NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 445

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

(CAS NO. 6533-68-2)

IN F344/N RATS AND B6C3F$_1$ MICE

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

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NTP TECHNICAL REPORT

ON THE

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STUDIES OF

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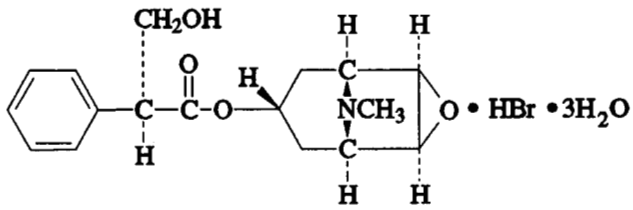
ABSTRACT



SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

CAS Number: 6533-68-2

Chemical Formula: $C_{17}H_{22}BrNO_4 \cdot 3H_2O$ Molecular Weight: 438.33

Synonyms: Scopolamine hydrobromide, 6,7-epoxytropan-3-yl, euscopol, hydroscine hydrobromide, hyoscine bromide, (−)-hyoscine hydrobromide, hysco, isoscopil, scopolammonium bromide, (s)-tropate hydrobromide trihydrate, *l*-tropyl-α-scopine
Trade names: Beldavrin, Kwells, Sereen, Scopos, Triptone

Scopolamine hydrobromide trihydrate is used in ophthalmic preparations and as a preanesthetic sedative. Its major use is in transdermal patches for the treatment of motion sickness. Scopolamine hydrobromide trihydrate was selected for study because of considerable human exposure resulting from its use in prescription and over-the-counter preparations. Scopolamine was a suspect carcinogen because it contains an aliphatic epoxide moiety which may act as a biological alkylating agent. Male and female F344/N rats and B6C3F$_1$ mice received scopolamine hydrobromide trihydrate (89% pure) in distilled water by gavage for 16 days, 14 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and mouse peripheral blood erythrocytes.

16-Day Study in Rats

Groups of five male and five female rats were administered 0, 75, 150, 300, 600, or 1,200 mg scopolamine hydrobromide trihydrate/kg body weight in distilled water by gavage for 16 days. All rats survived to the end of the study. The final mean body weights and body weight gains of males receiving 600 and 1,200 mg/kg and the mean body weight gain of males receiving 300 mg/kg were significantly lower than those of the control group. Clinical findings included bilateral pupillary dilation in all dosed animals and red eyelids in males and females receiving 1,200 mg/kg. There were no significant treatment-related gross or microscopic lesions.

16-Day Study in Mice

Groups of five male and five female mice were administered 0, 150, 250, 450, 900, or 1,800 mg scopolamine hydrobromide trihydrate/kg body weight in distilled water by gavage for 16 days. One male and two females receiving 1,800 mg/kg and one female receiving 150 mg/kg died during the study. The final mean body weights and body weight gains of dosed mice were similar to those of the control groups. Clinical findings related to scopolamine hydrobromide trihydrate administration included bilateral pupillary dilation and squinting in all dosed

males and females. The relative liver weights of males receiving 1,800 mg/kg and of females in all dosed groups were significantly greater than those of the control groups. There were no significant treatment-related gross or microscopic lesions.

14-Week Study in Rats

Groups of 10 male and 10 female rats were administered 0, 15, 45, 135, 400, or 1,200 mg scopolamine hydrobromide trihydrate/kg body weight in distilled water by gavage for 14 weeks. One female receiving 45 mg/kg, one male and one female receiving 135 mg/kg, six males and one female receiving 400 mg/kg, and eight males and seven females receiving 1,200 mg/kg died during the study. The final mean body weights and mean body weight gains of all dosed males and females were significantly lower than those of the control groups. Clinical findings included bilateral pupillary dilation in all dosed males and females and reddening of the eyes in 15 mg/kg males and 135, 400, and 1,200 mg/kg males and females.

Hematocrit, hemoglobin concentration, and/or erythrocyte count in male and female rats receiving 45 mg/kg or greater were slightly higher than those of the control groups. In general, these changes were most prominent in rats in the 400 and 1,200 mg/kg groups. Higher hematocrit, hemoglobin concentration, and erythrocyte count were likely due to hemoconcentration from dehydration (relative erythrocytosis). A minimal to mild mature neutrophilia, evidenced by higher segmented neutrophil numbers than in the control group, occurred in all dosed male rats.

Sperm morphology and vaginal cytology parameters in dosed rats were similar to those in the control groups.

Nine male and five female dosed rats died from esophageal obstructions consisting of feed and bedding material in the posterior pharynx. Tracheal obstruction occurred concurrently with esophageal obstruction as a result of food build-up in the oropharyngeal region. This condition is considered to be secondary to the inhibitory effects of scopolamine hydrobromide trihydrate on salivary gland secretions and on esophageal smooth muscle involved in swallowing. There were no other significant treatment-related gross or microscopic findings.

14-Week Study in Mice

Groups of 10 male and 10 female mice were administered 0, 15, 45, 135, 400, or 1,200 mg scopolamine hydrobromide trihydrate/kg body weight in distilled water by gavage for 14 weeks. One male receiving 135 mg/kg and two males and one female receiving 1,200 mg/kg died during the study. The final mean body weights and mean body weight gains of all dosed male groups and females receiving 45 mg/kg and above were significantly lower than those of the control groups. Clinical observations included bilateral pupillary dilation, hyperactivity, and hypoactivity.

A minimal to mild mature neutrophilia, similar to that which occurred in the 14-week rat study, occurred in male mice receiving 45 mg/kg or greater. As in the rat study, there was no microscopic evidence of inflammation that could account for the neutrophilia.

The estrous cycle length of 1,200 mg/kg females was significantly greater than that in the control group.

There were no significant treatment-related gross or microscopic lesions.

2-Year Study in Rats

Groups of 60 male and 60 female rats were administered 0, 1, 5, or 25 mg scopolamine hydrobromide trihydrate/kg body weight in distilled water by gavage for 104 weeks. Ten males and ten females from each dose group, excluding the 1 mg/kg female group, were evaluated at 15 months.

Survival, Body Weights, Clinical Findings, and Ophthalmic Examination Findings

The survival rates of female rats receiving 1 and 25 mg/kg were significantly lower than that of the control group. Mean body weights of 1 and 5 mg/kg males and females were similar to those of the controls throughout the study. However, mean body weights of 25 mg/kg males and females were generally lower than those of the control groups after

about week 25. Clinical findings included bilateral pupillary dilation in all dosed males and females. Ophthalmic examination revealed no significant findings.

Hematology

Compared to controls, hematocrit was slightly higher in the 25 mg/kg male rats, similar to the effects observed in the 14-week study; this is consistent with dehydration resulting in hemoconcentration. Reticulocyte numbers in the 25 mg/kg female rats were slightly lower than those in the controls. This result is consistent with the lower body weights, and thus a decreased nutritional status, exhibited by these animals.

Plasma Scopolamine Determinations

The serum scopolamine concentrations were 6 ng scopolamine/mL serum for the 5 mg/kg female sample and 12 and 28 ng/mL for the 25 mg/kg male and female samples, respectively. The amounts of scopolamine in the other serum samples were below the minimum detection limit (4 ng/mL) of the analysis method.

Neurobehavioral Findings

Horizontal motor activity of 25 mg/kg females was significantly greater than that of the control group on days 90, 180, and 360. Startle response of 5 and 25 mg/kg females was significantly lower than that of the control group on day 90. On day 180, passive avoidance of 25 mg/kg males was significantly lower than that of the control group.

Pathology Findings

The incidences of adenoma of the pituitary gland pars distalis decreased with increasing dose in both male and female rats; however, this trend was only significant in males (males: vehicle control, 19/49; 1 mg/kg, 17/49; 5 mg/kg, 13/50; 25 mg/kg, 10/50; females: 20/50, 13/60, 14/50, 10/50). The incidences of adenoma of the pituitary gland pars distalis in 25 mg/kg males and all groups of dosed females were below the NTP historical control range. The incidences of hyperplasia were not significantly different from those in the control groups.

The incidences of mononuclear cell leukemia in 25 mg/kg males and females were significantly lower than those of the control groups (males: 33/50, 21/50, 26/50, 24/50; females: 20/50, 6/60, 13/50, 4/50). The incidence of mononuclear cell leukemia in females receiving 25 mg/kg was well below the NTP historical range.

2-YEAR STUDY IN MICE

Groups of 70 male and 70 female mice were administered 0, 1, 5, or 25 mg scopolamine hydrobromide trihydrate/kg body weight in distilled water by gavage for 104 to 105 weeks. Ten control animals and ten animals from each dose level were evaluated at 15 months.

Survival, Body Weights, Clinical Findings, and Ophthalmic Examination Findings

Survival of dosed males and females was similar to that of the controls. The mean body weights of males and females receiving 1 mg/kg were similar to those of the control groups throughout the majority of the study. The mean body weights of 5 mg/kg males and females were slightly lower than those of the controls. The mean body weights of males and females receiving 25 mg/kg were lower than those of the control groups after week 13. Clinical findings included bilateral pupillary dilation in all dosed male and female groups. Ophthalmic examination revealed no significant findings.

Hematology

Hematocrit, hemoglobin concentration, and erythrocyte count in 25 mg/kg female mice were slightly lower than those in the control group. These results are consistent with development of a minimal normocytic, normochromic nonresponsive anemia. The anemia may be related to the lower body weights exhibited by these animals and are presumed to be due to a decreased nutritional status.

Pathology Findings

The combined incidences of hepatocellular neoplasms (adenoma or carcinoma) occurred with a significant negative trend in males and females (males: vehicle control, 30/50; 1 mg/kg, 33/50; 5 mg/kg, 14/50; 25 mg/kg, 15/50; females: 22/51, 21/50, 16/50, 9/51). The combined incidences of hepatocellular neoplasms in 5 and 25 mg/kg males were within the NTP historical control range. The incidences of clear cell foci and eosinophilic foci in dosed male

groups, and eosinophilic foci in 25 mg/kg females, were significantly lower than those of the control groups.

The incidences of many spontaneously occurring nonneoplastic lesions were significantly lower in dosed mice than in the control groups and usually decreased with increasing dose. These included kidney nephropathy, alveolar epithelial hyperplasia, hyperplasia of the pancreatic islets, bone marrow myelofibrosis, hyperplasia of the pituitary gland pars distalis, cystic hyperplasia of the uterus, and hematopoietic cell proliferation of the spleen. The decreased incidences of these spontaneous lesions were most likely a result of lower body weights in dosed animals.

GENETIC TOXICOLOGY

Scopolamine hydrobromide trihydrate did not induce mutations in any of five strains of *Salmonella typhimurium*, with or without S9 metabolic activation enzymes, nor did it induce sister chromatid exchanges in cultured Chinese hamster ovary cells, with or without S9. A weakly positive response was obtained, however, in a chromosomal aberrations test conducted in cultured Chinese hamster ovary cells with very high doses of scopolamine hydrobromide trihydrate in the presence of S9; without S9, no increase in aberrations was noted. Despite the evidence for chromosomal damage observed *in vitro*, no increase in the frequencies of micronucleated normochromatic erythrocytes was observed in peripheral blood samples of male or female mice exposed to scopolamine hydrobromide trihydrate for 14 weeks by gavage.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of scopolamine hydrobromide trihydrate in male or female F344/N rats or B6C3F$_1$ mice administered 1, 5, or 25 mg/kg.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Scopolamine Hydrobromide Trihydrate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 1, 5, or 25 mg/kg in water by gavage	0, 1, 5, or 25 mg/kg in water by gavage	0, 1, 5, or 25 mg/kg in water by gavage	0, 1, 5, or 25 mg/kg in water by gavage
Body weights	25 mg/kg group lower than control group	25 mg/kg group lower than control group	5 and 25 mg/kg groups lower than control group	5 and 25 mg/kg groups lower than control group
2-Year survival rates	20/50, 14/50, 22/50, 28/50	34/50, 17/60, 26/50, 22/50	40/50, 39/50, 39/50, 39/50	33/51, 36/50, 37/50, 38/51
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None
Levels of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA97, TA98, TA100, TA1535, and TA1537			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative without S9; weakly positive with S9			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:	Negative in male and female mice			

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 scopolamine hydrobromide trihydrate on June 20, 1995, 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 20, 1995, the Technical Report on the toxicology and carcinogenesis studies of scopolamine hydrobromide trihydrate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of scopolamine hydrobromide trihydrate by discussing the uses of the chemical and rationale for study, describing the experimental design, and reporting on survival and body weight effects. The proposed conclusions for the two-year gavage studies were *no evidence of carcinogenic activity* of scopolamine hydrobromide trihydrate in male or female F344/N rats or B6C3F$_1$ mice administered 1, 5, or 25 mg/kg.

During the 14-week study, rats receiving the higher doses experienced considerable mortality attributed to esophageal and tracheal obstruction by feed and bedding. This condition was considered secondary to the inhibitory effects of scopolamine on salivary secretion and the motility of smooth muscle involved in swallowing.

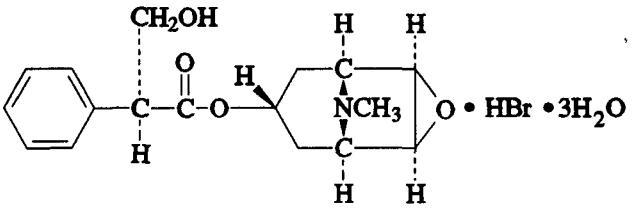
Dr. Klaassen, a principal reviewer, agreed with the proposed conclusions. He was surprised that more scopolamine could be administered by gavage than in the feed and asked for elaboration. Dr. Abdo explained that the problem with esophageal obstruction, even at lower doses, diminished the amount that could be administered in the feed. Dr. Klaassen noted that a decrease in body weight is often given as a explanation for a decrease in neoplasm incidence such as reported here, and suggested creating a graph that would let the reader evaluate this conclusion. Dr. J.K. Haseman, NIEHS, agreed this was a good idea and said he would evaluate two potential approaches to illustrate this association, one using a model based on logistic regression to predict neoplasm incidence for animals at a particular body weight, and the other looking empirically at a moving average of neoplasm incidence for animals in the database of a given weight range (Table 16).

Drs. Russo and Taylor, the other principal reviewers, agreed with the proposed conclusions. They were pleased that the report included neurological data allowing evaluation of neurobehavioral toxicity and data from pharmacokinetic studies enabling the correlation of toxic effects with plasma levels. Dr. Taylor questioned listing all therapeutic uses associated with scopolamine as in his experience the drug had not been employed for a number of the listed conditions during the last 20 years. Dr. Abdo said he would use the past tense to describe therapeutic uses that no longer apply.

Dr. R. Hart, NCTR, observed that body weight reductions may have a sparing effect relative to neurobehavior and other neurological endpoints. Dr. Goldsworthy strongly supported inclusion of pharmacokinetic studies, particularly encouraging their use in a more prospective fashion to help set dose levels for better comparisons across species. Dr. G. Lucier, NIEHS, agreed and said that an interdisciplinary toxicokinetics faculty has been established within the NIEHS to help determine the kinds of specific studies that should be incorporated into the study design for a chemical. In some cases the data obtained would aid in the development of a biologically based dose-response model. Dr. Miller said it would be useful to include actual drug doses and average duration of treatment commonly used in medical practice.

Dr. Klaassen moved that the Technical Report on scopolamine hydrobromide trihydrate be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Taylor seconded the motion, which was accepted unanimously with ten votes.

INTRODUCTION



SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

CAS Number: 6533-68-2

Chemical Formula: $C_{17}H_{22}BrNO_4 \bullet 3H_2O$ Molecular Weight: 438.33

Synonyms: Scopolamine hydrobromide, 6,7-epoxytropan-3-yl, euscopol, hydroscine hydrobromide, hyoscine bromide, (−)-hyoscine hydrobromide, hysco, isoscopil, scopolammonium bromide, (s)-tropate hydrobromide trihydrate, *l*-tropyl-α-scopine
Trade names: Beldavrin, Kwells, Sereen, Scopos, Triptone

CHEMICAL AND PHYSICAL PROPERTIES

Scopolamine hydrobromide trihydrate occurs as colorless or white crystals or as a white granular powder with a melting point of 195° to 199° C. It is soluble in water (66.7 g/100 mL) and alcohol (5 g/100 mL), slightly soluble in chloroform, and almost insoluble in ether (*Merck Index*, 1989).

PRODUCTION, USE, AND HUMAN EXPOSURE

Scopolamine (hyoscine) is a solanaceous alkaloid that is a natural product of plants of the Solanaceae family (Brown, 1990). It is the levorotatory form of the parent compound, atroscine. Scopolamine is an organic ester formed by the combination of an organic acid, tropic acid, and a complex organic base, scopine or 6,7-epoxytropine (Gearien, 1989). It is found chiefly in the shrubs *Hyoscyamus niger* (henbane) and *Scopolia carniolica*. Although scopolamine can be recovered from the mother liquors remaining after the crystallization of hyoscyamine, a tropic acid ester of tropine, it is routinely extracted from the leaves of *Datura metel* in India or from *Datura meteloides* in Mexico and imported to the United States (*Remington's Pharmaceutical Sciences*, 1975); data on the amount imported are not available. The accidental consumption of roots from *Datura stramonium*, which is commonly referred to by a variety of names including apple of Peru, Jimsonweed, Jamestown weed, devil's apple, thorn apple, stinkweed, stramonium, and loco weed, has produced acute toxic episodes (Labianca and Reeves, 1984; Brown, 1990).

Though no figures on the production of scopolamine or its derivatives were reported to the U.S. International Trade Commission from 1974 through 1977, the United States production during this interval was estimated to be less than 4.5×10^5 grams (USITC, 1977). The estimated overall oral and dermal human exposure to scopolamine and its salts (scopolamine hydrobromide, methyl scopolamine bromide, and methyl scopolamine nitrate) was 1.6×10^5 grams per year (NCI/SRI, 1979). A national prescription audit estimated that during 1980, 14,000 prescriptions were

written in the United States for ophthalmic preparations containing scopolamine (NDTI, 1980). Approximately 5.9 million prescriptions were written in 1986 for all scopolamine formulations (Dr. Vera Glocklin, Food and Drug Administration, personal communication to K.M. Abdo). More recent data were not available.

Scopolamine is used primarily for its antimuscarinic drug properties in the peripheral and central nervous system. Its major mechanism of action is via a competitive antagonism with the neurotransmitter acetylcholine at effector sites (exocrine glands and smooth and cardiac muscle) (Brown, 1990).

