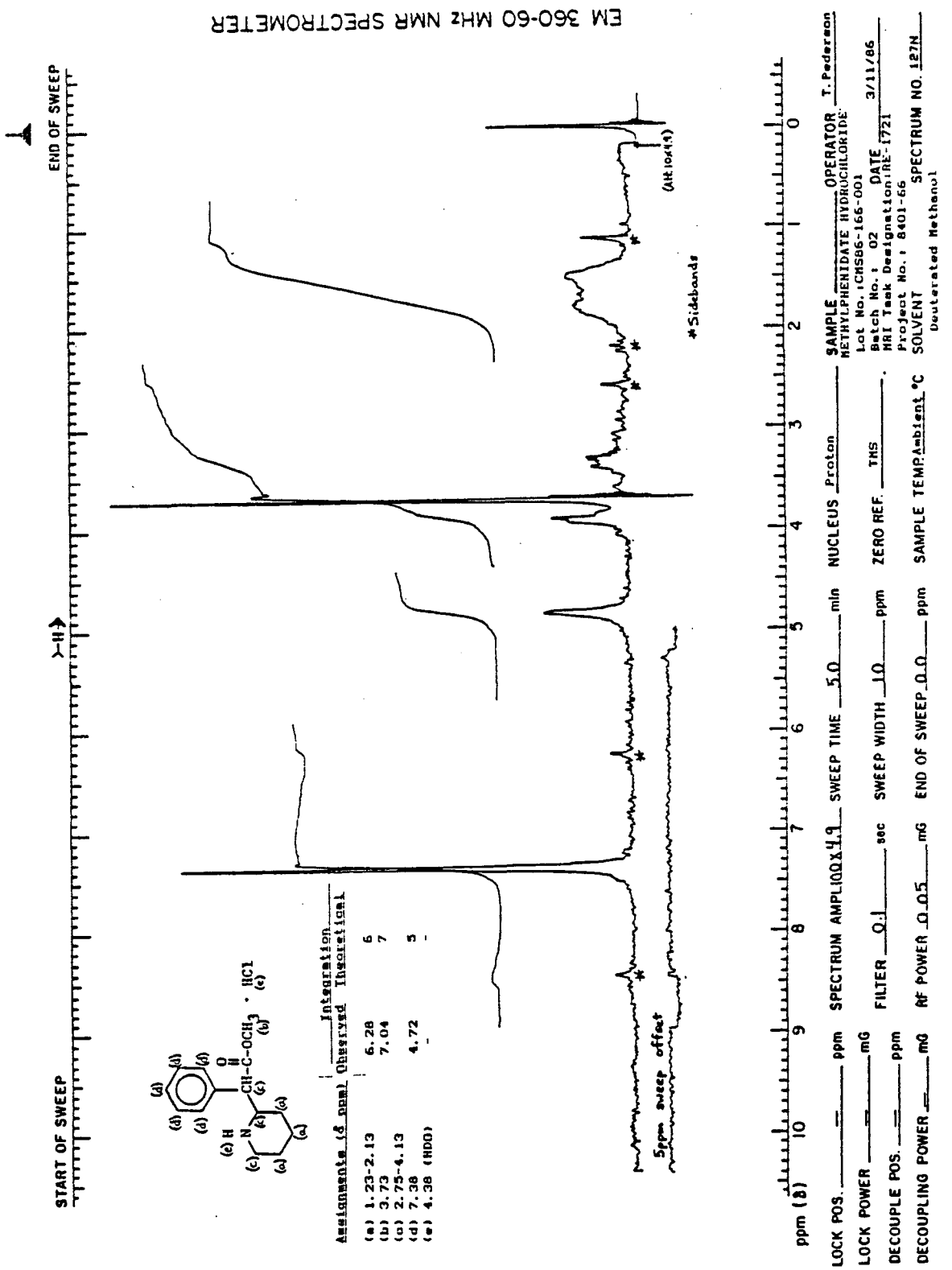

FIGURE I2
Nuclear Magnetic Resonance Spectrum of Methylphenidate Hydrochloride

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of Methylphenidate Hydrochloride