Central nervous system effects resulting from therapeutic doses of scopolamine characteristically include drowsiness, euphoria, amnesia, fatigue, and a reduction in rapid-eye-movement sleep (NRC, 1982; Brown, 1990). Excitatory effects regularly occur after large nontherapeutic doses and, in a small number of cases, have occurred unexpectedly following therapeutic doses (NRC, 1982). These effects include excitement, restlessness, hallucinations, and delirium.

Scopolamine use associated with its sedative and other central nervous system effects includes the treatment of acute mania and delirium; the symptomatic treatment of infantile cerebral palsy; the treatment of paralysis agitans and spastic states resulting from nervous system injuries; and in the diagnosis of psychomotor epilepsy (Wade, 1977; Reynolds, 1982). Scopolamine was previously included in many over-the-counter sleep aids, but was later withdrawn due to inadequate efficacy ratings coupled with the potential for adverse anticholinergic effects. Scopolamine has been used for the treatment of post-encephalitic parkinsonian tremors and by obstetricians during delivery in combination with morphine to induce a state of amnesia and partial analgesia referred to as "twilight sleep"; however, scopolamine is no longer the drug of choice in these cases. The major use of scopolamine is for the prevention of vestibular disorders such as motion sickness when given transdermally.

Peripheral nervous system effects that contribute to the therapeutic potential of scopolamine are pharmacologically associated with its ability to inhibit gastrointestinal and respiratory tract mucus secretions and its antispasmodic ability to relax smooth muscle in the respiratory tract, urinary bladder, and gastrointestinal tract including the gall bladder (Brown, 1990). Scopolamine has been used in cold and allergy medications and as a preanesthesia medication for its ability to inhibit mucous membrane secretions of the oral and respiratory passages (PDR, 1992). Scopolamine's antispasmodic effects are used in combination with antibiotics and analgesics for the treatment of urinary tract infections.

Because scopolamine inhibits gastric secretions and motility, it is particularly useful in treating ulcers and functional diarrhea. However, the therapeutic dose for such treatment is often high and results in undesirable peripheral and central nervous system side effects (Brown, 1990). Quaternary ammonium derivatives of scopolamine (methyl scopolamine bromide and methyl scopolamine nitrate) are indicated for such treatment to eliminate side effects involving the central nervous system; however, such derivatives usually require parenteral administration to achieve acceptable results.

Although scopolamine hydrobromide has not been officially approved by the FDA for therapeutic ophthalmic use, this use for scopolamine was under investigation (personal communication from Robert Linkous, FDA, 1989). Scopolamine is listed as an ophthalmic drug to be used exclusively for diagnostic purposes. Scopolamine blocks the cholinergic response of the sphincter muscle of the iris and the muscle of the ciliary body, resulting in pupillary dilation (mydriasis) and paralysis of accommodation (cycloplegia) (Wade, 1977; Reynolds, 1982; Brown, 1990). Indications for use include cycloplegic refraction and pupillary dilation for postoperative inflammatory conditions of the iris and uveal tract and to break synechia. Due to its long duration of action for 7 to 12 days (Brown, 1990), scopolamine hydrobromide is not recognized to be the drug of choice for ophthalmic use.

Scopolamine hydrobromide has occasionally been used in veterinary medicine in combination with morphine as a preanesthetic sedative in dogs (*Remington's Pharmaceutical Sciences*, 1975).

PHARMACOKINETICS, ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Structure-Activity Relationship

There are no structural relationships between scopolamine or its salts and any known carcinogens. Scopolamine has been suggested as a possible carcinogen because it contains an aliphatic epoxide moiety, but there is no evidence for its alkylating activity under physiological conditions (Ehrenberg and Hussain, 1981; Connors, 1984). The structure-activity relationships relative to the general class of anticholinergic drugs and their binding to muscarinic receptors have been extensively described, and are discussed below (Abramson *et al.*, 1969; Cullumbine, 1971; Abramson *et al.*, 1974; Beld and Ariëns, 1974; Lien *et al.*, 1976; Gearien, 1989; Brown, 1990).

There are several critical structural components of the scopolamine molecule that are involved in absorption, distribution, and pharmacological activity. The intact ester of tropic acid with the organic base, scopine, is essential for scopolamine's antimuscarinic activity. The presence of a free hydroxyl group in the acid portion of the ester is also important for enhanced biological activity. Demethylation of the nitrogen moiety reduces activity, while methyl quaternization increases biological activity. Quaternary ammonium derivatives are more potent in general than the parent compound upon parenteral administration but are poorly and unreliably absorbed orally and lack central nervous system activity due to poor penetration into the brain. Quaternization by higher alkyl groups diminishes biological activity. The asymmetrical carbon atom immediately adjacent to the benzene ring portion of tropic acid is important relative to the biological activity of scopolamine; i.e., scopolamine is L-hyoscine which is much more active than D-hyoscine. The acyl group or tropic acid portion of the molecule is considered responsible for the blocking action at the muscarinic receptors.

Experimental Animals

Studies have been performed that characterize scopolamine metabolism in the mouse, rat, guinea pig, and common marmoset (Werner and Schmidt, 1968). When [9-^{14}C]- and [9-$^{3}H_3$]-scopolamine hydrobromide were administered by an intraperitoneal injection to mice, radioactive scopolamine-9,1-β-D-glucuronide, aposcopolamine, 6-hydroxyhyoscyamine, scopine and unchanged scopolamine, and nonradioactive norscopolamine and norscopolamine-9,1-β-D-glucuronide were recovered from the urine. After intraperitoneal injections of [9-^{14}C]-scopolamine hydrobromide, 23% of the radioactivity of the *N*-methyl group was expired as $^{14}CO_2$ by the mouse, 5.9% by the rat, 12.5% by the guinea pig, and 4.5% by the marmoset. There was no racemization of scopolamine or any of its optically active metabolites. The scopine, 6-hydroxyhyoscyamine, and scopolamine-9,1-β-D-glucuronide fraction of mouse urine contained more radioactivity 25 hours after the oral administration of scopolamine hydrobromide than after the intraperitoneal route of administration. Overall, the major metabolite of scopolamine was shown to be scopolamine-9,1-β-D-glucuronide (Bayne *et al.*, 1975). An enzyme capable of hydrolyzing scopolamine, referred to as a tropinesterase for its major action, has been detected in various tissues including the serum of rabbits and the liver of guinea pigs (Cullumbine, 1971). In rabbits the ability of this enzyme to hydrolyze atropine is inherited through a gene that is incompletely dominant, and it is associated with another gene that influences the amount of black pigment in the fur. Scopolamine-*N*-butyl bromide undergoes biliary excretion in rats (Klaassen *et al.*, 1981); 21% of an intravenous dose (6 mg/kg) was excreted by this route within 4 hours.

Humans

In humans, scopolamine hydrobromide is readily absorbed from the gastrointestinal tract and enters the circulation when applied locally to mucosal membranes (Wade, 1977; NRC, 1982; Reynolds, 1982; Brown, 1990). Limited absorption occurs from the intact skin and the eye. Once in the systemic circulation, it readily crosses the blood-brain barrier (AMA, 1977). It binds to plasma proteins and is almost entirely metabolized in the liver (Wade, 1977; Reynolds, 1982). Peak serum concentrations are observed within 1 to 2 hours after an oral or intramuscular dose of scopolamine hydrobromide (Brand, 1969; Bayne *et al.*, 1975; Wade, 1977). Only about 1% of an oral dose of scopolamine is eliminated as the parent compound in the urine (NRC, 1982).

The pharmacokinetics and bioavailability of scopolamine hydrobromide were investigated in six healthy

male subjects receiving oral or intravenous doses of 0.4 mg (Putcha *et al.*, 1989). After intravenous administration, plasma concentrations of scopolamine declined in a biexponential fashion, with a rapid distribution phase and a comparatively slow elimination phase. Mean values for volume of distribution, systemic clearance, and renal clearance were 1.4 L/kg, 65.5 L/hour, and 4.2 L/hour, respectively. Mean peak plasma concentrations were 2.9 μg/mL following intravenous doses and 0.5 μg/mL following oral doses. The elimination half-life was 4.5 hours. Bioavailability of the oral doses was variable among subjects, ranging between 10.7% and 48.2%.

Ophthalmic effects due to local action of the scopolamine may persist for 3 to 7 days whereas systemic effects from oral or parenteral doses last 4 to 6 hours (Cullumbine, 1971). Even though the literature refers to an almost complete metabolism of scopolamine by humans, there are no studies documenting the metabolic pathways or characterizing the major and minor metabolites. It is known that scopolamine hydrobromide administered during the first stage of labor crosses the placental barrier, and traces have been detected in the milk of exposed nursing mothers (Wade, 1977; Reynolds, 1982).

TOXICITY

Experimental Animals

The LD_{50} values for scopolamine hydrobromide listed in Table 1 have been determined with various routes of administration in different species (RTECS, 1982).

Humans

The 1984 edition of *Clinical Toxicology of Commercial Products* (Gosselin *et al*, 1984) assigned a toxicity rating of five (extremely toxic) to scopolamine; previous editions (Gleason *et al.*, 1969; Gosselin *et al.*, 1976) assigned the higher toxicity rating of six (supertoxic). Both ratings underline the acute toxic nature of scopolamine. Although fatalities from exposure are rare (Gosselin *et al.*, 1984), they have occasionally occurred, usually in children (*Remington's Pharmaceutical Sciences*, 1975; NRC, 1982). A fatal human dose is estimated to be about 8 mg/kg, with death usually occurring within 24 hours of the initial exposure (Theines and Haley, 1972). Compared to LD_{50} values noted in experimental animals, humans appear more susceptible to the lethal action of scopolamine than experimental animals. Symptoms of toxicity in humans occur promptly and may persist for hours or days. Very low doses of scopolamine elicit a variety of adverse acute reactions, including idiosyncratic effects, following therapeutic doses. Accidental poisonings from as little as four drops of 0.25% scopolamine solution, equivalent to 0.45 mg scopolamine (Goldfrank *et al.*, 1982), from a single 0.5 mg transdermal patch of scopolamine (Rodysill and Warren, 1983), and from a 0.3 mg Kwells motion sickness tablet (Hindson, 1958) have caused acute toxic psychosis.

Scopolamine exposure can produce symptoms of acute toxicity involving the peripheral nervous system, including thirst due to drying of the mouth

TABLE 1
Scopolamine Hydrobromide Toxicity (LD_{50}) in Experimental Animals[a]

Species	Route	Dose (mg/kg)
Rat	Oral	1,270
Rat	Subcutaneous	3,800
Rat	Intraduodenal	670
Mouse	Oral	1,880
Mouse	Intraperitoneal	650
Mouse	Subcutaneous	1,650
Mouse	Intravenous	203
Guinea Pig	Subcutaneous	850

[a] RTECS, 1982

and throat, photophobia caused by dilated pupils, loss of accommodation for near vision (blurred vision), increased intraocular pressure (glaucoma), fever due to flushing and drying of the skin, urinary retention, and bradycardia (25-200 mg) or tachycardia followed by bradycardia (300-600 mg) (Thienes and Haley, 1972; Wade, 1977; Reynolds, 1982; Brown, 1990).

Central nervous system manifestations of acute scopolamine exposure include both cerebral excitement and depression. After large doses, the excitement component is less commonly noted and usually occurs earlier and is of shorter duration than that observed after smaller doses. This component may be expressed as euphoria, delirium, hyperactivity, disorientation, psychotic behavior, and hallucinations. The depressive cerebral component following therapeutic doses is expressed by an amnesic and sedative hypnotic state while toxic doses may elicit depression, muscular weakness, disequilibrium, and coma. Chronic toxic symptoms include recent memory loss, mental confusion, and hallucinations with repeated episodes of theta wave activity in the electroencephalogram (Thienes and Haley, 1972). Psychological dependence may occur but discontinuance of drug exposure does not induce physical withdrawal symptoms (Goldfrank *et al.*, 1982). A 1-week recovery period is required to remove symptoms of chronic exposure (Thienes and Haley, 1972).

Rare cases of scopolamine-induced hypersensitivity have been documented following mucous membrane exposures to eye drops; this hypersensitivity was characterized by edema of the uvula, glottis, and lips as well as generalized urticaria (Guill *et al.*, 1979). Sensitized patients become more sensitive to the drug after repeated exposures, as manifested by ever-decreasing exposure times required to elicit the allergic response.

During the years 1969 to 1980, a total of 37 adverse reactions to scopolamine were documented (FDA 1988). Twenty-three of these reports indicated nervous system disorders and 14 outlined cardiovascular disorders. Toxic psychosis occurred in a 67-year old female with insulin-dependent diabetes who received six to eight drops of a cycloplegic ophthalmic solution consisting of atropine (20 mg/mL), scopolamine hydrobromide (5 mg/mL), and phenylephrine hydrochloride (40 mg/mL). The symptoms abated after intravenous administration of physostigmine (Kortabarria *et al.*, 1990). Toxic coma occurred in a 6-year old boy who was given two drops per eye of an ophthalmic solution containing 2% atropine, 0.5% scopolamine hydrobromide, and 45% phenylephrine hydrochloride. The patient recovered following treatment with physostigmine salicylate (two 9.5 mg intravenous injections given 10 minutes apart; Nadal *et al.*, 1987).

Fetotoxicity can result from scopolamine exposure. In one study, scopolamine (0.43 mg) was administered alone or in combination with sedatives, analgesics, or both to 56 pregnant women during labor and the fetal heart rate was evaluated with a fetal monitor (Boehm and Growdon, 1974). There was a decrease in fetal heart rate baseline variability (an indication of fetal distress) in 42% of the patients treated exclusively with scopolamine and in 75% of those patients receiving scopolamine in combination with other drugs. Scopolamine toxicity was also reported in a newborn whose mother received multiple doses of scopolamine (two doses each of 0.2, 0.3, and 0.4 mg) with merperidine, lorfan, and "general inhalation" (Evens and Leopold, 1980). The toxic symptoms included an increased body temperature (100.4°F) and pulse rate (200 beats/minute), lethargy, and a barrel-chested appearance without respiratory distress.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

The potential adverse consequences of scopolamine exposure on fetal development and reproductive parameters have been investigated in experimental animal studies including those sponsored by the NTP.

In a study using CF-1 mice, scopolamine was found to be "non-teratogenic in the doses employed" (Iuliucci, 1973). However, when administered together with morphine sulfate, scopolamine enhanced morphine-induced exencephaly in the offspring. In a study conducted with New Zealand White rabbits, pregnant does were given scopolamine hydrobromide in drinking water (0.010 mg/mL) or untreated drinking water from the 10th through the 14th day of gestation (McBride *et al.*, 1982). The

calculated intake of scopolamine ranged from 0.424 to 0.582 mg/kg per day for the eight treated animals in the study. No malformed pups were observed in the control group. On gestation day 22, scopolamine significantly increased the incidence of malformations in the treated group. In two of the eight treated litters, all of the live fetuses exhibited malformations. No malformed live fetuses were observed in the other six treated litters. Malformations observed in these two litters included exencephaly, hydrocephaly, buphthalmia, and microphthalmia.

In a companion study (McBride *et al.*,1982), scopolamine hydrobromide was administered intramuscularly at 12 hour intervals to one or two pregnant New Zealand White rabbits at doses ranging from 0.037 to 0.185 mg/kg per injection on gestation days 10 through 14. The eight untreated animals in the drinking water study also served as controls for this study. The doe receiving 0.137 mg/kg per injection died on the first day of treatment and the doe receiving 0.185 mg/kg per injection died on the second day of treatment. Both does died of tachycardia induced by the injection. The other does exhibited clinical signs of distress, which the authors attributed to cardiac effects of the drug. On gestation day 22, no malformed fetuses were observed in any of the 38 live fetuses examined. The authors also noted a significant increase in the incidence of resorptions when the data from the combined treatment groups (oral and intramuscular) were compared to the control group.

McBride *et al.* (1982) also described a study in which sterile saline or 0.1 or 0.2 mg scopolamine hydrobromide was injected into white leghorn chicken eggs (100 eggs/group) after 96 hours of incubation. The chick embryos were then examined on day 12 of incubation. The incidences of malformation were 0%, 34%, and 78% for the control, 0.1 mg, and 0.2 mg treatment groups, respectively. The primary malformation in both scopolamine-treated groups was gastroschisis, with all of the malformed embryos exhibiting this defect. Other malformations observed were reduction deformities of the leg, wing deformities, and microphthalmia. A significant increase in the number of embryo deaths was also observed when the control group was compared with the combined treatment groups.

The NTP sponsored teratology studies of scopolamine hydrobromide using time-pregnant CD-1 mice and CD rats (data on file at NIEHS). Scopolamine hydrobromide (0, 10, 100, 450, and 900 mg/kg per day) dissolved in water was administered by gavage on gestation day 6 through gestation day 15. The animals were sacrificed and cesarean sections were performed on gestation day 17 (mice) and gestation day 20 (rats). The results of these studies showed that rats exposed *in utero* to 450 or 900 mg/kg scopolamine hydrobromide developed short ribs and that *in utero* exposure of rats to 100, 450, and 900 mg/kg scopolamine was associated with marginal, non-dose-related reductions in fetal body weight and marginal, non-dose-related increases in the incidences of fetal malformations in the presence of maternal toxicity (reduced body weight and weight gain). The investigators concluded that there was no evidence of teratogenesis in mice, even though a high level of congenital malformations and anatomical variations was noted. Maternal and fetal body weights of mice were reduced at the 450 and 900 mg/kg dose levels.

Humans

No information on the reproductive or developmental toxicity of scopolamine hydrobromide trihydrate in humans was found in the literature (NLM, 1994).

CARCINOGENICITY

Experimental Animals

No information on the carcinogenicity of scopolamine hydrobromide trihydrate in experimental animals was found in the literature (NLM, 1994).

Humans

No epidemiological studies or case reports examining the relationship between exposure to scopolamine hydrobromide and human cancer were found in the literature (NLM, 1994).

GENETIC TOXICITY

The mutagenicity data for scopolamine hydrobromide trihydrate found in the literature were limited to two published reports. Fluck *et al.* (1976) observed no growth inhibition due to DNA damage in *Escherichia coli* treated with up to 4 mg/well scopolamine hydrobromide in the absence of S9 metabolic activation. In the second report, HeLa cells, treated for 5 hours with a 1% solution of scopolamine HBr without S9, showed an increase in chromatid breaks 46 hours after the initiation of exposure (Vrba, 1967); HeLa cells analyzed 22 hours after the addition of scopolamine (1%) to the culture medium showed no increase in the frequency of chromatid breaks. In addition, the author reported that no induction of chromatid breaks was noted in human leukocytes or BSC K cells treated in similar fashion, but no supporting data were included for this observation.

The non-salt analogue, scopolamine, showed no evidence of mutagenic activity in *Salmonella typhimurium* strains TA98, TA100, or TA1537 with or without metabolic activation (Waskell, 1978; Glatt *et al.*, 1983). A second structural analogue, scopolan, did not induce chromosome non-disjunction or crossing-over in *Aspergillus nidulans* (Bignami *et al.*, 1974).

STUDY RATIONALE

Scopolamine hydrobromide trihydrate was nominated by the National Cancer Institute for toxicology and carcinogenicity testing because of considerable human exposure resulting from its use as a prescription or an over-the-counter drug and because it is a representative chemical from a class of alkaloids. Scopolamine is a suspect carcinogen because it contains an aliphatic epoxide moiety which may act as a biological alkylating agent. Its major use is in transdermal patches for the treatment of motion sickness. Scopolamine hydrobromide trihydrate potentially could be used for the treatment of various ailments including acute mania, diarrhea, gastric and duodenal ulcers, gastrointestinal spasm, excessive salivation and sweating, and infantile cerebral palsy. It is also used as a mydriatic and cycloplegic agent and has been used as an over-the-counter sleeping aid. Thus human exposure occurs by several routes including oral, dermal, subcutaneous, and ocular exposure. The route of administration selected for the NTP studies was gavage because it mimics the oral exposure route in humans and higher doses can be administered to the animal than can be achieved by the dosed feed route of administration.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

Scopolamine hydrobromide trihydrate was obtained in two lots, one from Rebeco Chemicals, Inc. (New York, NY; lot 14188), and one from Henley and Company, Inc. (New York, NY; lot 283). Lot 14188 was used during the 16-day studies, and lot 283 was used during the 14-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), (Appendix J). Reports on analyses performed in support of the scopolamine hydrobromide trihydrate studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a white powder, was identified as scopolamine hydrobromide trihydrate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of both lots was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and high-performance liquid chromatography. Weight loss on drying was determined for lot 14188.

For lot 14188, elemental analyses for carbon, hydrogen, nitrogen, and bromine were in agreement with the theoretical values for scopolamine hydrobromide trihydrate. Karl Fischer water analysis indicated 10.8% ± 0.3% water. Weight loss on drying indicated 10.8% ± 0.02% water. Functional group titration indicated a purity of 101.9% ± 0.1%. Thin-layer chromatography by one system indicated a major spot, two trace impurities, and one slight trace impurity. Thin-layer chromatography by another system indicated a major spot and one trace impurity. High-performance liquid chromatography revealed a major peak and one impurity with an area of 0.1% relative to the major peak. Major peak comparisons of lot 14188 with a solution of dried United States Pharmacopeia XX (USP) reference standard scopolamine hydrobromide indicated that lot 14188 contained 88.8% ± 0.2% scopolamine hydrobromide relative to the USP reference. Lot 14188 was determined to contain 89% scopolamine hydrobromide and 11% water. The theoretical values for scopolamine hydrobromide trihydrate are 87.7% scopolamine hydrobromide and 12.3% water.

For lot 283, elemental analyses for carbon, hydrogen, nitrogen, and bromine were in agreement with the theoretical values for scopolamine hydrobromide trihydrate. Karl Fischer water analysis indicated 11.2% ± 0.2% water. Functional group titration indicated a purity of 101.7% ± 0.6%. Thin-layer chromatography indicated a major spot and one trace impurity. High-performance liquid chromatography revealed a major peak and one impurity with an area of 0.2% relative to the major peak. Major peak comparisons of lot 283 with a solution of dried USP reference standard scopolamine hydrobromide indicated that lot 283 contained 89.2% ± 0.3% scopolamine hydrobromide relative to the USP reference. Major peak comparisons of lot 283 with lot 14188 indicated a purity of 100.0% ± 0.4% relative to lot 14188. Lot 283 was also determined to contain 89% scopolamine hydrobromide and 11% water.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using high-performance liquid chromatography. These studies indicated that scopolamine hydrobromide trihydrate was stable as a bulk chemical for 2 weeks when stored protected from light at room temperature in sealed containers under a nitrogen headspace. To ensure stability, the bulk chemical was stored in amber glass jars at approximately 25°C under a nitrogen headspace.

Stability was monitored by the study laboratory during the 16-day, 14-week, and 2-year studies using high-performance liquid chromatography and potentiometric titration (2-year studies). No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations for the 16-day and 14-week studies were prepared every two weeks. For the 2-year rat study, dose formulations were prepared weekly for the first four months every 2 weeks thereafter. Dose formulations were prepared every 2 weeks throughout the 2-year mouse study. Formulations were prepared by mixing scopolamine hydrobromide trihydrate with water (Table J1). Stability studies of the 11 and 0.2 mg/mL dose formulations were performed by the analytical chemistry laboratory using high-performance liquid chromatography. The dose formulations, when stored at room temperature and protected from light, were stable for at least 3 weeks.

Periodic analyses of the dose formulations of scopolamine hydrobromide trihydrate were conducted at the study laboratory and analytical chemistry laboratory using ultraviolet/visible spectrometry (16-day and 14-week studies) or high-performance liquid chromatography (2-year studies). During the 16-day studies, the formulations were analyzed at the beginning of the studies (Table J2). For the 14-week and 2-year studies, the formulations were analyzed every 6 to 8 weeks (Tables J3 and J4). During the 16-day studies, 70% (7/10) of the dose formulations were within 10% of the target concentration with no value differing more than 16% from the target concentration. All of the dose formulations analyzed during the 14-week studies were within 10% of the target concentration. During the 2-year studies, 92% (72/78) of the dose formulations were within 10% of the target concentration with no value differing more than 20% from the target concentration. For the 14-week and 2-year studies, results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results of the study laboratory (Table J5).

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Facility (Frederick, MD). On receipt the rats and mice were 29 days old. Animals were quarantined for 12 days and were approximately 6 weeks old on the first day of the study. Groups of five male and five female rats and mice received scopolamine hydrobromide trihydrate in distilled water by gavage at doses of 0, 75, 150, 300, 600, or 1,200 mg/kg body weight (rats) or 0, 150, 250, 450, 900, or 1,800 mg/kg (mice). Feed and water were available *ad libitum*. Rats were housed five per cage and mice were housed individually. Clinical findings were recorded twice daily for rats and mice. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 2.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. Complete histopathologic examinations were performed on all control rats and mice, and on rats receiving 1,200 mg/kg and mice receiving 1,800 mg/kg. In addition, the livers of female rats receiving 600 mg/kg, the liver of one male rat receiving 75 mg/kg, and the livers, spleens, and thymuses of male and female mice receiving 900 mg/kg were examined.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to scopolamine hydrobromide trihydrate 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 Simonsen Laboratories, Inc. (Gilroy, CA). On receipt, the rats were 4 weeks old and mice were 5 weeks old. Animals were quarantined for 12 (rats) or 16 (mice) days and were 6 or 7 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female sentinel rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice received scopolamine hydrobromide trihydrate in distilled water by gavage at doses of 0, 15, 45, 135, 400, or 1,200 mg/kg body weight. Feed and water were available *ad libitum*. Rats were housed five per

cage and mice were housed individually. Clinical findings and feed consumption were recorded weekly. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 2.

At the end of the 14-week studies, blood for hematology was collected via the retroorbital sinus from rats and mice under carbon dioxide anesthesia. Samples were placed in containers containing EDTA as an anticoagulant. Hematology parameters were measured on an Ortho ELT-8 hematology analyzer (Ortho Instruments, Westwood, MA). Differential leukocyte counts, morphologic evaluations of blood cells and platelets, and reticulocyte counts were determined by light microscopy of blood films stained with a combination of methylene blue and buffered Wright-Giemsa stain. The hematology parameters measured are listed in Table 2.

At the end of the studies, samples for sperm morphology and vaginal cytology evaluations were collected from rats receiving 0, 45, 135, or 400 mg/kg and mice receiving 0, 135, 400, or 1,200 mg/kg. The parameters evaluated are listed in Table 2. Methods used were those described in the NTP's sperm and vaginal cytology evaluations protocol (NTP, 1983). For 7 consecutive days prior to the scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and aspirated samples of vaginal fluid and cells were transferred to slides and stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). All males were evaluated for sperm morphology, count, and motility. The right testis and right epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution and finely minced. The tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. Four sperm morphology slides were prepared for each animal evaluated. An aliquot of killed sperm suspension was stained in a test tube, spread on a microscope slide with coverslip, and examined.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right ovary, right testis, thymus, and uterus 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. Complete histopathologic examinations were performed on all control rats and mice, male rats receiving 135 mg/kg or higher, female rats receiving 400 mg/kg or higher, male and female mice receiving 1,200 mg/kg and one male mouse receiving 135 mg/kg that died early. Table 2 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 60 male and 60 female rats and 70 male and 70 female mice received scopolamine hydrobromide trihydrate in distilled water by gavage at doses of 0, 1, 5, or 25 mg/kg body weight. Ten male and ten female rats and mice from each group received ophthalmic examinations during quarantine and at 15 months. These mice were removed from the study following the 15 month examination without necropsy. The 10 male and 10 female rats used for ophthalmic examination and an additional 10 male and 10 female mice from each group were evaluated at 15 months for alterations in hematology, histopathology, and organ weights. The rats bled for hematology analyses were bled again 1 hour after dosing for determination of scopolamine levels in plasma.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. Rats and mice were quarantined for 14 days before the beginning of the studies. Five male and five female rats and mice

were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to 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 for 7 consecutive days each month by cage. Cages and racks were rotated 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. During the first 13 weeks, clinical findings were recorded every three to four weeks for rats and every three to six weeks for mice. Clinical findings were recorded monthly thereafter. Body weights were recorded weekly for 13 weeks, monthly thereafter, and at the end of the studies. Before the studies began, 10 male and 10 female rats and mice per group were randomly selected for ophthalmic examination. These animals were examined again at 15 months. No mydriatic agent was used to facilitate the examinations. Funduscopic examination was accomplished using an ophthalmoscope; examinations of the anterior chamber were performed using a slit-lamp biomicroscope. Mice that received ophthalmic exams were discarded without further evaluation.

At the 15-month interim evaluation, within the hour after dosing, blood for hematology was collected via the retroorbital sinus of rats and mice anesthetized with a mixture of carbon dioxide and oxygen. Because of a flooding incident that killed 16 female rats receiving 1 mg/kg, no females in this dose group were bled or necropsied at 15 months. The hematology parameters measured are listed in Table 2; methods used were similar to those used in the 14-week studies. Additionally, the rats bled at 15 months for hematology analyses were bled an hour after dosing by cardiac puncture under CO_2:O_2 anesthesia for plasma scopolamine determination studies. Rats and mice bled for hematology at the 15-month interim evaluation were necropsied.

Blood samples collected for plasma scopolamine determinations were sent to Midwest Research Institute (Kansas City, MO). Analyses was performed using gas chromatography and mass spectroscopy.

A complete necropsy and microscopic examination were performed on all core study animals. At the 15-month interim evaluations the right epididymis, right kidney, liver, and right testis of rats and mice were weighed (excluding female rats receiving 1 mg/kg). At necropsy, all organs and tissues were examined for grossly visible lesions. Major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 2.

Additional groups of 10 male and 10 female rats receiving scopolamine hydrobromide trihydrate in water by gavage at doses of 0, 1, 5, or 25 mg/kg body weight were administered neurobehavioral tests prior to the study, on the first day of study, and after 3, 6, 9, 12, and 24 months of dosing. The same animals were used at each time point. These neurobehavioral tests included motor activity, grip strength, thermal sensitivity, startle responsiveness, and passive avoidance. Further details of these evaluations are outlined in Appendix I.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the liver,

pituitary gland, and spleen of male and female rats, the parathyroid gland, thyroid gland, and stomach of male rats, and the ovaries of female rats. In mice, the liver, forestomach, thyroid gland, lung, and kidney of males and females, teeth, pancreatic islets, and preputial gland of males, and the pituitary gland, uterus, and bone marrow of female mice were examined.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of quality assessment pathologists, the PWG chairperson, 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 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 ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary glands and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, 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 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 dosed 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 dosed 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, refer to 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 dosed 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). Hematology and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportions of the observation period that an animal was in a given estrous state), an arcsine transformation was used to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across dose levels.

Historical Control Data

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

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year 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 scopolamine hydrobromide trihydrate was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of scopolamine hydrobromide trihydrate 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* test alone. The predictivity for 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 Gavage Studies of Scopolamine Hydrobromide Trihydrate

16-Day Studies	14-Week Studies	2-Year Studies
Study Laboratory		
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Battelle Columbus Laboratories (Columbus, OH)
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 Facility (Frederick, MD)	Simonsen Laboratories, Inc. (Gilroy, CA)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies		
12 days	Rats: 12 days Mice: 16 days	14 days
Average Age When Studies Began		
6 weeks	Rats: 6 weeks Mice: 7 weeks	6 weeks
Date of First Dose		
Rats: 1-2 July 1985 Mice: 8-9 July 1985	Rats: 17 March 1986 Mice: 21 March 1986	Rats: 20 October 1988 Mice: 22 September 1988
Duration of Dosing		
16 days	14 weeks	Rats: 104 weeks Mice: 104-105 weeks
Date of Last Dose		
Rats: 17-18 July 1985 Mice: 23-24 July 1985	Rats: 17-19 June 1986 Mice: 24-26 June 1986	Rats: 17 October 1990 Mice: 20 September 1990
Necropsy Dates		
Rats: 18-19 July 1985 Mice: 24-25 July 1985	Rats: 18-20 June 1986 Mice: 25-27 June 1986	Rats: 15-month interim evaluation — 18 January (males)-19 January (females) 1990 terminal sacrifice —15-17 October 1990 Mice: 15-month interim evaluation — 21-22 December 1990 terminal sacrifice —17-21 September 1990
Average Age at Necropsy		
8 weeks	Rats: 19-20 weeks Mice: 20-21 weeks	Rats: 110 weeks Mice: 111 weeks

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of Scopolamine Hydrobromide Trihydrate (continued)

16-Day Studies	14-Week Studies	2-Year Studies
Size of Study Groups 5 males and 5 females	10 males and 10 females	15-Month interim — Rats: 10 males and 10 females received ophthalmic examinations, were bled for hematology and plasma scopolamine levels, and necropsied for histological examination and organ weights Mice: 10 males and 10 females were bled for hematology and necropsied for histological examination and organ weights 10 males and 10 females received ophthalmic examinations and were discarded without necropsy Terminal — 50 male and 50 female rats and mice
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weight.	Same as 16-day studies	Same as 16-day studies
Animals per Cage Rats: 5 Mice: 1	Rats: 5 Mice: 1	Rats: 5 Mice: 1
Method of Animal Identification Toe clip	Toe clip	Rats: Tail tattoo Mice: Toe clip
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Water Distribution Tap water (City of Birmingham Municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 16-day studies	Tap water (Columbus Municipal Supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*
Cages Polycarbonate (Lab Products Inc., Maywood, NJ), changed twice weekly	Same as 16-day studies	Same as 16-day studies
Bedding BetaChips® (Northeastern Products Co., Warrensburg, NY)	Same as 16-day studies	Sani-Chip® hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ)

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of Scopolamine Hydrobromide Trihydrate (continued)

16-Day Studies	14-Week Studies	2-Year Studies
Cage Filters		
Fiber filters	Reemay® spun-bonded polyester (Andico, Birmingham, AL)	DuPont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH)
Racks		
Stainless steel	Stainless steel (Lab Products Inc., Maywood, NJ), rotated once every 2 weeks	Stainless steel (Lab Products Inc., Maywood, NJ) rotated once every 2 weeks
Animal Room Environment		
Temperature: 20.0° to 24.0° C (rats); 21.0° to 24.0° C (mice) Relative humidity: 43% to 57% (rats); 45% to 55% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour	Temperature: 20.0° to 25.0° C (rats); 20.0° to 24.9° C (mice) Relative humidity: 45% to 66% (rats); 45% to 71% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour	Temperature: 20.7° to 23.3° C (rats); 20.0° to 24.4° C (mice) Relative humidity: 24% to 72% (rats); 30% to 73% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour
Doses		
Rats: 0, 75, 150, 300, 600, or 1,200 mg/kg Mice: 0, 150, 250, 450, 900, or 1,800 mg/kg	0, 15, 45, 135, 400, or 1,200 mg/kg	0, 1, 5, or 25 mg/kg
Type and Frequency of Observation		
Observed twice daily; animals were weighed initially, weekly, and at the end of the studies. Clinical findings were recorded twice daily.	Observed twice daily; animals were weighed initially, weekly, and at the end of the studies. Clinical observations were recorded weekly. Feed consumption was measured weekly by cage.	Observed twice daily; clinical observations were recorded every 3-4 weeks (rats) or 3-6 weeks (mice) during the first 13 weeks and monthly thereafter; body weights were recorded weekly through week 13, monthly thereafter, and at the end of the studies. Feed consumption was measured by cage for 7 consecutive days each month.
Method of Sacrifice		
CO_2 asphyxiation	CO_2 asphyxiation	CO_2 asphyxiation
Necropsy		
All animals were necropsied. Organs weighed included the brain, heart, right kidney, liver, lungs, right testis, and thymus.	All animals were necropsied. Organs weighed included the brain, heart, right kidney, liver, lungs, right ovary, right testis, thymus, and uterus.	All core-study animals were necropsied. Organs weighed at the 15-month interim evaluations were the right epididymis, right kidney, liver, and right testis (excluding female rats receiving 1 mg/kg).