14-Day Studies	13-Week Studies	2-Year Studies
Preparation		
A premix of feed and methylphenidate hydrochloride was prepared, then layered into the remaining feed and blended in a Patterson-Kelly twin-shell blender with the intensifier bar on for 5 minutes and off for 10 minutes. Doses were prepared weekly.	Same as 14-day studies	Same as 14-day studies
Chemical Lot Number		
M1088	M1088	CMS86-166-001
Maximum Storage Time		
2 weeks	2 weeks	2 weeks
Storage Conditions		
Stored in double plastic bags at 4° C	Same as 14-day studies	Same as 14-day studies
Study Laboratory		
Hazleton Laboratories America, Inc. (Madison, WI)	Same as 14-day studies	TSI Mason Research Institute (Worcester, MA)
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 14-day studies	Same as 14-day studies

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Day Feed Studies of Methylphenidate Hydrochloride

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
8 June 1983	8 June 1983	16	14.8	–8
		62	59.0	–5
		250	254	+2
		1,000	952	–5
		4,000	4,010	0

[a] Results of duplicate analyses

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of Methylphenidate Hydrochloride

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
6 October 1983	7–9 October 1983	125	142	+14
		250	247	–1
		500	508	+2
		1,000	1,055	+6
		2,000	2,120	+6
1 December 1983	1–2 December 1983	125	121	–3
		250	236	–6
		500	508	+2
		1,000	1,035	+4
		2,000	2,015	+1
30 December 1983	30 December 1983 – 1 January 1984	125	157	+26
		250	252	+1
		500	507	+1
		1,000	976	–2
		2,000	2,035	+2
30 December 1983[b]	5–6 January 1984	125	110	–12
30 December 1983[c]	5–6 January 1984	125	98	–21
5 January 1984	5–6 January 1984	125	130	+4
		250	264	+6
		500	532	+6
		1,000	992	–1
		2,000	1,995	0

[a] Results of duplicate analyses
[b] Results of remix
[c] Test diet mixed on 30 December 1984 and diluted with basal diet on 3 January 1985 and remixed prior to feeding to animals.

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Methylphenidate Hydrochloride

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Rats				
15 July 1986	21 July 1986	1,000	957[b]	–4
		1,000	979[c]	–2
		1,000	950[d]	–5
13 August 1986	15 August 1986	100	96	–4
		100	89	–11
		500	464	–7
		500	456	–9
		1,000	903	–10
		1,000	925	–8
16 September 1986	18 September 1986	100	92	–8
		500	499	0
		500	498	0
		1,000	904	–10
11 November 1986	12 November 1986	100	104	+4
		100	105	+5
		500	456	–9
		500	482	–4
		500	492	–2
		1,000	922	–8
		1,000	1,080	+8
12 January 1987	13 January 1987	100	106	+6
		500	488	–2
		500	509	+2
		1,000	1,001	0
2 March 1987	4 March 1987	100	79	–21
		500	453	–9
		500	431	–14
		1,000	803	–20
9 March 1987[e]	9 March 1987	100	99	–1
		500	476	–5
		1,000	941	–6
27 April 1987	27 April 1987	100	96	–4
		100	91	–9
		100	96	–4
		500	410	–18
		500	412	–18
		500	409	–18
		1,000	869	–13
		1,000	830	–17
		1,000	832	–17

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Methylphenidate Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Rats (continued)				
4 May 1987[e]	4 May 1987	500	505	+1
		500	480[c]	–4
		500	507[b]	+1
		500	477[d]	–5
		1,000	969	–3
		1,000	966	–3
22 June 1987	23 June 1987	100	88	–12
		500	430	–14
		500	454	–9
		1,000	944	–6
24 June 1987[e]	25 June 1987	100	92	–8
		500	434	–13
29 June 1987[e]	29 June 1987	500	474	–5
17 August 1987	17 August 1987	100	96	–4
		100	101	+1
		500	496	–1
		500	486	–3
		500	484	–3
		1,000	994	–1
		1,000	983	–2
12 October 1987	12 October 1987	100	98	–2
		100	106	+6
		500	499	0
		500	496	–1
		500	505	+1
		1,000	989	–1
		1,000	995	–1
7 December 1987	7 December 1987	100	99	–1
		100	102	+2
		500	494	–1
		500	501	0
		500	503	+1
		1,000	1,025	+3
		1,000	1,000	0
1 February 1988	1 February 1988	100	94	–6
		100	96	–4
		500	490	–2
		500	487	–3
		500	487	–3
		1,000	970	–3
		1,000	1,004	0