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of Scopolamine Hydrobromide Trihydrate (continued)

16-Day Studies	14-Week Studies	2-Year Studies
Clinical Pathology		
None	At the end of the 14-week studies, blood was collected from the retro-orbital sinus of rats and mice. ***Hematology:*** hematocrit; hemoglobin; erythrocyte, reticulocyte, and nucleated erythrocyte counts (rats); mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; platelet count; and leukocyte count and differentials.	At the 15-month interim evaluation, blood for hematology was collected from the retroorbital sinus of rats and mice under CO_2:O_2 anesthesia (excluding female rats that received 1 mg/kg). The hematology parameters measured were the same as those in the 14-week studies.
Histopathology		
Complete histopathologic examinations were performed on all control rats and mice, as well as rats receiving 1,200 mg/kg and mice receiving 1,800 mg/kg. In addition to gross lesions, tissue masses and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland (rats) esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. The liver of female rats receiving 600 mg/kg, the liver of one male receiving 75 mg/kg, and the liver, spleen, and thymus of male and female mice receiving 900 mg/kg were also examined.	Complete histopathologic examinations were performed on all control rats and mice, male rats receiving 135 mg/kg or higher, female rats receiving 400 mg/kg or higher, male and female mice receiving 1,200 mg/kg and one male mouse receiving 135 mg/kg that died early. In addition to gross lesions, tissue masses and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland (rats), esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathologic examinations were performed on all core-study animals. In addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), liver, lung, lymph nodes (mandibular or mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of Scopolamine Hydrobromide Trihydrate (continued)

16-Day Studies	14-Week Studies	2-Year Studies
Sperm Morphology and Vaginal Cytology Evaluations		
None	Sperm and vaginal fluid samples were evaluated in 0, 45, 135, and 400 mg/kg rats and 0, 135, 400 and 1,200 mg/kg mice at the end of the studies. The parameters evaluated in males were sperm count, morphology, and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal fluid samples were collected for up to 7 consecutive days prior to the end of the studies for vaginal cytology evaluations. The parameters evaluated in females were relative frequency of estrous stages and estrous cycle length.	None
Ophthalmic Examination		
None	None	10 male and 10 female rats and mice per dose group received ophthalmic examinations at the beginning of the study and again at the 15-month interim evaluation.
Plasma Scopolamine Determination		
None	None	At 15 months, 10 male and 10 female rats were bled for plasma scopolamine determinations. (Rats had been bled one hour earlier for hematology evaluations.)
Neurobehavioral Studies		
None	None	Ten male and ten female rats per dose group were administered neurobehavioral tests prior to the study, on the first day of study, and after 3, 6, 9, 12, and 24 months of exposure. These tests included evaluations of motor activity, grip strength, thermal sensitivity, startle responsiveness, and passive avoidance.

RESULTS

RATS

16-DAY STUDY

All rats survived to the end of the study (Table 3). The final mean body weights and body weight gains of males receiving 600 and 1,200 mg/kg and the mean body weight gain of males receiving 300 mg/kg were significantly lower than those of the control group.

Clinical findings included bilateral pupillary dilation in all dosed animals and red eyelids in males and females receiving 1,200 mg/kg. No biologically significant changes in organ weights were observed (Table F1). There were no biologically significant treatment-related gross or microscopic lesions, and the high dose selected for the 14-week study was 1,200 mg/kg, the same as that in the 16-day study.

TABLE 3
Survival and Body Weights of Rats in the 16-Day Gavage Study of Scopolamine Hydrobromide Trihydrate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	116 ± 3	186 ± 2	69 ± 1	
75	5/5	119 ± 4	175 ± 5	55 ± 2	94
150	5/5	116 ± 2	174 ± 6	58 ± 4	94
300	5/5	118 ± 4	173 ± 4	56 ± 2*	93
600	5/5	116 ± 3	166 ± 6**	50 ± 5**	89
1,200	5/5	125 ± 7	166 ± 5**	41 ± 8**	90
Female					
0	5/5	103 ± 4	140 ± 5	37 ± 2	
75	5/5	103 ± 4	133 ± 5	30 ± 6	95
150	5/5	105 ± 4	134 ± 4	29 ± 1	96
300	5/5	102 ± 3	134 ± 4	31 ± 1	96
600	5/5	105 ± 2	138 ± 3	32 ± 1	98
1,200	5/5	105 ± 2	135 ± 3	31 ± 4	97

* 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/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

14-WEEK STUDY

One female receiving 45 mg/kg, one male and one female receiving 135 mg/kg, six males and one female receiving 400 mg/kg, and eight males and seven females receiving 1,200 mg/kg died during the study (Table 4). The final mean body weights and mean body weight gains of all dosed males and females were significantly lower than those of the control groups. Clinical findings included bilateral pupillary dilation in all dosed males and females and reddening of the eyes in 15 mg/kg males and 135, 400, and 1,200 mg/kg males and females.

Hyperactivity was visually observed in a few dosed males and females (males: 0 mg/kg, 0/10; 15 mg/kg, 0/10; 45 mg/kg, 1/10; 135 mg/kg, 1/10; 400 mg/kg, 0/10; 1,200 mg/kg, 1/10; females: 0/10, 2/10, 5/10, 3/10, 1/10, 1/10). Hypoactivity was also visually observed in some other dosed males and females (males: 0/10, 0/10, 0/10, 0/10, 3/10, 3/10; females: 0/10, 0/10, 0/10, 1/10, 1/10, 5/10) and increased with increasing dose.

The hematology data for rats in the 14-week study are listed in Table G1. Hematocrit, hemoglobin

TABLE 4
Survival and Body Weights of Rats in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	116 ± 3	341 ± 6	225 ± 5	
15	10/10	116 ± 3	312 ± 7**	197 ± 6**	92
45	10/10	115 ± 3	302 ± 4**	188 ± 5**	89
135	8/10[c]	114 ± 3	300 ± 7**	186 ± 5**	88
400	4/10[d]	115 ± 2	304 ± 3**	188 ± 7**	89
1,200	2/10[e]	116 ± 2	277 ± 37**	163 ± 30**	81
Female					
0	10/10	96 ± 1	203 ± 2	107 ± 2	
15	10/10	97 ± 1	193 ± 2**	96 ± 2**	95
45	9/10[f]	98 ± 2	196 ± 2*	97 ± 1**	97
135	9/10[g]	95 ± 1	190 ± 2**	96 ± 3**	94
400	9/10[f]	96 ± 1	189 ± 2**	93 ± 3**	93
1,200	3/10[h]	95 ± 1	192 ± 6**	95 ± 5**	94

* 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/number initially in group. Subsequent calculations are based on animals surviving to the end of the study
[b] Weights and weight changes are given as mean ± standard error.
[c] Week of death: 7, 14
[d] Week of death: 1, 2, 7, 7, 13, 13
[e] Week of death: 1, 1, 1, 3, 4, 5, 9, 14
[f] Week of death: 4
[g] Week of death: 8
[h] Week of death: 1, 2, 5, 6, 7, 7, 10

concentration, and/or erythrocyte count in male and female rats receiving 45 mg/kg or greater were slightly higher than those of the control groups. In general, these differences were most prominent in the 400 and 1,200 mg/kg groups. Higher hematocrit, hemoglobin concentration, and erythrocyte count would be consistent with the hemoconcentration associated with dehydration (relative erythrocytosis). The mortality and lower body weights of the dosed animals suggest that the dosed rats did not eat or drink as much as the controls and some dehydration would have occurred. A minimal to mild mature neutrophilia, evidenced by higher segmented neutrophil numbers than those in the control group, occurred in all dosed male rats. Neutrophilia is often a result of an increased tissue demand for granulocytes due to inflammation. There was, however, no microscopic evidence of inflammation that could account for the neutrophilia. Thus, other mechanisms that alter granulopoiesis and/or rate of release from the bone marrow, redistribution of neutrophils between the marginal and the circulating pools, or increase the intravascular neutrophil life span could be considered. Other hematology differences were sporadic and were not treatment related.

The absolute and relative liver weights of 1,200 mg/kg females were significantly greater than those of the control group. The absolute and relative thymus weights of 15, 45, 135, and 400 mg/kg males and females and 1,200 mg/kg females were significantly lower than those of the control groups (Table F2).

Sperm morphology and vaginal cytology parameters in dosed rats were similar to those in the control groups (Table H1).

Some males (0/10, 0/10, 0/10, 2/10, 3/10, 4/10) and females (0/10, 0/10, 1/10, 1/10, 0/10, 3/10) died from esophageal obstructions consisting of feed and bedding material in the posterior pharynx. Tracheal obstruction occurred concurrently with esophageal obstruction as a result of food build-up in the oropharyngeal region. This condition is considered to be secondary to the inhibitory effects of scopolamine hydrobromide trihydrate on salivary gland secretions and on esophageal smooth muscle involved in swallowing. There were no other significant treatment-related gross or microscopic findings.

Dose Selection Rationale: Based on lower mean body weights in all dosed animals and lower survival in 400 mg/kg males and 1,200 mg/kg males and females compared to body weights and survival in the control groups, doses selected for the 2-year studies were 1, 5, and 25 mg/kg.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves (Figure 1). Survival of female rats receiving 1 and 25 mg/kg was significantly lower than that of the control group. The lower survival in 1 mg/kg females was due primarily to a cage flooding accident resulting from a malfunctioning automatic watering system valve.

Body Weights, Clinical Findings, and Ophthalmic Examination Findings

Mean body weights of 1 and 5 mg/kg males and females were similar to those of the controls throughout the study (Figure 2; Tables 6 and 7). The mean body weight of 25 mg/kg males was slightly lower than that of the control group from about week 25 through week 97. The mean body weight of 25 mg/kg females was lower than that of the control group from week 25, and the final mean body weight was 81% that of the controls. Clinical findings included bilateral pupillary dilation in all dosed males and females. Ophthalmic examination revealed no significant findings.

Hematology

The hematology data for rats at the 15-month interim evaluation in the 2-year study are listed in Table G2. Compared to controls, hematocrit was slightly higher in the 25 mg/kg male rats, similar to effects observed in the 14-week study; this would be consistent with dehydration resulting in hemoconcentration. The reticulocyte count in 25 mg/kg female rats was slightly lower than that in the control group. This result is consistent with the lower body weights, and thus a decreased nutritional status, exhibited by these animals.

Plasma Scopolamine Determinations

Serum samples collected from rats 1 hour after dosing were analyzed to determine serum scopolamine concentrations. Serum scopolamine concentration analyses indicated 6 ng scopolamine/mL serum for the 5 mg/kg female sample and 12 and 28 ng/mL for the 25 mg/kg male and female samples, respectively. The amounts of scopolamine in the other serum samples were below the minimum detection limit (4 ng/mL) of the analysis method.

Neurobehavioral Findings

Horizontal motor activity of 25 mg/kg females was significantly greater than that of the control group on days 90, 180, and 360. The startle response of 5 and 25 mg/kg females was significantly lower than that of the control group on day 90. On day 180, passive avoidance by 25 mg/kg males was significantly lower than that by the control group (Appendix I).

TABLE 5
Survival of Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	2	2	1	1
Moribund	23	30	20	17
Natural deaths	5	4	7	4
Animals surviving to study termination	20	14	22	28
Percent probability of survival at the end of study[b]	42	30	45	58
Mean survival (days)[c]	625	610	632	620
Survival analysis[d]	P=0.057N	P=0.219	P=0.995N	P=0.274N
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	0	10	10
Accidental deaths[a]	0	18[e]	2	5
Moribund	13	10	6	7
Natural deaths	3	15	16	16
Animals surviving to study termination	34	17	26	22
Percent probability of survival at the end of study	69	41	56	53
Mean survival (days)	643	476	622	539
Survival analysis	P=0.311	P=0.002	P=0.286	P=0.041

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

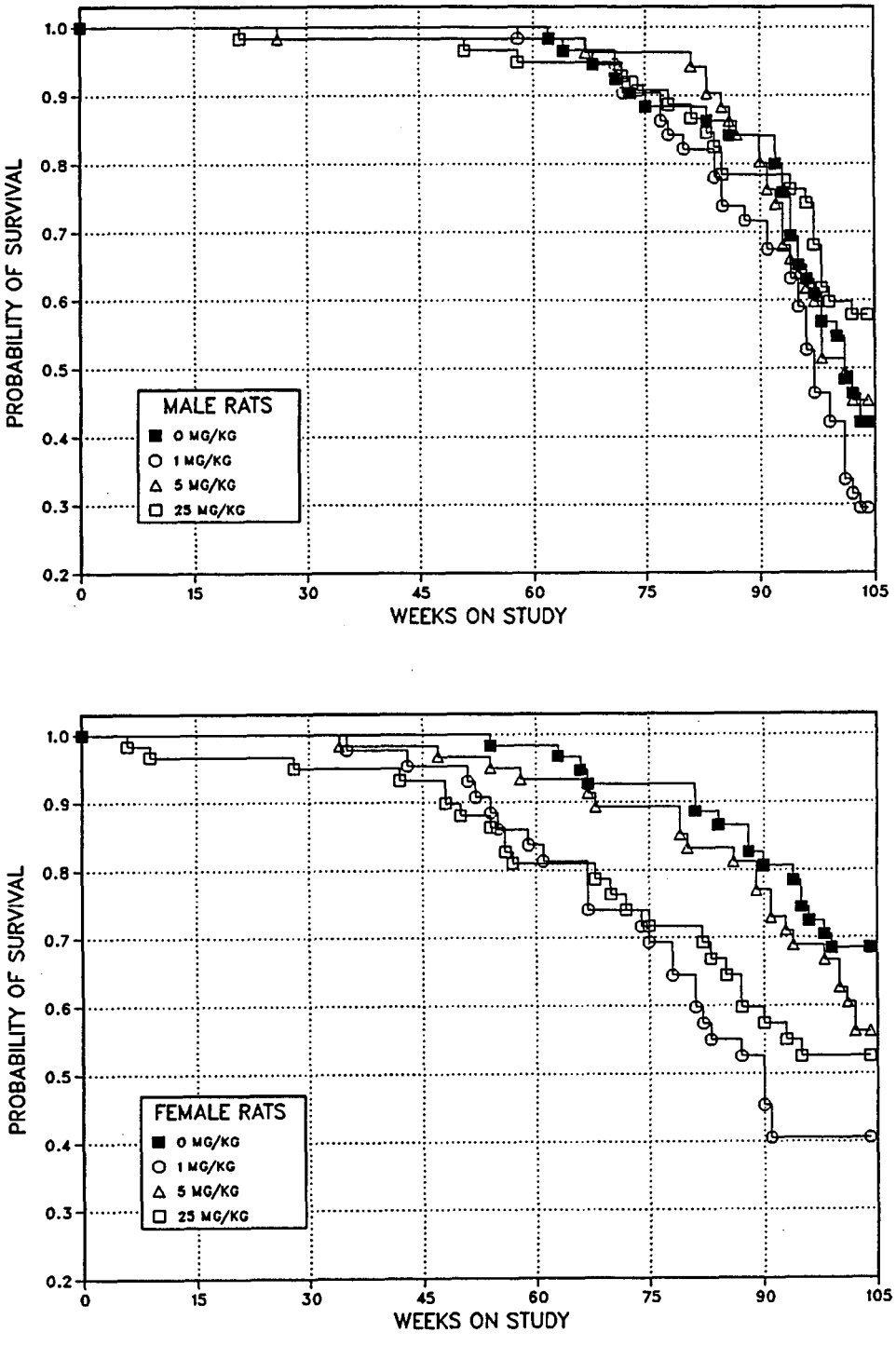


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Scopolamine Hydrobromide Trihydrate in Water by Gavage for 2 Years

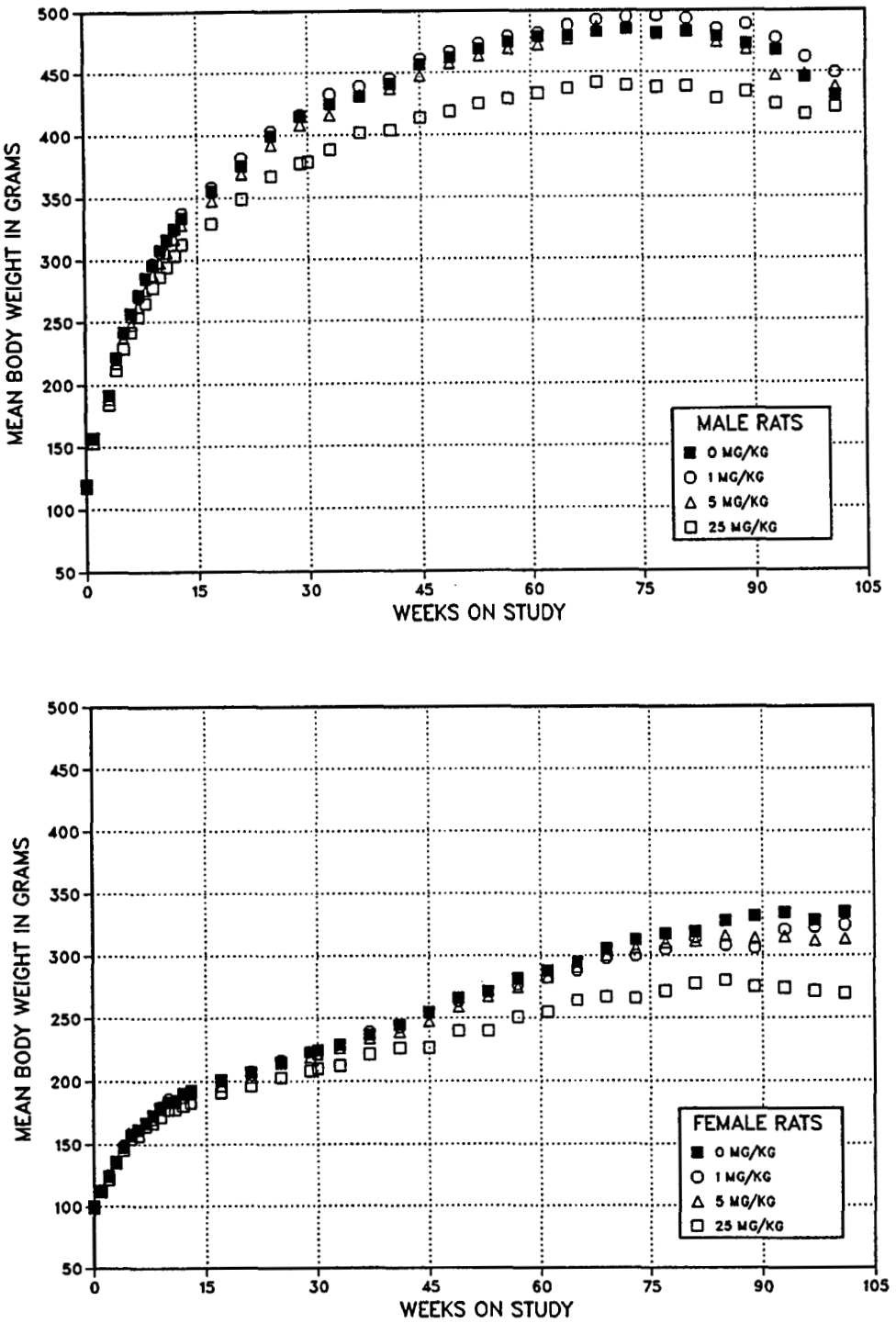


FIGURE 2
Growth Curves for Male and Female Rats Administered Scopolamine Hydrobromide Trihydrate in Water by Gavage for 2 Years

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

Weeks on Study	Vehicle Control		1 mg/kg			5 mg/kg			25 mg/kg		
	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	131	60	129	99	60	129	99	60	128	98	60
2	157	60	157	100	60	157	100	60	153	97	60
3	192	60	192	100	60	188	98	60	184	96	60
4	222	60	221	100	60	217	98	60	212	95	60
5	242	60	241	100	60	237	98	60	229	95	60
6	257	60	255	99	60	248	96	60	242	94	60
7	272	60	270	99	60	263	97	60	254	93	60
8	286	60	285	100	60	276	97	60	265	93	60
9	296	60	298	101	60	288	97	60	278	94	60
10	308	60	307	99	60	298	97	60	287	93	60
11	317	60	316	100	60	306	97	60	295	93	60
12	325	60	324	100	60	317	98	60	304	93	60
13	334	60	338	101	60	328	98	60	313	94	60
17	356	60	358	101	60	347	98	60	329	93	60
21	375	60	382	102	60	369	98	60	349	93	59
25	400	60	403	101	60	392	98	60	367	92	58
29	415	60	416	100	60	408	98	59	377	91	58
33	425	60	433	102	60	416	98	59	388	92	58
37	431	60	439	102	60	432	100	59	402	93	58
41	441	59	445	101	60	437	99	59	404	92	58
45	457	59	461	101	59	448	98	59	414	91	58
49	462	59	467	101	59	457	99	59	419	91	58
53	469	59	473	101	59	463	99	59	425	91	57
57	475	59	479	101	59	469	99	59	429	90	57
61	479	59	482	101	58	472	99	59	433	90	56
65	479	57	488	102	57	477	100	59	437	91	56
69[a]	483	46	492	102	47	487	101	48	442	92	46
73	485	45	495	102	44	485	100	48	439	91	45
77	482	43	495	103	44	481	100	48	438	91	44
81	483	43	493	102	39	485	101	48	439	91	43
85	479	41	485	101	37	474	99	45	429	90	40
89	473	40	489	103	34	468	99	42	434	92	38
93	468	38	478	102	32	448	96	36	424	91	38
97	446	30	462	104	25	448	101	30	416	93	36
101	431	26	449	104	20	438	102	25	422	98	29
Mean for weeks											
1-13	257		256	100		250	97		242	94	
14-52	418		423	101		412	99		383	92	
53-101	472		482	102		469	99		431	91	

[a] Interim evaluation occurred at week 66.

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

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	1 mg/kg Av. Wt. (g)	1 mg/kg Wt. (% of controls)	1 mg/kg No. of Survivors	5 mg/kg Av. Wt. (g)	5 mg/kg Wt. (% of controls)	5 mg/kg No. of Survivors	25 mg/kg Av. Wt. (g)	25 mg/kg Wt. (% of controls)	25 mg/kg No. of Survivors
1	107	60	107	100	60	107	100	60	105	99	60
2	124	60	125	101	60	122	98	60	122	98	60
3	136	60	136	100	60	136	100	60	135	99	60
4	148	60	149	101	60	148	100	60	145	99	60
5	158	60	159	101	60	157	100	60	155	98	60
6	162	60	161	100	60	161	99	60	157	97	60
7	168	60	168	100	60	167	99	60	164	98	59
8	174	60	173	100	60	170	98	60	167	96	59
9	179	60	180	101	60	178	99	60	172	96	58
10	184	60	186	101	60	184	100	60	178	97	58
11	184	60	185	101	60	185	100	60	178	97	58
12	190	60	190	100	60	188	99	60	181	95	58
13	193	60	192	99	60	191	99	60	184	95	58
17	201	60	200	100	60	197	98	60	192	96	58
21	207	60	208	100	60	203	98	60	197	95	58
25	215	60	216	101	60	214	100	60	203	94	58
29	223	60	223	100	59	219	98	60	208	93	56
33	229	60	226	99	43	226	99	60	212	93	56
37	237	60	239	101	42	234	99	59	221	93	55
41	245	60	243	99	42	239	98	59	226	92	55
45	255	60	255	100	41	248	97	59	226	89	54
49	266	60	264	99	41	259	97	58	240	90	51
53	271	60	271	100	39	267	99	58	240	88	50
57	282	59	277	98	36	275	97	57	251	89	46
61	288	59	282	98	34	282	98	56	255	89	46
65	295	58	288	98	34	291	99	56	264	90	46
69[a]	306	46	298	98	31	300	98	44	267	87	35
73	313	46	300	96	31	306	98	44	266	85	31
77	318	46	306	96	29	311	98	44	271	85	30
81	320	46	315	99	26	312	98	41	278	87	30
85	328	43	308	94	23	316	96	41	280	85	28
89	332	41	306	92	22	314	95	40	275	83	25
93	335	40	321	96	17	315	94	35	274	82	24
97	329	36	323	98	17	312	95	33	272	83	22
101	335	34	325	97	17	314	94	29	270	81	22
Mean for weeks											
1-13	162		162	100		161	99		157	97	
14-52	231		230	100		227	98		214	93	
53-101	312		302	97		301	96		266	85	

[a] Interim evaluation occurred at week 66. Due to mortality involving the flooding incident at week 30, no females receiving 1 mg/kg were included in the interim evaluation.

Pathology and Statistical Analysis

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the pituitary gland and incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analysis of primary neoplasms that occurred with 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.

Pituitary Gland: The incidences of adenoma of the pituitary gland pars distalis decreased with increasing dose in both male and female rats; however, this trend was only significant in males (males: vehicle control, 19/49; 1 mg/kg, 17/49; 5 mg/kg, 13/50; 25 mg/kg, 10/50; females: 20/50, 13/60, 14/50, 10/50; Tables A3 and B3). The incidences of pituitary gland pars distalis adenoma in 25 mg/kg males and all groups of dosed females were below those observed in historical control data from recent NTP 2-year gavage studies. In general, the incidences of hyperplasia were not significantly different from those in the control groups (Tables A5 and B5).

Mononuclear Cell Leukemia: The incidences of mononuclear cell leukemia in 25 mg/kg males and females were significantly lower than those of the control groups (Tables 8, A3, and B3). The incidence of mononuclear cell leukemia in females receiving 25 mg/kg was well below the historical control range observed in recent 2-year gavage studies (Tables 8 and B4b).

Table 8
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
Mononuclear Cell Leukemia[a]				
Overall rate[b]	33/50 (66%)	21/50 (42%)	26/50 (52%)	24/50 (48%)
Adjusted rate[c]	86.0%	73.3%	66.5%	59.3%
Terminal rate[d]	15/20 (75%)	8/14 (57%)	10/22 (45%)	12/28 (43%)
First incidence (days)	443	533	463	504
Life table test[e]	P=0.034N	P=0.240N	P=0.139N	P=0.017N
Female				
Mononuclear Cell Leukemia[f]				
Overall rate	20/50 (40%)	6/60 (10%)	13/50 (26%)	4/50 (8%)
Adjusted rate	47.7%	26.9%	38.8%	13.9%
Terminal rate	13/34 (38%)	2/17 (12%)	7/26 (27%)	2/22 (9%)
First incidence (days)	374	519	555	392
Life table test	P=0.022N	P=0.138N	P=0.307N	P=0.011N

[a] Historical incidence for 2-year NTP water gavage studies with vehicle control groups (mean ± standard deviation): 173/367 (47.1% ± 9.2%); range 34%-56%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the control and that dosed group. The life table test considers neoplasms in animals dying prior to the terminal kill as (directly or indirectly) the cause of death. A negative trend or lower incidence in a dosed group is indicated by N.
[f] Historical incidence: 99/368 (26.9% ± 7.6%); range 16%-40%

MICE

16-DAY STUDY

One male and two females receiving 1,800 mg/kg and one female receiving 150 mg/kg died during the study (Table 9). The final mean body weights and body weight gains of dosed mice were similar to those of the control groups. Clinical findings related to scopolamine administration included bilateral pupillary dilation and squinting in all dosed males and females.

The absolute organ weights of dosed males were similar to those of the control group (Table F4). The relative liver weights of males receiving 1,800 mg/kg and of females in all dosed groups were significantly greater than those of the control group. There were no significant incidences of treatment-related gross or microscopic lesions.

Based on mortality among 1,800 mg/kg males and females, doses selected for the 14-week study were 15, 45, 135, 400 and 1,200 mg/kg.

TABLE 9
Survival and Body Weights of Mice in the 16-Day Gavage Study of Scopolamine Hydrobromide Trihydrate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	20.2 ± 0.5	22.4 ± 0.2	2.2 ± 0.5	
150	5/5	20.8 ± 0.4	22.6 ± 0.5	1.8 ± 0.6	101
250	5/5	20.4 ± 0.8	21.6 ± 0.6	1.2 ± 0.5	96
450	5/5	20.6 ± 0.5	22.6 ± 0.7	2.0 ± 0.6	101
900	5/5	20.6 ± 0.2	22.0 ± 0.5	1.4 ± 0.4	98
1,800	4/5[c]	21.2 ± 0.6	22.8 ± 0.9	1.3 ± 0.3	102
Female					
0	5/5	18.2 ± 0.4	19.8 ± 0.6	1.6 ± 0.5	
150	4/5[c]	18.6 ± 0.2	19.0 ± 0.4	0.3 ± 0.3	96
250	5/5	18.0 ± 0.3	19.2 ± 0.2	1.2 ± 0.4	97
450	5/5	18.0 ± 0.6	18.8 ± 0.4	0.8 ± 0.4	95
900	5/5	18.0 ± 0.6	18.8 ± 0.5	0.8 ± 0.5	95
1,800	3/5[d]	18.2 ± 0.5	18.3 ± 0.7	0.0 ± 0.0	93

[a] Number of animals surviving/number initially in group. Subsequent calculations are based on animals surviving to the end of the study.
[b] Weights and weight changes are given as mean ± standard error. Differences from the control are not significant by Williams' or Dunnett's test.
[c] Day of death: 4
[d] Day of death: 4, 4

14-WEEK STUDY

One male receiving 135 mg/kg and two males and one female receiving 1,200 mg/kg died during the study (Table 10). The final mean body weights and mean body weight gains of all dosed male groups and females receiving 45 mg/kg and above were significantly lower than those of the control groups. Clinical observations included bilateral pupillary dilation, hyperactivity, and hypoactivity.

The hematology data for mice in the 14-week study are listed in Table G3. A minimal to mild mature neutrophilia, similar to that which occurred in the 14-week rat study, occurred in male mice receiving 45 mg/kg or higher. As with the rat study, there was no microscopic evidence of inflammation that could account for the neutrophilia. Mechanisms that could be considered include: alterations in granulopoiesis and/or rate of release from the bone marrow, shifts in the distribution of neutrophils between the marginal and circulating vascular pools, or increases in the intravascular neutrophil life span.

The estrous cycle length of 1,200 mg/kg females was significantly greater than that in the control group (Table H2). Sperm morphology parameters in dosed males were similar to those in the control group.

There were no significant differences in organ weights (Table F5) or incidences of treatment-related gross or microscopic lesions.

Dose Selection Rationale: Based on lower survival in 1,200 mg/kg mice and lower mean body weights of mice exposed to 45, 135, 400, and 1,200 mg/kg, doses selected for use in the 2-year study were 1, 5, and 25 mg/kg.

TABLE 10
Survival and Body Weights of Mice in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	23.8 ± 0.4	32.7 ± 1.0	8.9 ± 0.8	
15	10/10	24.6 ± 0.3	29.1 ± 0.4**	4.5 ± 0.5**	89
45	10/10	24.2 ± 0.3	28.8 ± 0.6**	4.6 ± 0.6**	88
135	9/10[c]	24.3 ± 0.4	29.3 ± 0.6**	4.9 ± 0.6**	89
400	10/10	24.4 ± 0.4	28.7 ± 0.8**	4.3 ± 0.8**	88
1,200	8/10[d]	24.7 ± 0.3	28.9 ± 0.6**	4.2 ± 0.6**	88
Female					
0	10/10	19.2 ± 0.2	28.0 ± 0.5	8.8 ± 0.5	
15	10/10	18.9 ± 0.5	26.9 ± 0.4	8.0 ± 0.4	96
45	10/10	19.7 ± 0.2	26.5 ± 0.3*	6.8 ± 0.4**	95
135	10/10	19.5 ± 0.5	26.1 ± 0.4**	6.6 ± 0.6**	93
400	10/10	19.4 ± 0.3	26.2 ± 0.5**	6.8 ± 0.3**	93
1,200	9/10[e]	19.2 ± 0.2	25.5 ± 0.4**	6.4 ± 0.4**	91

* 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/number initially in group. Subsequent calculations are based on animals surviving to the end of the study.
[b] Weights and weight changes are given as mean ± standard error.
[c] Week of death: 10
[d] Week of death: 10, 12
[e] Week of death: 1

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 11 and in the Kaplan-Meier survival curves (Figure 3). Survival of dosed male and females was similar to that of the controls.

Body Weights, Clinical Findings, and Ophthalmic Examination Findings

The mean body weights of males and females receiving 1 mg/kg were similar to those of the control groups throughout the study (Figure 4; Tables 12 and 13). The mean body weights of males and females receiving 5 mg/kg were slightly lower than those of the control groups. The mean body weights of males and females receiving 25 mg/kg were lower than those of the control groups after week 13. The final mean body weights of males and females receiving 25 mg/kg were 19% (males) and 16% (females) lower than those of the control groups. Clinical findings included bilateral pupillary dilation in all dosed male and female groups. Ophthalmic examinations resulted in no significant findings.

TABLE 11
Survival of Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
Animals initially in study	70	70	70	70
15-Month interim evaluation[a,b]	20	20	20	20
Accidental deaths[a]	0	0	2	2
Moribund	4	7	4	7
Natural deaths	6	4	5	2
Animals surviving to study termination	40	39	39	39
Percent probability of survival at the end of study[c]	81	79	82	83
Mean survival (days)[d]	632	635	614	622
Survival analysis[e]	P=0.934N	P=0.992	P=1.000N	P=1.000N
Female				
Animals initially in study	70	70	70	70
15-Month interim evaluation[a,b]	19	20	20	19
Accidental deaths[a]	2	0	1	0
Moribund	9	11	7	7
Natural deaths	7	3	5	6
Animals surviving to study termination	33	36	37	38
Percent probability of survival at the end of study	67	73	77	76
Mean survival (days)	617	624	614	624
Survival analysis	P=0.775N	P=0.835N	P=0.571N	P=0.656

[a] Censored from survival analyses
[b] Includes 10 animals per group that received ophthalmic examinations only
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[e] 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 dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

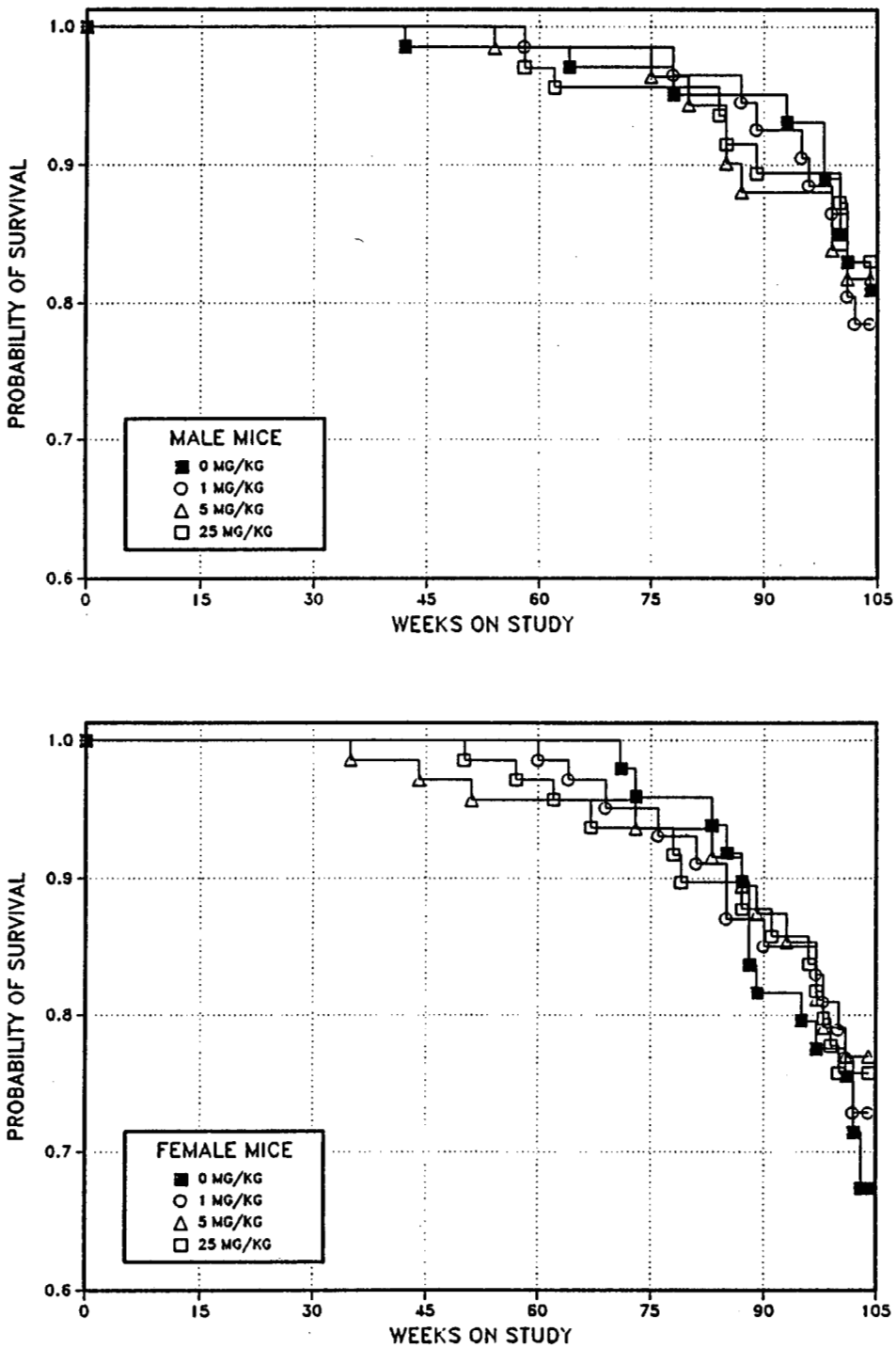


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Scopolamine Hydrobromide Trihydrate in Water by Gavage for 2 Years