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Methylphenidate Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Rats (continued)				
28 March 1988	28 March 1988	100	92	–8
		500	500	0
		500	501	0
		1,000	1,030	+3
23 May 1988	23 May 1988	100	94	–6
		100	96	–4
		500	511	+2
		500	492	–2
		500	508	+2
		1,000	993	–1
		1,000	993	–1
1 August 1988	1 August 1988	100	96	–4
		100	99	–1
		500	497	–1
		500	514	+3
		1,000	955	–5
		1,000	981	–2
Mice				
15 July 1986	23 July 1986	50	46[b]	–8
		50	51[c]	+2
		50	49[d]	–2
23 July 1986	24 July 1986	50	53	+6
		250	275	+10
		500	481	–4
16 September 1986	18 September 1986	50	52	+4
		250	258	+3
		500	499	0
		500	498	0
11 November 1986	12 November 1986	50	54	+8
		250	252	+1
		500	456	–9
		500	482	–4
		500	492	–2
12 January 1987	13 January 1987	50	52	+4
		250	254	+2
		500	488	–2
		500	509	+2

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Methylphenidate Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Mice (continued)				
2 March 1987	4 March 1987	50	46	–8
		250	218	–13
		500	453	–9
		500	431	–14
9 March 1987[e]	9 March 1987	250	253	+1
		500	476	–5
27 April 1987	27 April 1987	50	50	0
		250	217	–13
		500	410	–18
		500	412	–18
		500	409	–18
4 May 1987[e]	4 May 1987	250	232	–7
		500	505	+1
		500	480[c]	–4
		500	507[b]	+1
		500	477[d]	–5
22 June 1987	23 June 1987	50	46	–8
		250	246	–2
		500	430	–14
		500	454	–9
24 June 1987[e]	25 June 1987	500	434	–13
29 June 1987[e]	29 June 1987	500	474	–5
17 August 1987	17 August 1987	50	47	–6
		250	260	+4
		500	496	–1
		500	486	–3
		500	484	–3
12 October 1987	12 October 1987	50	53	+6
		250	250	0
		500	499	0
		500	496	–1
		500	505	+1
7 December 1987	7 December 1987	50	51	+2
		250	253	+1
		500	494	–1
		500	501	0
		500	503	+1

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Methylphenidate Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Mice (continued)				
1 February 1988	1 February 1988	50	49	–2
		250	240	–4
		500	490	–2
		500	487	–3
		500	487	–3
28 March 1988	28 March 1988	50	50	0
		250	251	0
		500	500	0
		500	501	0
23 May 1988	23 May 1988	50	47	–6
		250	245	–2
		500	511	+2
		500	492	–2
		500	508	+2
1 August 1988	1 August 1988	500	497	–1
		500	514	+3

[a] Results of duplicate analyses
[b] Sample selection from top left of twin-shell blender
[c] Sample selection from top right of twin-shell blender
[d] Sample selection from bottom of twin-shell blender
[e] Results of remix

TABLE I5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Feed Studies of Methylphenidate Hydrochloride

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies (Hazleton Laboratories America, Inc.)			
30 December 1983	125	130	125 ± 2
3 January 1984	125	98	101.6 ± 8.4
5 January 1984	125	130	125 ± 5
2-Year Studies (TSI Mason Research Institute)			
Rats			
12 January 1987	1,000	1,001	935 ± 9
2 March 1987	1,000	803	758 ± 27
27 April 1987	1,000	830	823 ± 1
7 December 1987	100	99	97.6 ± 1.8
Mice			
23 July 1986	250	275	243 ± 2
22 June 1987	50	46	48.6 ± 0.8

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard error)

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

Week	0 ppm		100 ppm			500 ppm			1,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	13.6	150	13.6	150	9	13.0	147	44	12.7	145	88
5	14.8	215	15.5	220	7	15.0	211	36	15.3	211	73
9	16.4	271	16.8	273	6	17.0	274	31	17.4	269	65
12	16.1	314	16.8	315	5	16.9	314	27	17.7	310	57
16	19.0	336	16.1	337	5	15.7	332	24	15.6	323	48
21	17.1	362	16.9	362	5	17.6	358	25	17.2	348	49
25	15.8	372	16.0	370	4	15.8	362	22	17.5	352	50
29	16.0	387	16.5	389	4	15.9	374	21	15.9	366	44
33	18.2	391	18.7	397	5	19.0	380	25	17.7	373	47
37	17.6	399	18.0	407	4	17.5	380	23	17.9	380	47
41	16.6	396	16.0	403	4	16.2	381	21	16.6	379	44
45	16.4	407	16.0	413	4	15.6	384	20	15.7	382	41
49	16.5	405	16.2	412	4	16.9	379	22	16.7	376	45
53	17.6	419	17.3	425	4	17.8	394	23	17.4	388	45
56	17.1	415	16.3	423	4	15.7	385	20	16.1	387	42
62	17.4	421	18.2	428	4	18.6	395	24	18.5	391	47
65	16.4	420	16.4	430	4	16.1	395	20	16.7	389	43
69	16.7	424	17.0	433	4	16.4	393	21	16.7	391	43
73	20.4	431	20.8	441	5	21.0	398	26	20.3	397	51
77	18.1	427	17.5	430	4	16.8	397	21	16.2	388	42
81	15.8	423	15.8	427	4	15.4	395	20	16.2	393	41
85	15.2	426	15.1	429	4	15.7	404	19	15.2	385	40
89	14.8	425	15.0	432	4	15.1	398	19	15.5	384	41
93	14.7	414	15.0	423	4	14.2	393	18	14.5	373	39
97	13.5	410	14.3	417	3	13.9	389	18	14.4	367	39
101	14.5	400	14.4	411	4	13.1	378	17	13.8	364	38
104	14.4	391	15.1	400	4	13.7	372	18	13.6	353	39
Mean for weeks											
1-13	15.2	238	15.7	239	7	15.5	237	34	15.8	234	71
14-52	17.0	384	16.7	388	4	16.7	370	23	16.8	364	46
53-104	16.2	418	16.3	425	4	16.0	392	20	16.1	382	42

[a] Grams of feed consumed per animal per day.
[b] Milligrams of methylphenidate hydrochloride consumed per kilogram body weight per day.

TABLE J2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Methylphenidate Hydrochloride

Week	0 ppm		100 ppm			500 ppm			1,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	11.0	122	10.7	121	9	10.1	117	43	9.6	114	85
6	10.9	156	10.7	150	7	11.6	154	38	10.5	143	73
10	11.6	184	11.6	178	7	11.8	177	33	11.5	170	68
13	10.2	197	10.7	193	6	10.8	192	28	10.9	188	58
17	10.8	207	11.0	203	5	10.7	202	27	10.7	195	55
22	10.0	211	10.2	206	5	9.8	204	24	10.1	198	51
26	10.8	215	11.1	210	5	10.7	207	26	10.9	202	54
30	12.0	225	12.1	221	6	12.0	215	28	10.9	204	53
34	11.0	233	11.3	226	5	11.3	218	26	10.4	208	50
39	10.7	238	11.1	230	5	10.4	221	24	10.8	214	51
42	12.2	244	11.6	234	5	11.4	227	25	10.8	214	50
46	12.0	252	11.3	240	5	10.7	222	24	10.7	210	51
50	11.3	256	11.6	246	5	11.1	230	24	10.8	215	50
54	12.7	265	11.8	257	5	10.9	235	23	10.8	218	50
58	11.4	271	12.4	256	5	11.7	237	25	10.4	218	48
62	12.0	281	12.6	271	5	10.3	243	21	10.3	222	46
69	12.1	297	13.7	286	5	14.1	257	28	11.4	230	50
74	12.6	308	14.2	298	5	13.3	266	25	12.2	240	51
78	13.1	312	13.3	305	4	12.2	273	22	11.2	241	47
82	13.2	324	12.5	313	4	12.4	282	22	11.9	247	48
86	12.0	326	12.1	316	4	12.1	288	21	11.1	253	44
90	11.2	325	11.3	320	4	11.9	293	20	11.0	252	43
94	11.0	314	11.9	314	4	11.8	290	20	12.0	251	48
98	12.4	326	11.5	310	4	11.2	290	19	11.2	251	45
102	12.2	315	11.1	301	4	11.2	280	20	10.8	247	44
105	12.3	317	10.5	302	4	11.0	276	20	11.9	252	47
Mean for weeks											
1-13	10.9	165	10.9	160	7	11.1	160	36	10.6	154	71
14-52	11.2	231	11.3	224	5	10.9	216	25	10.7	207	52
53-105	12.2	306	12.2	296	4	11.9	270	22	11.2	240	47