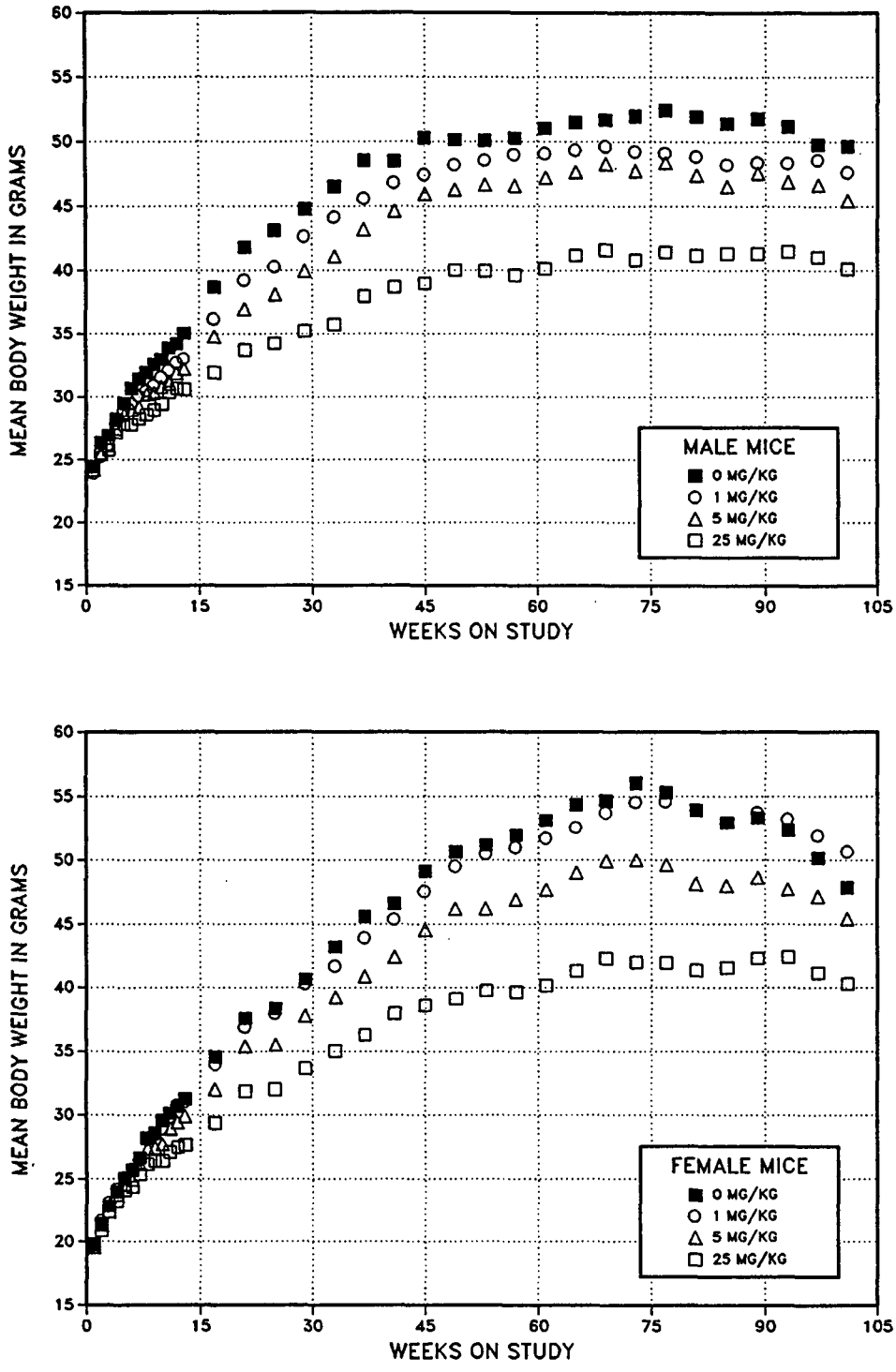


FIGURE 4
Growth Curves for Male and Female Mice Administered Scopolamine Hydrobromide Trihydrate in Water by Gavage for 2 Years

TABLE 12
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	1 mg/kg Av. Wt. (g)	1 mg/kg Wt. (% of controls)	1 mg/kg No. of Survivors	5 mg/kg Av. Wt. (g)	5 mg/kg Wt. (% of controls)	5 mg/kg No. of Survivors	25 mg/kg Av. Wt. (g)	25 mg/kg Wt. (% of controls)	25 mg/kg No. of Survivors
1	24.3	70	24.1	99	70	24.2	100	70	24.1	99	70
2	26.1	70	25.4	97	70	25.5	98	70	25.4	97	70
3	26.6	70	26.1	98	70	26.2	99	70	25.7	97	70
4	28.0	70	27.9	100	70	27.5	98	70	27.0	96	70
5	29.2	70	28.8	99	70	28.6	98	70	27.8	95	70
6	30.2	70	29.5	98	70	29.1	96	70	27.8	92	70
7	30.9	70	30.3	98	70	29.5	96	70	28.2	91	70
8	31.4	70	30.8	98	70	30.4	97	69	28.5	91	70
9	31.9	70	31.1	98	70	30.3	95	69	28.7	90	70
10	32.5	70	31.8	98	70	30.9	95	69	29.2	90	70
11	33.4	70	32.5	97	70	31.3	94	69	30.1	90	70
12	33.7	70	32.9	98	70	32.0	95	69	30.5	91	70
13	34.5	70	33.2	96	70	32.4	94	69	30.5	88	70
17	38.0	70	36.5	96	70	34.9	92	69	31.9	84	70
21	40.9	70	39.5	97	70	37.2	91	68	33.4	82	70
25	42.1	70	40.7	97	70	38.5	91	68	34.0	81	70
29	43.8	70	43.0	98	70	40.3	92	68	34.9	80	70
33	45.5	70	44.8	99	70	41.6	91	68	35.6	78	70
37	47.9	70	46.0	96	70	43.9	92	68	37.6	79	70
41	47.8	70	47.2	99	70	45.1	94	68	38.3	80	70
45	49.7	69	47.4	95	70	46.3	93	68	38.9	78	69
49	49.7	69	48.7	98	70	46.5	94	68	39.7	80	69
53	49.7	69	48.7	98	70	47.0	95	68	39.8	80	69
57	49.8	69	49.3	99	70	7.2	95	67	39.1	79	69
61	50.5	69	49.6	98	69	47.8	95	67	39.8	79	67
65	50.9	67	49.7	98	69	48.1	95	67	40.8	80	66
69[a]	51.7	48	49.6	96	49	48.3	93	47	41.6	81	46
73	52.0	48	49.2	95	49	47.8	92	47	40.8	79	46
77	52.4	48	49.1	94	49	48.4	92	46	41.4	79	46
81	51.9	47	48.8	94	48	47.4	91	45	41.1	79	46
85	51.4	47	48.2	94	48	46.5	91	44	41.3	80	45
89	51.8	47	48.4	93	46	47.6	92	42	41.3	80	44
93	51.2	46	48.4	95	46	46.9	92	42	41.5	81	42
97	49.8	46	48.6	98	44	46.7	94	42	41.0	82	42
101	49.7	42	47.6	96	42	45.5	92	40	40.1	81	40
Mean for weeks											
1-13	30.2		29.6	98		29.1	96		28.0	93	
14-52	45.0		43.8	97		41.6	92		36.0	80	
53-101	51.0		48.9	96		47.3	93		40.7	80	

[a] Interim evaluation occurred at week 66. Includes 10 animals per group that received ophthalmic examinations only.

TABLE 13
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

Weeks on Study	Vehicle Control		1 mg/kg			5 mg/kg			25 mg/kg		
	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	19.8	70	19.8	100	70	19.6	99	70	19.7	100	70
2	21.4	69	21.7	101	70	21.3	100	70	20.9	98	70
3	22.6	69	23.1	102	70	22.9	101	70	22.4	99	70
4	23.9	69	24.1	101	70	23.8	100	70	23.2	97	70
5	25.0	69	25.1	100	70	24.7	99	70	24.1	96	70
6	25.6	69	25.8	101	70	25.1	98	70[b]	24.4	95	70
7	26.6	69	26.4	99	70	26.2	99	70	25.3	95	70
8	28.2	69	28.0	99	70	27.4	97	70	26.2	93	70
9	28.7	69	28.4	99	70	27.5	96	70	26.3	92	70
10	29.6	69	28.9	98	70	27.8	94	70	26.5	90	70
11	30.1	69	29.8	99	70	28.9	96	70	27.1	90	70
12	30.7	69	30.6	100	70	29.4	96	70	27.6	90	70
13	31.2	69	30.9	99	70	29.6	95	70	27.6	89	70
17	34.8	69	33.9	97	70	32.0	92	70	29.3	84	70
21	37.7	69	36.8	98	70	35.4	94	70	31.8	84	70
25	38.7	69	37.9	98	70	35.6	92	70	32.1	83	70
29	41.0	69	40.3	98	70	37.9	92	70	33.6	82	70
33	43.5	69	41.8	96	70	39.2	90	70	35.1	81	70
37	45.8	69	43.9	96	70	41.0	90	69	36.2	78	70
41	47.0	69	45.4	97	70	42.4	90	69	37.9	81	70
45	49.5	69	47.6	96	70	44.5	90	68	38.5	78	70
49	51.0	69	49.6	97	70	46.1	90	68	39.1	77	70
53	51.4	69	50.4	98	70	46.4	90	67	39.7	77	69
57	52.0	68	51.1	98	70	46.9	90	66	39.5	76	69
61	53.0	68	51.6	97	69	47.8	90	66	40.0	76	68
65	54.0	68	52.4	97	68	48.9	91	66	41.1	76	67
69[a]	54.7	49	53.7	98	48	49.9	91	46	42.3	77	47
73	56.0	48	54.5	97	47	50.0	89	45	42.0	75	47
77	55.3	47	54.6	99	46	49.6	90	45	42.0	76	47
81	53.9	47	53.9	100	45	48.2	89	45	41.4	77	45
85	52.9	46	52.9	100	44	48.0	91	44	41.6	79	45
89	53.3	40	53.7	101	43	48.6	91	42	42.3	79	44
93	52.4	40	53.2	102	42	47.7	91	41	42.4	81	43
97	50.2	39	51.9	103	41	47.2	94	40	41.1	82	41
101	47.9	38	50.7	106	38	45.4	95	38	40.3	84	38
Mean for weeks											
1-13	26.4		26.4	100		25.7	97		24.7	94	
14-52	43.2		41.9	97		39.3	91		34.8	81	
53-101	52.8		52.7	100		48.0	91		41.2	78	

[a] Interim evaluation occurred at week 66. Includes 10 animals per group that received ophthalmic examinations only.
[b] Number of animals weighed for this week was less than the number of animals surviving

Hematology

The hematology data for mice at the 15-month interim evaluation in the 2-year study are listed in Table G4. Hematocrit level, hemoglobin concentration, and erythrocyte count in 25 mg/kg female mice were slightly lower than those in the control group. This result would be consistent with development of a minimal normocytic, normochromic nonresponsive anemia. The anemia would be consistent with the lower body weights exhibited by these animals and would be presumed to be related to a decreased nutritional status. The mouse hematology results differ from those which occurred in the rat study. It should be noted that all erythron changes, in both the rat and mouse studies, were minimal and that hemoconcentration related to dehydration could mask a minimal anemia.

Pathology and Statistical Analysis

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the liver and other organs. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analysis of primary neoplasms that occurred with 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: The incidences of hepatocellular adenoma in 5 mg/kg males and 25 mg/kg males and females were significantly lower than those of the control groups (Tables 14, C3, and D3). The incidence of hepatocellular carcinoma in 1 mg/kg males was significantly greater than that in the control group. The combined incidences of hepatocellular neoplasms followed a significant negative trend in males and females. A hepatoblastoma occurred in one 1 mg/kg male. The combined incidences of hepatocellular neoplasms in control males and females, 1 mg/kg male mice, and all female dosed groups exceeded the range observed in control mice in historical NTP 2-year gavage studies (Tables 14, C4a, and D4a). The combined incidences of neoplasms in 5 and 25 mg/kg males were within the NTP historical control range.

The incidences of clear cell foci and eosinophilic foci in dosed male groups were significantly lower than those of the control group, and decreased with increasing dose (Tables 14 and C5). The incidence of eosinophilic focus in 25 mg/kg females was significantly lower than that in the control group (Tables 14 and D5).

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Clear Cell Focus[a]	1	1	1	0
Eosinophilic Focus	1	2	1	0
Mixed Cell Focus	1	0	2	0
Hepatocellular Adenoma	1	2	1	0
Hepatocellular Carcinoma	0	0	0	1
2-Year Study				
Number Examined Microscopically	50	50	50	50
Basophilic Focus	3	4	3	0
Clear Cell Focus	12	4*	2**	0**
Eosinophilic Focus	21	12*	7**	2**
Mixed Cell Focus	5	7	7	1
Hepatocellular Adenoma	26	22	9**	8**
Hepatocellular Carcinoma	6	15*	6	7
Hepatocellular Adenoma or Carcinoma[b]				
Overall rate[c]	30/50 (60%)	33/50 (66%)	14/50 (28%)	15/50 (30%)
Adjusted rate[d]	65.2%	67.3%	32.5%	35.3%
Terminal rate[e]	24/40 (60%)	23/39 (59%)	10/39 (26%)	12/39 (31%)
First incidence (days)	680	405	594	587
Logistic regression test[f]	P=0.001N	P=0.348	P=0.002N	P=0.004N

(continued)

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Female				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Basophilic Focus	0	0	1	0
Mixed Cell Focus	1	1	0	0
Hepatocellular Adenoma	1	0	0	0
2-Year Study				
Number Examined Microscopically	51	50	50	51
Basophilic Focus	1	2	3	3
Clear cell Focus	0	1	0	0
Eosinophilic Focus	17	10	13	9*
Mixed cell Focus	6	6	3	3
Hepatocellular Adenoma	15	18	9	6*
Hepatocellular Carcinoma	8	6	8	4
Hepatocellular Adenoma or Carcinoma[g]				
Overall rate	22/51 (43%)	21/50 (42%)	16/50 (32%)	9/51 (18%)
Adjusted rate	57.1%	55.0%	37.0%	23.1%
Terminal rate	17/33 (52%)	19/36 (53%)	10/37 (27%)	8/38 (21%)
First incidence (days)	594	676	578	694
Logistic regression test	P=0.002N	P=0.466N	P=0.165N	P=0.003N

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Historical incidence for 2-year NTP water gavage studies with vehicle control groups (mean ± standard deviation): 74/315 (23.5% ± 7.2%); range 14%-36%
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the control and that dosed group. The logistic regression test regards neoplasms occurring in animals prior to the terminal kill as nonfatal. A negative trend or lower incidence in a dosed group is indicated by N.
[g] Historical incidence: 21/315 (6.7% ± 4.2%); range 2%-12%

Other Organs: The incidences of many spontaneously occurring nonneoplastic lesions were significantly lower in dosed male and female mice than those in the control groups and usually decreased with increasing dose (Tables 15, C5, and D5). At 15 months, the incidence of kidney nephropathy in 25 mg/kg males was significantly lower than that in the control group. At 2 years, the incidences of kidney nephropathy in 25 mg/kg males and females were significantly lower than the incidences in the control groups. Compared to the control group, the incidences of hyperplasia of the pancreatic islets in 5 and 25 mg/kg males were significantly lower. The incidence of alveolar epithelial hyperplasia in 25 mg/kg males was significantly lower than that of the control group. The incidence of bone marrow myelofibrosis in 25 mg/kg females was significantly lower than that in the control group. Incidences of hyperplasia of the pituitary gland pars distalis in 5 and 25 mg/kg females and cystic hyperplasia of the uterus and hematopoietic cell proliferation in the spleen in 25 mg/kg females were also significantly lower than those in the control group. The decreased incidences of these spontaneous lesions were most likely a result of lower body weights in dosed versus control animals.

TABLE 15
Incidences of Selected Nonneoplastic Lesions in Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
15-Month Interim Evaluation				
Kidney[a]	10	10	10	10
Nephropathy[b]	10 (1.2)[c]	9 (1.0)	10 (1.0)	6* (1.0)
Pancreatic Islets	10	10	10	10
Hyperplasia	3 (1.3)	7 (1.4)	4 (1.5)	0
2-Year Study				
Kidney	50	50	50	50
Nephropathy	48 (1.0)	46 (1.3)	42 (1.1)	37** (1.1)
Lung	50	50	50	50
Alveolar Epithelial Hyperplasia	8 (1.5)	3 (2.0)	2 (1.0)	1* (1.0)
Pancreatic Islets	50	50	50	50
Hyperplasia	29 (1.6)	23 (1.4)	8** (1.3)	2** (2.5)

(continued)

TABLE 15
Incidences of Selected Nonneoplastic Lesions in Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Female				
15-Month Interim Evaluation				
Bone marrow	10	10	10	10
Myelofibrosis	1 (1.0)	2 (1.5)	0	0
Kidney	10	10	10	10
Nephropathy	5 (1.0)	3 (1.0)	1 (1.0)	2 (1.0)
Pituitary Gland (Pars Distalis)	10	10	10	10
Hyperplasia	3 (1.0)	0	0	1 (1.0)
Uterus	10	10	10	10
Cystic Hyperplasia	5 (2.2)	8 (1.4)	4 (2.0)	4 (1.5)
2-Year Study				
Bone Marrow	51	50	50	51
Myelofibrosis	22 (1.2)	21 (1.1)	15 (1.3)	13* (1.2)
Kidney	51	50	50	51
Nephropathy	23 (1.0)	21 (1.0)	26 (1.0)	10** (1.1)
Pituitary Gland (Pars Distalis)	50	47	47	46
Hyperplasia	24 (1.8)	15 (1.5)	11** (1.3)	13* (1.8)
Spleen	51	50	50	51
Hematopoietic Cell Proliferation	17 (1.9)	11 (2.3)	17 (1.9)	7* (2.3)
Uterus	51	50	50	51
Cystic Hyperplasia	38 (2.3)	29* (2.1)	30 (1.9)	23** (1.5)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of mice with organ/tissue examined microscopically
[b] Number of mice with lesion
[c] Average severity grade of lesions in affected animals (1=minimal; 2=mild; 3=moderate; 4=marked)

GENETIC TOXICOLOGY

Scopolamine hydrobromide trihydrate (100 to 10,000 μg/plate) did not induce mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537, with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1). In cytogenetic tests with cultured Chinese hamster ovary cells, no convincing induction of sister chromatid exchanges was noted with scopolamine hydrobromide trihydrate doses up to 500 μg/mL without S9 or 5,000 μg/mL with S9 (Table E2). Results from the first two trials conducted with S9, which appeared to clearly demonstrate a significant increase in sister chromatid exchanges, were called into question by the observation of a pH shift in the culture medium produced by the high doses (2,000 μg/mL and higher) of scopolamine hydrobromide trihydrate, which coincided with the increases in sister chromatid exchanges. Therefore, a third trial was conducted, in which the pH of the culture medium was adjusted with *N*-(2-hydroxymethyl)piperazine-*N*′-(2-ethanesulfonic acid) (HEPES) buffer. Results of this third trial were negative and the overall assay results were also considered to be negative. The increases in sister chromatid exchanges noted in the presence of S9 were attributed to the alteration in pH produced by high concentrations of scopolamine hydrobromide trihydrate. No induction of chromosomal aberrations was observed in cultured Chinese hamster ovary cells treated with scopolamine hydrobromide trihydrate without S9, but with S9, even in the presence of HEPES buffer to maintain optimum pH, increases in the percentage of cells with aberrations were noted in each of two trials, at the highest dose tested (5,000 μg/mL) (Table E3).