[a] Grams of feed consumed per animal per day.
[b] Milligrams of methylphenidate hydrochloride consumed per kilogram body weight per day.

TABLE J3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride

Week	0 ppm		50 ppm			250 ppm			500 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.0	23.4	4.0	23.0	9	4.0	22.8	43	3.9	22.2	89
5	5.0	26.7	5.1	26.8	10	5.3	25.7	51	5.5	26.0	105
9	5.1	29.4	5.5	28.5	10	5.8	28.2	52	5.7	28.1	101
13	4.8	32.6	4.9	31.6	8	4.9	30.6	40	5.6	30.5	91
17	4.6	35.1	5.0	35.1	7	5.1	33.2	38	5.1	33.5	76
21	4.2	37.9	4.3	38.0	6	4.3	35.7	30	4.5	35.8	63
25	4.4	39.4	4.6	40.0	6	4.4	38.1	29	4.6	37.5	61
29	4.4	41.1	4.4	41.5	5	4.4	39.4	28	4.3	39.4	55
33	4.6	42.6	4.5	42.8	5	4.6	40.4	28	4.7	39.9	58
37	4.3	44.1	4.6	44.1	5	4.4	41.6	27	4.6	42.0	54
41	4.8	44.1	4.8	44.4	5	4.5	42.1	27	4.8	42.7	56
45	4.8	45.1	4.5	45.3	5	4.5	42.8	26	4.6	43.5	53
48	4.6	45.3	4.5	45.0	5	4.4	42.8	26	4.4	42.7	52
53	4.2	43.6	4.2	44.9	5	4.2	42.1	25	4.3	42.0	51
57	4.7	43.9	4.7	44.2	5	4.5	41.5	27	4.7	41.5	56
61	4.5	43.0	4.8	44.1	5	4.7	40.8	29	4.9	41.3	59
66	4.4	44.4	4.8	45.5	5	4.6	42.0	27	4.8	43.1	56
69	4.7	43.7	4.7	44.6	5	4.7	41.4	28	4.9	42.4	57
73	4.8	44.3	4.6	44.7	5	4.6	41.7	28	4.9	42.8	57
77	5.0	44.9	5.0	44.7	6	5.0	40.7	31	5.0	42.6	58
81	4.9	46.2	5.2	46.5	6	5.1	42.4	30	5.3	44.7	60
85	5.2	46.1	4.7	46.4	5	5.1	42.4	30	5.3	44.1	60
89	4.7	45.8	4.8	46.1	5	4.9	43.0	28	4.7	44.3	53
93	4.6	45.9	4.5	47.3	5	4.4	42.6	26	4.3	44.5	48
97	4.9	44.6	4.9	45.7	5	4.8	41.1	29	5.0	43.9	57
101	4.7	44.8	4.8	44.8	5	4.7	40.8	29	4.7	43.1	54
104	4.8	45.6	4.8	44.4	5	4.7	40.5	29	4.8	42.3	56
Mean for weeks											
1-13	4.7	28.0	4.9	27.5	9	5.0	26.8	47	5.2	26.7	97
14-52	4.5	41.6	4.6	41.8	6	4.5	39.6	29	4.6	39.7	59
53-104	4.7	44.8	4.8	45.3	5	4.7	41.6	28	4.8	43.0	56

[a] Grams of feed consumed per animal per day.
[b] Milligrams of methylphenidate hydrochloride consumed per kilogram body weight per day.

TABLE J4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Methylphenidate Hydrochloride

Week	0 ppm		50 ppm			250 ppm			500 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.7	18.9	4.2	19.0	11	4.2	18.7	56	4.4	18.9	117
5	5.6	21.4	5.0	21.8	11	5.6	21.7	65	5.8	21.8	133
10	5.9	25.0	5.6	25.0	11	5.9	24.1	61	5.7	24.7	116
14	5.9	27.4	5.9	27.6	11	5.9	25.9	57	5.8	26.8	108
17	5.5	30.4	5.9	30.3	10	6.2	28.9	54	6.5	29.8	109
21	4.9	32.8	5.1	32.1	8	5.0	31.1	41	4.9	33.0	75
25	5.7	34.3	5.6	33.5	8	5.8	33.8	43	5.8	35.3	82
30	5.5	36.0	5.4	34.9	8	5.4	34.7	39	5.1	36.4	71
34	5.5	38.5	5.3	37.7	7	5.8	37.1	39	5.7	38.6	73
38	5.5	39.4	5.6	38.5	7	5.5	38.1	36	5.4	39.4	68
42	5.2	40.1	5.5	39.4	7	5.7	38.9	37	5.5	40.7	68
46	5.1	41.2	5.1	40.8	6	5.4	40.6	33	5.3	41.9	64
50	5.4	41.6	5.4	40.9	7	5.1	40.3	32	5.1	41.3	62
54	5.1	40.1	5.3	40.2	7	4.8	40.0	30	5.2	41.6	63
58	5.2	40.2	5.5	39.5	7	5.5	38.8	36	5.7	40.1	71
62	5.5	41.3	5.4	39.8	7	5.3	39.7	33	5.2	41.1	64
66	5.1	40.8	5.2	40.5	6	5.5	40.4	34	5.3	41.4	64
69	6.1	42.6	5.5	41.3	7	6.0	41.9	36	6.0	43.1	69
73	6.2	42.7	6.3	42.5	7	6.3	42.1	38	6.3	43.6	72
78	5.8	43.1	5.7	42.6	7	5.7	42.4	34	5.8	44.0	66
82	6.8	45.1	5.9	43.6	7	5.9	43.2	34	5.7	45.7	62
86	5.8	44.4	5.5	44.0	6	6.0	44.1	34	5.9	45.1	65
90	5.6	43.5	5.5	44.1	6	5.8	44.1	33	5.7	44.8	63
94	5.8	44.6	5.9	44.7	7	5.8	43.9	33	5.9	44.3	67
98	5.7	43.4	5.8	43.8	7	5.8	42.4	34	6.2	44.7	69
102	5.1	43.5	5.5	43.6	6	5.4	41.0	33	5.5	43.3	63
105	5.6	43.7	5.9	42.8	7	6.2	40.7	38	6.1	42.4	72
Mean for weeks											
1-13	5.4	21.8	4.9	21.9	11	5.2	21.5	61	5.3	21.8	122
14-52	5.4	36.2	5.5	35.6	8	5.6	34.9	41	5.5	36.3	78
53-105	5.7	42.8	5.6	42.4	7	5.7	41.8	34	5.7	43.2	67

[a] Grams of feed consumed per animal per day.
[b] Milligrams of methylphenidate hydrochloride consumed per kilogram body weight per day.