Despite the evidence for induction of chromosomal damage in cultured Chinese hamster ovary cells *in vitro*, no increase in the frequency of micronucleated normochromatic erythrocytes was noted in peripheral blood samples obtained from male and female mice at the end of the 14-week gavage studies of scopolamine hydrobromide trihydrate (Table E4).

DISCUSSION AND CONCLUSIONS

Scopolamine hydrobromide trihydrate, a white crystalline or granular powder, is a solanaceous alkaloid derived from the Solanaceae family (Brown, 1990). Its major use is in transdermal patches for the treatment of motion sickness. Scopolamine hydrobromide is an anticholinergic drug which is used for the treatment of various ailments including acute mania, diarrhea, gastric and duodenal ulcers, gastrointestinal spasm, excessive salivation and sweating, and infantile cerebral palsy. It is also used as a mydriatic and cycloplegic agent and as an over-the-counter sleeping aid.

Scopolamine hydrobromide trihydrate was nominated to the NTP for toxicology and carcinogenicity testing by the National Cancer Institute because of considerable human exposure resulting from its use as a prescription or over-the-counter drug and as a representative chemical from a class of alkaloids. Scopolamine hydrobromide trihydrate is a suspect carcinogen because it contains an aliphatic epoxide moiety, which may act as a biological alkylating agent. Toxicology and carcinogenicity studies were conducted by administering scopolamine hydrobromide trihydrate in distilled water by gavage once daily, 5 days per week, for 16 days, 14 weeks, or 2 years to male and female F344/N rats and B6C3F$_1$ mice. The gavage route of exposure was chosen because this route mimics oral exposure in humans, and because higher doses can be administered to the animal than can be achieved by the dosed feed route of administration.

The results of the 16-day and 14-week studies in rats suggest that male rats are less tolerant to scopolamine hydrobromide trihydrate than females. In the 16-day rat study, body weight depression was observed in males administered 300 mg/kg or greater; no significant body weight depression occurred in dosed females. In the 14-week study, final mean body weights of dosed males ranged from 11% to 19% less than the final mean body weight of the control group. In dosed female rats, final mean body weights ranged from 3% to 7% lower than the final mean body weight of the control group. In the 14-week study, survival of female rats was also higher than that of males. Early deaths of dosed males and females were caused by esophageal obstruction and concurrent tracheal obstruction, as indicated by the accumulation of feed at these sites. This obstruction was considered to be related to the inhibitory effect of scopolamine hydrobromide trihydrate on salivary gland secretions and on esophageal smooth muscle contractions (i.e. swallowing).

In mice, no clear effects were observed in body weights or survival of dosed male or female animals during the 16-day or the 14-week studies. The differences from controls of body weights in 1,200 mg/kg male and female mice in the 14-week study were similar (male: 12%; female: 9%). Similar numbers of chemical-related deaths were observed in males and females receiving 1,800 mg/kg scopolamine hydrobromide trihydrate in the 16-day study and in those receiving 1,200 mg/kg in the 14-week study.

The low absolute weights of various organs observed in rats and mice receiving scopolamine hydrobromide trihydrate in the 14-week studies were considered to be related to the body weight depressions observed in these dosed groups because the relative weights of these organs in dosed rats and mice were not significantly different from those of the controls. The bilateral pupillary dilation observed in the 16-day and 14-week studies in dosed rats and mice was a manifestation of the pharmacologic effect of scopolamine hydrobromide trihydrate.

The increases in hematocrit values and hemoglobin concentrations observed in dosed rats in the 14-week study were mild and could have been the result of dehydration, while the increases in segmented neutrophil counts observed in dosed rats could have been due to stress. These hematologic differences were probably secondary to the pharmacologic effects of this chemical.

No significant chemical-related lesions were observed in rats or mice in the 16-day and the 14-week studies.

Based on the mortality and lower body weights observed in the 14-week studies, the doses of scopolamine hydrobromide trihydrate selected for the 2-year studies were 1, 5, and 25 mg/kg for rats and mice.

In the 2-year rat study, survival of 1 and 25 mg/kg females was lower than that of controls. Survival of male and female mice receiving scopolamine hydrobromide trihydrate was not significantly different from that of the control groups. Mean body weights of 25 mg/kg male and female rats and mice and 5 mg/kg male and female mice were lower than those of the controls throughout the studies. Based on the lower body weights and poor survival at higher doses, the doses used in the 2-year studies were considered to be sufficiently high for determining the potential carcinogenicity of scopolamine hydrobromide trihydrate.

The therapeutic oral dose of scopolamine for humans is 0.6 mg (*Goodman and Gilman's*, 1985). Compared to the peak scopolamine plasma concentration observed in humans receiving an oral dose of 0.4 mg, the plasma concentrations of scopolamine hydrobromide trihydrate in rats from the 5 mg/kg group were 12 times greater and in the 25 mg/kg groups the concentrations were 24 to 56 times greater.

No increased incidences of neoplasms that could be attributed scopolamine hydrobromide trihydrate administration were observed in male or female rats.

Dose-related negative trends in the incidences of pituitary gland adenoma and mononuclear cell leukemia were observed in male and female rats. The incidences of these neoplasms in the 25 mg/kg groups were significantly lower than those in the control groups (pituitary gland adenoma: vehicle control, 19/49; 25 mg/kg, 10/50 [males]; 20/50, 10/50 [females]; mononuclear cell leukemia: 33/50, 24/50 [males]; 20/50, 4/50 [females]).

The influence of body weight on the incidence of these neoplasms has been reported by other researchers. Seilkop (1995) found a positive relationship between body weight and the incidence of pituitary gland neoplasms in male and female F344 rats. Body weight reduction, as a result of dietary restriction, also has been shown to decrease the incidence of mononuclear cell leukemia in F344 rats (Masoro, 1993). The decreased incidence of pituitary neoplasms may be associated with lower body weight gains. However, lower body weight cannot totally account for the decreased incidence of leukemia observed in female rats.

In the 2-year mouse study, no increased incidences of neoplasms could be attributed to scopolamine hydrobromide trihydrate administration in males or females. There was a dose-related negative trend in the incidences of hepatocellular neoplasms in both male and female mice.

Liver tumor incidences in male and female B6C3F$_1$ mice have been demonstrated to be correlated with body weight. Using NTP historical control data, Seilkop (1995) derived a logistic regression model for predicting liver tumor incidences based on survival and body weight at 1 year. Application of this model to the scopolamine hydrobromide trihydrate data is summarized in Table 16.

With the exception of 5 mg/kg male mice, the observed liver neoplasm incidences are very similar to what would be expected in control animals of equivalent body weight and survival. Thus, the decreased incidences of liver neoplasms in male and female mice are primarily a reflection of the reduced body weight in the dosed groups. In addition, the mean body weights of the control animals in this study were 25% to 30% higher than those of control animals in previous water gavage studies in the NTP historical control database. This observation may help explain the relatively high liver neoplasm incidences in control animals from this study compared with the NTP historical rates reported in this study.

No increased incidences of nonneoplastic lesions in male or female mice could be attributed to scopolamine hydrobromide trihydrate administration; however, there were dose-related negative trends in the incidences of clear cell and eosinophilic foci of

TABLE 16
Analysis of Liver Neoplasm Incidences Using the Seilkop (1995) Logistic Regression Model

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
n[a]	50	50	48	49
Mean 1-Year Body Weights (g)	50.0	48.6	46.7	39.9
Liver Neoplasm Incidence				
Observed	30 (60%)	33 (66%)	14 (29%)	15 (31%)
Predicted	65%	61%	54%	34%
Female				
n	50	50	47	50
Mean 1-Year Body Weights (g)	51.2	50.5	46.2	39.8
Liver Neoplasm Incidence				
Observed	22 (44%)	21 (42%)	16 (34%)	9 (18%)
Predicted	46%	44%	35%	22%

[a] Excludes animals dying prior to one year

the liver in dosed male groups, and a decreased incidence of eosinophilic foci in 25 mg/kg female mice. There were also decreased incidences of common spontaneously occurring lesions in male and female mice receiving scopolamine hydrobromide trihydrate. These included pancreatic islet hyperplasia (males), alveolar epithelial hyperplasia (males), kidney nephropathy, pituitary gland pars distalis hyperplasia (females), bone marrow myelofibrosis (females), uterine cystic hyperplasia, and hematopoietic cell proliferation in the spleen (females). Decreased incidences of these spontaneous lesions were most likely a result of lower body weights in dosed groups.

The results of the self-selection studies of Ross *et al.* (1983a,b) support the view that reduced body weight gains in rodents are associated with lower incidences of spontaneous disease. The body weights of mature rats correlated linearly with the incidence of spontaneous neoplasms. Those rats that grew rapidly developed anterior pituitary neoplasms more readily than slower growing rats. Tucker (1979) observed a decreased incidence of pituitary gland neoplasms with dietary restriction (20% less feed than *ad libitum* intake) and the associated body weight gain depression. Additionally, dietary restriction and associated body weight depression inhibits the development of a variety of neoplasms, including leukemia (Albanes, 1987; Weindruch and Walford, 1988; Boissonneult, 1991).

Chronic repeated administration of scopolamine hydrobromide trihydrate marginally affected performance by rats in three of the five neurobehavioral tests employed during this study. These results are the only observations documenting the effects of chronic scopolamine hydrobromide trihydrate exposure on rodent behavior.

Although hyperactivity occurred in 25 mg/kg rats from day 1 (females) and on day 180 (males), only the increased horizontal activity in females on treatment days 90, 180, and 360 was statistically significant. Scopolamine-induced hyperactivity (ambulation) after acute exposures in rats has been demonstrated by several investigators using lower doses (0.25 to 4.0 mg/kg) and different routes of administration (subcutaneous and intraperitoneal) (Reiter and McPhail, 1982; Sanberg *et al.*, 1987; Crofton *et al.*,

1991). Other investigators have demonstrated both scopolamine-induced increases (Bauer, 1984) and decreases (Horsburgh and Hughes, 1981) in vertical activity (rearings) following intraperitoneal exposure. There was a nonsignificant tendency for female rats receiving 5 and 25 mg/kg scopolamine hydrobromide trihydrate on days 90 through 360 to show an increased rearing response during this study. Reiter and McPhail (1982) describe a variety of operational factors which influence motor activity including the decreased tendency for scopolamine to induce hyperactivity as the environmental complexity (novel stimuli) is increased. This concept was supported by Renner *et al.* (1992), who noted decreased preferences for novelty by scopolamine-treated rats in an open field arena. MacMahon *et al.* (1981) concluded that scopolamine has adverse affects in rats by pairing treatments (unconditioned stimulus) with novel stimuli (conditioned stimulus). Their conclusion was based on observation that the conditioned stimulus was avoided during a free choice test.

The startle response to tactile stimulation was attenuated in female rats receiving 5 and 25 mg/kg scopolamine hydrobromide trihydrate. This effect occurred as an isolated incidence (90 day test interval) and could not be attributed to any effects on musculature (grip strength test). A depressed startle response could possibly be ascribed to reduced attention/vigilance, an effect sometimes associated with scopolamine exposures (Wesnes and Revell, 1984; Wesnes and Warburton, 1984; Lydon and Nakajima, 1992).

Although rats receiving 25 mg/kg scopolamine hydrobromide trihydrate on study days 180 through 720 tended to score lower passive avoidance latency scores, this effect was significant only on study day 180 in 25 mg/kg males. In rats, lower passive avoidance latency scores following acute scopolamine hydrobromide trihydrate treatment at lower doses (0.1 to 1.0 mg/kg) have been previously reported (Blozovski and Hennocq, 1982; Elrod and Buccafusco, 1988). These findings may be indicators of learning and memory deficits (Cabe and Eckerman, 1982). Scopolamine-treated humans (Drachman, 1978; Caine *et al.*, 1981) and other mammals including rodents (Lenègre *et al.*, 1988) are models for amnesia in the development of nootropic drugs. Nootropic drugs enhance memory and attenuate experimental amnesia (Lenègre *et al.*, 1988). There are reports that experimentally induced scopolamine deficits in learning and memory become more pronounced with age in humans (Flicker *et al.*, 1992; Molchan *et al.*, 1992). While our results at study day 720 suggest depressed latency scores at lower doses, they are not statistically significant.

These neurobehavioral findings do not support a robust scopolamine effect on passive avoidance responses. A possible explanation may involve an accommodation or adjustment of the nervous system to chronic repeated exposures. Tilson and Harry (1982) note that the Fischer rat strain tends to more efficiently acquire or learn avoidance behavior and is resistant to scopolamine-induced decrements in this behavior. It should also be noted that scopolamine affects both the peripheral and central nervous systems and that higher doses of the drug might induce conflicting results on the peripheral nervous system (Andrews *et al.*, 1994). In this regard this study is unique in that it uses chronic oral gavage exposure and comparatively high doses. The lack of significant clinical observations and the low scopolamine serum concentrations do not support the view that scopolamine-induced peripheral nervous system effects could have altered avoidance behavior. Finally, the absence of a scopolamine effect on pawlick latency suggests that scopolamine-induced analgesia could not have disrupted avoidance behavior by decreasing latency scores.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of scopolamine hydrobromide trihydrate in male or female F344/N rats or B6C3F$_1$ mice administered 1, 5, or 25 mg/kg.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

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

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	2	2	1	1
Moribund	23	30	20	17
Natural deaths	5	4	7	4
Survivors				
Terminal sacrifice	20	14	22	28
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Endocrine System				
Adrenal medulla	(10)	(10)	(10)	(10)
Pheochromocytoma benign				1 (10%)
Pituitary gland	(10)	(9)	(10)	(10)
Pars distalis, adenoma			1 (10%)	1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, adenoma				1 (10%)
Genital System				
Preputial gland	(10)	(10)	(9)	(10)
Adenoma			1 (11%)	
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	5 (50%)	6 (60%)	6 (60%)	6 (60%)
Interstitial cell, adenoma	4 (40%)	2 (20%)	3 (30%)	3 (30%)
Integumentary System				
Skin	(10)	(10)	(10)	(9)
Squamous cell papilloma				1 (11%)
Musculoskeletal System				
Bone	(10)	(10)	(10)	(10)
Osteosarcoma				1 (10%)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear	1 (10%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Intestine large, colon	(50)	(50)	(50)	(50)
Leiomyoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma	1 (2%)	1 (2%)		
Hepatocellular adenoma	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Mesentery	(7)	(13)	(22)	(14)
Carcinoma, metastatic, islets, pancreatic		1 (8%)		
Osteosarcoma, metastatic, uncertain primary site			1 (5%)	
Pancreas	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Acinus, adenoma	1 (2%)			
Salivary glands	(50)	(49)	(50)	(49)
Schwannoma malignant	1 (2%)			
Tongue		(1)		
Squamous cell papilloma		1 (100%)		
Tooth			(1)	(1)
Gingiva, squamous cell carcinoma			1 (100%)	1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma NOS			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign	8 (16%)	11 (22%)	9 (18%)	8 (16%)
Bilateral, pheochromocytoma benign	3 (6%)	2 (4%)	3 (6%)	1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	2 (4%)	1 (2%)	
Carcinoma		1 (2%)		
Parathyroid gland	(46)	(45)	(46)	(49)
Adenoma		1 (2%)		
Pituitary gland	(49)	(49)	(50)	(50)
Pars distalis, adenoma	19 (39%)	17 (35%)	13 (26%)	10 (20%)
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma			1 (2%)	
C-cell, adenoma	1 (2%)	4 (8%)	2 (4%)	1 (2%)
C-cell, carcinoma	1 (2%)		3 (6%)	
Follicular cell, adenoma	3 (6%)	2 (4%)	1 (2%)	
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Preputial gland	(50)	(50)	(49)	(50)
Adenoma	3 (6%)	1 (2%)	3 (6%)	2 (4%)
Carcinoma		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Bilateral, interstitial cell, adenoma	38 (76%)	30 (60%)	35 (70%)	41 (82%)
Interstitial cell, adenoma	5 (10%)	12 (24%)	11 (22%)	3 (6%)
Hematopoietic System				
Lymph node	(5)	(8)	(5)	(9)
Mediastinal, osteosarcoma, metastatic, uncertain primary site			1 (20%)	
Lymph node, mandibular	(50)	(49)	(50)	(49)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Fibroma		1 (2%)		
Hemangiosarcoma				1 (2%)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Thymus	(46)	(46)	(48)	(47)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Thymoma malignant				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Integumentary System				
Mammary gland	(48)	(48)	(49)	(49)
Fibroadenoma	3 (6%)	8 (17%)	3 (6%)	2 (4%)
Fibroadenoma, multiple				1 (2%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma				1 (2%)
Fibroma	4 (8%)	3 (6%)	3 (6%)	2 (4%)
Fibroma, multiple	1 (2%)			1 (2%)
Fibrous histiocytoma			1 (2%)	
Keratoacanthoma	3 (6%)	3 (6%)	3 (6%)	2 (4%)
Keratoacanthoma, multiple	1 (2%)			
Sarcoma	1 (2%)			
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma		3 (6%)		1 (2%)
Sebaceous gland, adenoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)	1 (2%)	1 (2%)	
Skeletal muscle	(1)	(1)	(1)	
Carcinoma, metastatic, islets, pancreatic		1 (100%)		
Osteosarcoma, metastatic, uncertain primary site			1 (100%)	
Sarcoma	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma NOS			1 (2%)	
Spinal cord	(9)	(7)	(6)	(5)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)	
Alveolar/bronchiolar carcinoma	1 (2%)			
Osteosarcoma, metastatic, bone	1 (2%)	1 (2%)		
Squamous cell carcinoma, metastatic, tooth				1 (2%)
Special Senses System				
Eye	(1)	(1)	(1)	(1)
Harderian gland	(1)		(1)	
Adenoma	1 (100%)			
Zymbal's gland		(2)	(2)	(2)
Carcinoma		2 (100%)	2 (100%)	2 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Fibroma		1 (2%)		
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Renal tubule, adenoma	1 (2%)			
Renal tubule, carcinoma	1 (2%)		1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Leukemia mononuclear	33 (66%)	21 (42%)	26 (52%)	24 (48%)
Mesothelioma NOS	1 (2%)	1 (2%)	4 (8%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	9	8	10	9
2-Year study	49	49	49	48
Total primary neoplasms				
15-Month interim evaluation	10	8	11	14
2-Year study	145	132	132	112
Total animals with benign neoplasms				
15-Month interim evaluation	9	8	10	9
2-Year study	48	49	48	48
Total benign neoplasms				
15-Month interim evaluation	9	8	11	13
2-Year study	101	104	91	80
Total animals with malignant neoplasms				
15-Month interim evaluation	1			1
2-Year study	38	27	30	28
Total malignant neoplasms				
15-Month interim evaluation	1			1
2-Year study	43	27	35	29
Total animals with metastatic neoplasms				
2-Year study	1	2	1	1
Total metastatic neoplasms				
2-Year study	1	3	10	1
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	6	3
Total uncertain neoplasms				
2-Year study	3	4	17	8