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

TABLE K1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K2
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 K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.66 ± 0.78	21.30 – 24.10	25
Crude fat (% by weight)	5.49 ± 0.30	4.80 – 5.90	25
Crude fiber (% by weight)	3.54 ± 0.32	3.00 – 4.40	25
Ash (% by weight)	6.61 ± 0.93	2.41 – 7.27	25
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 – 1.390	10
Cystine	0.306 ± 0.075	0.181 – 0.400	10
Glycine	1.160 ± 0.050	1.060 – 1.220	10
Histidine	0.580 ± 0.024	0.531 – 0.608	10
Isoleucine	0.917 ± 0.034	0.867 – 0.965	10
Leucine	1.972 ± 0.052	1.850 – 2.040	10
Lysine	1.273 ± 0.051	1.200 – 1.370	10
Methionine	0.437 ± 0.115	0.306 – 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 – 1.110	10
Threonine	0.896 ± 0.055	0.824 – 0.985	10
Tryptophan	0.223 ± 0.160	0.107 – 0.671	10
Tyrosine	0.677 ± 0.105	0.564 – 0.794	10
Valine	1.089 ± 0.057	0.962 – 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 – 2.570	9
Linolenic	0.277 ± 0.036	0.210 – 0.320	9
Vitamins			
Vitamin A (IU/kg)	6,211 ± 992	4,500 – 8,240	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α–Tocopherol (ppm)	36.92 ± 9.32	22.5 – 48.9	9
Thiamine (ppm)	19.76 ± 2.65	15.0 – 28.0	25
Riboflavin (ppm)	7.92 ± 0.93	6.10 – 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 – 150.0	9
Pantothenic Acid (ppm)	30.30 ± 3.60	23.0 – 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 – 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 – 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 – 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 – 65.0	10
Choline (ppm)	3,068 ± 314	2,400 – 3,430	9
Minerals			
Calcium (%)	1.24 ± 0.12	0.96 – 1.45	25
Phosphorus (%)	0.96 ± 0.06	0.85 – 1.10	25
Potassium (%)	0.887 ± 0.067	0.772 – 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.315 ± 0.344	0.258 – 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 – 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 – 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 – 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 – 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 – 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 – 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 – 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 – 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 – 1.150	6

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.35 ± 0.29	0.05 – 0.98	25
Cadmium (ppm)	<0.10		25
Lead (ppm)	0.25 ± 0.16	0.05 – 0.60	25
Mercury (ppm)	0.05 ± 0.01	0.05 – 0.08	25
Selenium (ppm)	0.37 ± 0.10	0.20 – 0.60	25
Aflatoxins (ppb)	<5.0		25
Nitrate nitrogen (ppm)[b]	22.28 ± 8.54	10.00 – 37.00	25
Nitrite nitrogen (ppm)[b]	0.24 ± 0.26	<0.10 – 1.00	25
BHA (ppm)[c]	2.20 ± 1.07	<0.10 – 6.00	25
BHT (ppm)[c]	1.00 ± 0.27	<1.00 – 2.00	25
Aerobic plate count (CFU/g)[d]	294,360 ± 313,925	37,000 – 1,200,000	25
Coliform (MPN/g)[e]	181.0 ± 233.0	<3.00 – 1,100	25
E. coli (MPN/g)	4.76 ± 7.97	<3.00 – 43.00	25
Total Nitrosoamines (ppb)[f]	9.59 ± 3.67	3.90 – 19.40	25
N–Nitrosodimethylamine (ppb)[f]	7.78 ± 3.07	2.90 – 14.00	25
N–Nitrosopyrrolidine (ppb)[f]	1.80 ± 1.45	1.00 – 5.40	25
Pesticides (ppm)			
α–BHC[g]	<0.01		25
ß–BHC	<0.02		25
γ–BHC	<0.01		25
δ–BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.1		25
Estimated PCBs	<0.2		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.1		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.17 ± 0.20	0.05 – 0.85	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

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

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Rats

At the end of the 13-week study, serum was collected from the orbital sinuses of control male and female rats. The samples were processed appropriately and were submitted to Microbiological Associates, Inc. (Bethesda, MD) for viral titer screening. The following tests were performed:

Method of Analysis	Time of Analysis
ELISA	
Mycoplasma	Study termination
RCV/SDA	Study termination
(Rat coronavirus/sialodacryoadenitis virus)	
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
PVM (Pneumonia virus of mice)	Study termination
Sendai	Study termination

For the 2-year study, serum was collected from the retroorbital sinus of four to five male and four to five female rats at the beginning of the study, at approximately 6-month intervals during the study, and from five male and five female animals at terminal sacrifice. Because some sentinel animals showed positive viral titers for RCV/SDA, additional animals were bled at various time points to monitor the sera titers. Blood from each collection was appropriately processed, shipped to Microbiological Associates, Inc., and screened for the following:

Method of Analysis	Time of Analysis
ELISA	
Mycoplasma arthritidis	24 months
Mycoplasma pulmonis	24 months
PVM	6, 7, 16, 18, and 24 months
RCV/SDA	Study initiation, 6, 7, 16, 18, and 24 months
Sendai	Study initiation, 6, 7, 16, 18, and 24 months
Hemagglutination Inhibition	
H-1	6, 7, 16, 18, and 24 months
KRV	6, 7, 16, 18, and 24 months
Immunofluorescence Assay	
RCV/SDA	16 and 24 months

Mice

At the end of the 13-week studies, serum was collected from the orbital sinuses of control male and female mice. The samples were processed appropriately and were submitted to Microbiological Associates, Inc. for viral titer screening. The following tests were performed:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus	Study termination
ELISA	
Mycoplasma	Study termination
RCV/SDA	Study termination
Hemagglutination Inhibition	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
MVM (minute virus of mice)	Study termination
PVM	Study termination
Polyoma virus	Study termination
Reovirus 3	Study termination
Sendai	Study termination

For the 2-year study, serum was collected from the retroorbital sinus of two to five male and two to five female mice at the beginning of the study, at 6, 12, and 20 months into the study, and from five male and five female animals at terminal sacrifice. Blood from each collection was appropriately processed, shipped to Microbiological Associates, Inc., and screened for the following:

Method of Analysis	Time of Analysis
ELISA	
CARB (Cilia-associated respiratory bacillus)	12 months
Ectromelia virus	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
LCM	12 and 18 months
MVM	12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
MHV (Mouse hepatitis virus)	6, 12, 18, and 24 months
M. arthritidis	24 months
M. pulmonis	24 months
PVM	6, 12, 18, and 24 months
Reovirus 3	6 and 12 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
K (Papovavirus)	6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months
MVM	6 months
Immunofluorescence Assay	
EDIM (Epizootic diarrhea of infant mice)	6, 12, 18, and 24 months
LCM	6 and 24 months
Reovirus 3	20 and 24 months

Results of serology testing for sentinel animals are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Feed Studies of Methylphenidate Hydrochloride

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
Rats		
Study termination	0/10	None positive
Mice		
Study termination	0/10	None positive
2-Year Studies		
Rats		
Study initiation	0/10	None positive
6 months	9/10	RCV/SDA
7 months	2/2	RCV/SDA
16 months	7/9	RCV/SDA[a]
	2/9	RCV/SDA[b]
18 months	7/9	RCV/SDA
24 months	1/5	*Mycoplasma arthritidis*
	9/10	RCV/SDA[a]
	4/5	RCV/SDA[b]
Mice		
6 months	0/9	None positive
12 months	0/10	None positive
18 months	0/7	None positive
24 months	0/5	None positive

[a] Positive using ELISA
[b] Positive using immunofluorescence assay

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene

TR No.	CHEMICAL
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl)phosphonium Sulfate & Tetrakis(hydroxymethyl)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

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TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	α-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
384	1,2,3-Trichloropropane
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
398	Polybrominated Biphenyls
399	Titanocene Dichloride
400	2,3-Dibromo-1-propanol
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
404	5,5-Diphenylhydantoin
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-stilbenedisulfonic Acid
413	Ethylene Glycol
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Yellow 4
420	Triamterene
421	Talc
422	Coumarin
423	Dihydrocoumarin
424	*o*-Benzyl-*p*-chlorophenol
425	Promethazine Hydrochloride
426	Corn Oil, Safflower Oil, and Tricaprylin
427	Turmeric Oleoresin
428	Manganese (II) Sulfate Monohydrate
429	Diethylphthalate
430	C.I. Direct Blue 218
431	Benzyl Acetate
432	Barium Chloride Dihydrate
433	Tricresyl Phosphate
434	1,3-Butadiene
435	4,4'-Thiobis(6-*t*-butyl-*m*-cresol)
436	*t*-Butyl Alcohol
437	Hexachlorocyclopentadiene
440	Ozone and Ozone/NNK
442	*p*-Nitrobenzoic Acid
443	Oxazepam
444	*o*-Benzyl-*p*-chlorophenol

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