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

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

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

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 0 2	7 0 6	7 1 3	7 2 0	7 2 0	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	0 5 0	0 6 0	0 1 5	0 2 7	0 3 2	0 1 6	0 2 3	0 4 5	0 4 8	0 5 3	0 5 5	0 0 1	0 0 7	0 1 2	0 1 3	0 1 4	0 2 2	0 2 5	0 3 4	0 3 7	0 4 0	0 4 1	0 4 4	0 4 6	0 5 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																					X					1
Hepatocellular adenoma				X																						1
Mesentery	+		+		+										+											7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma											X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X			X		X											X				X	X				8
Bilateral, pheochromocytoma benign					X						X															3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X				X									X						3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Pars distalis, adenoma		X		X	X		X			X	X							X			X		X	X		19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										1
C-cell, carcinoma																								X		1
Follicular cell, adenoma																						X				3
Follicular cell, carcinoma																					X					1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	2 7 3	4 3 0	4 4 3	4 7 1	4 9 2	5 0 8	5 2 3	5 6 6	5 8 1	6 0 0	6 0 9	6 3 2	6 4 7	6 4 5	6 4 9	6 5 5	6 5 6	6 5 6	6 6 0	6 6 3	6 7 1	6 7 3	6 8 6	6 8 6	6 9 8	7 0 2
Carcass ID Number	0 3 3	0 4 9	0 3 8	0 3 1	0 2 4	0 5 8	0 2 9	0 2 0	0 0 6	0 1 7	0 2 8	0 4 7	0 1 0	0 4 2	0 4 2	0 4 8	0 4 3	0 3 0	0 3 0	0 5 4	0 5 7	0 1 8	0 1 9	0 0 4	0 3 9
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																						
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	X
Interstitial cell, adenoma													X													
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+							+				+				+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																					X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma														X		X			X							
Fibroma, multiple																		X								
Keratoacanthoma																										
Keratoacanthoma, multiple																										
Sarcoma												X														
Squamous cell carcinoma																										
Sebaceous gland, adenoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma												X														
Skeletal muscle																	+									
Sarcoma																	X									
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve										+		+				+							+		+	+
Spinal cord										+		+				+							+		+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																										X
Osteosarcoma, metastatic, bone												X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 0 2	7 0 6	7 1 3	7 2 0	7 2 0	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	0 5 0	0 6 0	0 1 5	0 2 7	0 3 2	0 1 6	0 2 3	0 4 5	0 4 8	0 5 3	0 5 5	0 0 1	0 0 7	0 1 2	0 1 3	0 1 4	0 2 2	0 2 5	0 3 4	0 3 7	0 4 0	0 4 1	0 4 4	0 4 6	0 4 9	0 5 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																	X						3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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		38
Interstitial cell, adenoma					X			X										X							X	5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+																									5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma	X												X													3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																X										4
Fibroma, multiple																										1
Keratoacanthoma			X			X											X									3
Keratoacanthoma, multiple											X															1
Sarcoma																										1
Squamous cell carcinoma											X															1
Sebaceous gland, adenoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve		+		+	+																					9
Spinal cord		+		+	+																					9
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	2 7 3	4 3 0	4 4 3	4 7 1	4 9 2	5 0 8	5 2 3	5 6 6	5 8 1	6 0 0	6 3 9	6 4 2	6 4 5	6 4 9	6 5 5	6 5 6	6 5 6	6 6 0	6 6 3	6 7 1	6 7 3	6 8 6	6 8 6	6 9 8	7 0 2
Carcass ID Number	0 3 3	0 4 9	0 3 8	0 3 1	0 2 4	0 5 8	0 2 9	0 2 0	0 0 6	0 1 7	0 2 8	0 4 7	0 1 0	0 0 2	0 4 2	0 0 8	0 4 3	0 3 0	0 0 9	0 5 4	0 5 7	0 1 8	0 1 9	0 0 4	0 3 9
Special Senses System																									
Ear																			+						
Eye																									
Harderian gland																			+						
Adenoma																			X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X		X		X	X	X				X	X		X	X	X		X	X	X	X
Mesothelioma NOS																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 0 2	7 0 6	7 1 3	7 2 0	7 2 0	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	0 5 0	0 6 0	0 1 5	0 2 7	0 3 2	0 1 6	0 2 3	0 4 5	0 4 8	0 5 3	0 5 5	0 0 1	0 0 7	0 1 2	1 1 3	1 1 4	1 2 2	2 2 5	2 3 4	3 3 7	4 4 0	4 4 1	4 4 4	4 4 6	5 5 9	Total Tissues/ Tumors	
Special Senses System																										
Ear		+							+																3	
Eye			+																						1	
Harderian gland																									1	
Adenoma																									1	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Renal tubule, adenoma											X														1	
Renal tubule, carcinoma												X													1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear	X			X	X	X	X		X	X	X		X			X	X	X	X	X		X	X	X	33	
Mesothelioma NOS																									1	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	6 7 8	6 7 8	6 7 8	6 8 8	6 8 8	7 0 2	7 0 2	7 0 2	7 0 6	7 1 3	7 1 5	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	0 6 2	0 9 0	1 0 6	1 0 2	1 1 1	0 8 2	0 9 2	0 9 3	1 2 0	1 1 8	0 7 0	0 6 1	0 6 9	0 7 2	0 7 3	0 7 6	0 8 3	0 8 7	0 9 7	1 0 0	1 0 1	1 0 4	1 1 0	1 1 2	1 1 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma												X														1
Hepatocellular adenoma				X																						2
Mesentery	+		+			+			+	+			+		+	+			+					+		13
Carcinoma, metastatic, islets, pancreatic																								X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue		+																								1
Squamous cell papilloma		X																								1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign					X	X							X	X		X	X	X								11
Bilateral, pheochromocytoma benign											X										X					2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																								X	2
Carcinoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	M	45
Adenoma														X												1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X	X	X		X		X	X													X	X		17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X																		X						4
Follicular cell, adenoma	X																						X			2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	2 8 1	4 0 4	4 4 6	4 9 2	5 0 4	5 0 4	5 3 3	5 3 3	5 4 0	5 6 0	5 6 1	5 8 3	5 8 5	5 8 9	5 9 2	6 1 2	6 3 1	6 3 2	6 5 6	6 5 8	6 6 0	6 6 0	6 6 6	6 6 9	6 7 1
Carcass ID Number	0 6 3	0 9 1	1 1 9	0 6 7	0 6 5	0 8 6	0 9 8	1 1 7	0 6 6	0 9 5	0 7 8	0 9 6	0 7 5	0 8 0	0 7 7	0 9 4	1 0 7	0 7 9	1 1 4	1 0 9	1 0 3	1 0 5	0 8 5	1 1 5	0 8 8
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X			X	X			X	X	X	X	X	X	X				X	X	
Interstitial cell, adenoma		X						X				X										X			X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node														+			+								+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma		X			X	X			X																
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X			X			
Keratoacanthoma																									
Squamous cell papilloma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																						X			
Skeletal muscle																									
Carcinoma, metastatic, islets, pancreatic																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																					+				
Spinal cord																					+				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	6 7 8	6 7 8	6 7 8	6 8 8	6 8 8	7 0 2	7 0 2	7 0 2	7 0 6	7 1 3	7 1 5	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	0 6 2	0 9 0	1 0 6	1 0 2	1 1 1	0 8 2	0 9 2	0 9 3	1 2 0	1 1 8	0 7 0	0 6 1	0 6 9	0 7 2	0 7 3	0 7 6	0 8 3	0 8 7	0 9 7	0 9 0	1 0 1	1 0 4	1 1 0	1 1 2	1 1 3	Total Tissues/ Tumors
Genital System (continued)																										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X			X	X	X	X			X	X	X	X		X	X	X	X		X	X			X	30
Interstitial cell, adenoma	X			X					X						X					X			X	X		12
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+		+	+								+												8
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma		X																								1
Thymus	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma								X				X			X					X						8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																		X								3
Keratoacanthoma							X								X					X						3
Squamous cell papilloma																				X			X			3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																								+		1
Carcinoma, metastatic, islets, pancreatic																								X		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve		+	+			+			+	+				+												7
Spinal cord		+	+			+			+	+				+												7
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	2 8 1	4 0 4	4 4 6	4 9 2	5 0 4	5 0 4	5 3 3	5 3 3	5 4 0	5 6 0	5 6 1	5 8 3	5 8 5	5 8 9	5 9 2	6 1 2	6 3 1	6 3 2	6 5 6	6 5 8	6 6 0	6 6 0	6 6 6	6 7 1
Carcass ID Number	0 6 3	0 9 1	1 1 9	0 6 7	0 6 5	0 8 6	0 9 8	1 1 7	0 6 6	0 9 5	0 7 8	0 9 6	0 7 5	0 8 0	0 7 7	0 9 4	1 0 7	0 7 9	1 1 4	1 0 9	1 0 3	1 0 5	0 8 5	1 1 5	0 8 8
Special Senses System																								
Eye																								
Zymbal's gland												+			+									
Carcinoma												X			X									
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X			X	X			X	X					X	X
Mesothelioma NOS																						X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	6 7 8	6 7 8	6 7 8	6 8 8	6 8 8	7 0 2	7 0 2	7 0 2	7 0 6	7 1 3	7 1 5	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	0 6 2	0 9 0	1 0 6	1 0 2	1 1 1	0 8 2	0 9 2	0 9 3	1 2 0	1 1 8	0 7 0	0 6 1	0 6 9	0 7 2	0 7 3	0 7 6	0 8 3	0 8 7	0 9 7	0 0 0	1 0 1	1 0 4	1 1 0	1 1 2	1 1 3	Total Tissues/ Tumors
Special Senses System																										
Eye		+																								1
Zymbal's gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma											X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X		X	X							X	X		X	X			X	X	X		X	21
Mesothelioma NOS																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg

Number of Days on Study	1 7 8	4 6 3	5 6 5	5 7 6	5 7 6	5 8 9	5 9 6	6 0 9	6 2 5	6 2 7	6 3 1	6 3 1	6 3 1	6 4 3	6 4 6	6 4 6	6 4 9	6 5 6	6 5 0	6 6 6	6 7 3	6 8 1	6 8 6	6 8 6	6 8 6
Carcass ID Number	1 4 9	1 2 6	1 7 0	1 5 4	1 5 7	1 3 7	1 2 7	1 3 3	1 4 2	1 4 8	1 3 5	1 7 1	1 7 7	1 8 0	1 4 0	1 4 4	1 3 4	1 2 9	1 2 5	1 7 3	1 2 8	1 2 4	1 3 1	1 4 0	1 6 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X																		
Osteosarcoma, metastatic, uncertain primary site																									
Mesentery			+	+	+		+	+	+		+	+					+			+	+			+	
Osteosarcoma, metastatic, uncertain primary site																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Gingiva, squamous cell carcinoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma NOS																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X								X	X	X	X	
Bilateral, pheochromocytoma benign						X																			X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X				X		X			X	X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																					X				
C-cell, adenoma															X										
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	7 0 6	7 1 3	7 1 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	1 3 8	1 5 2	1 5 8	1 2 2	1 4 1	1 5 6	1 6 9	1 7 4	1 7 6	1 7 8	1 7 9	1 2 3	1 3 6	1 3 9	1 4 3	1 4 6	1 5 0	1 5 1	1 6 1	1 6 2	1 6 6	1 6 7	1 6 8	1 7 2	1 7 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X											2
Osteosarcoma, metastatic, uncertain primary site																		X								1
Mesentery						+		+	+				+		+	+	+	+					+	+		22
Osteosarcoma, metastatic, uncertain primary site																		X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, uncertain primary site																		X								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																									+	1
Gingiva, squamous cell carcinoma																									X	1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma NOS																								X		1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X								X					X				X			9
Bilateral, pheochromocytoma benign			X																							3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X	X									X	X		X						X			13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma		X																								2
C-cell, carcinoma											X					X							X			3
Follicular cell, adenoma			X																							1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	1 7 8	4 6 3	5 6 5	5 7 6	5 7 6	5 8 9	5 9 6	6 0 9	6 2 5	6 2 7	6 3 1	6 3 1	6 3 1	6 4 3	6 4 6	6 4 6	6 4 9	6 5 6	6 5 0	6 6 6	6 7 3	6 8 1	6 8 6	6 8 6	6 8 6
Carcass ID Number	1 4 9	1 2 6	1 7 0	1 5 4	1 5 7	1 3 7	1 2 7	1 3 3	1 4 2	1 4 8	1 3 5	1 7 1	1 7 7	1 8 0	1 4 0	1 4 4	1 3 4	1 2 9	1 2 5	1 7 3	1 2 8	1 2 4	1 3 1	1 6 0	1 6 5
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																									
Penis						+																			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X				X		X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																									
Bilateral, interstitial cell, adenoma			X	X		X		X	X	X	X			X				X	X	X	X	X			X
Interstitial cell, adenoma					X		X					X	X		X	X								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+			+									+				
Mediastinal, osteosarcoma, metastatic, uncertain primary site																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																									
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																		X							
Fibrous histiocytoma															X										
Keratoacanthoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									X
Skeletal muscle																									
Osteosarcoma, metastatic, uncertain primary site																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS																									
Peripheral nerve										+	+									+	+				
Spinal cord										+	+									+	+				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	7 0 6	7 1 3	7 1 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	1 3 8	1 5 2	1 5 8	1 2 2	1 4 1	1 5 6	1 6 9	1 7 4	1 7 6	1 7 8	1 7 9	1 2 3	1 3 6	1 3 9	1 4 3	1 4 6	1 5 0	1 5 1	1 6 1	1 6 2	1 6 6	1 6 7	1 6 8	1 7 2	1 7 5	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, uncertain primary site																		X								1
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Adenoma																										3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, uncertain primary site																		X								1
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	35
Interstitial cell, adenoma		X		X										X			X									11
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node												+						+								5
Mediastinal, osteosarcoma, metastatic, uncertain primary site																		X								1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, uncertain primary site																		X								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Osteosarcoma, metastatic, uncertain primary site																		X								1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma												X									X					3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma					X													X								3
Fibrous histiocytoma																										1
Keratoacanthoma						X		X																		3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																		+								1
Osteosarcoma, metastatic, uncertain primary site																		X								1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma NOS																								X		1
Peripheral nerve		+															+									6
Spinal cord		+															+									6

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	1 7 8	4 6 3	5 6 5	5 7 6	5 7 6	5 8 9	5 9 6	6 0 9	6 2 5	6 2 7	6 3 1	6 3 1	6 3 1	6 4 3	6 4 6	6 4 6	6 4 9	6 5 6	6 6 0	6 6 6	6 7 3	6 8 1	6 8 6	6 8 6	6 8 6
Carcass ID Number	1 4 9	1 2 6	1 7 0	1 5 4	1 5 7	1 3 7	1 2 7	1 3 3	1 4 2	1 4 8	1 3 5	1 7 1	1 7 7	1 8 0	1 4 0	1 4 4	1 3 4	1 2 9	1 2 5	1 7 3	1 2 8	1 2 4	1 3 1	1 6 0	1 6 5
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Special Senses System																									
Ear																									
Eye																								+	
Harderian gland										+															
Zymbal's gland																			+						
Carcinoma																			X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																									
Renal tubule, carcinoma					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X		X	X			X		X		X		X			X	X	X		X	X	X
Mesothelioma NOS			X					X	X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	7 0 6	7 1 3	7 1 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	1 3 8	1 5 2	1 5 8	1 2 2	1 4 1	1 5 6	1 6 9	1 7 4	1 7 6	1 7 8	1 7 9	1 2 3	1 3 6	1 3 9	1 4 3	1 4 6	1 5 0	1 5 1	1 6 1	1 6 2	1 6 6	1 6 7	1 6 8	1 7 2	1 7 5	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear																	+									1
Eye																										1
Harderian gland																										1
Zymbal's gland				+																						2
Carcinoma				X																						2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, uncertain primary site																		X								1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X			X					X	X	X		X				X	X	X	X			26
Mesothelioma NOS																							X			4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	2 0 8	2 1 5	2 1 7	2 1 8	2 1 9	2 2 3	2 2 4	2 2 6	2 3 2	2 3 5	2 3 9	2 8 5	2 8 8	2 8 9	2 9 1	2 9 2	2 9 7	2 0 1	2 0 5	2 0 9	2 1 1	2 1 4	2 2 7	2 3 4	2 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X																	2
Mesentery							+														+		+	+	+	14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																			+							1
Gingiva, squamous cell carcinoma																			X							1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X	X			X															X				X	8
Bilateral, pheochromocytoma benign							X																			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X	X								X												10
Pars intermedia, adenoma																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X											1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X															X								2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	41
Interstitial cell, adenoma																X										3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	1 2 6	1 4 4	3 5 1	4 0 4	5 0 4	5 1 6	5 4 0	5 6 5	5 7 5	5 8 4	5 8 9	5 8 9	6 5 6	6 6 6	6 7 3	6 7 3	6 7 9	6 8 4	6 8 5	6 8 6	6 9 2	7 1 3	7 2 6	7 2 6	7 2 6
Carcass ID Number	2 0 0 6	2 0 3	1 9 6	1 9 8	2 0 4	2 1 3	2 1 0	2 3 6	2 2 9	2 2 5	1 8 3	2 3 8	2 3 3	2 1 6	1 9 9	2 3 2	2 3 1	1 8 1	2 2 1	1 8 6	1 9 4	2 2 8	1 8 4	1 9 5	2 0 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+			+	+		+	+	+					+				+		+	
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+
Thymoma malignant							X																		
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Fibroadenoma																									
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								X	
Fibroma																									
Fibroma, multiple																			X						
Keratoacanthoma																					X				
Squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve									+					+		+						+			
Spinal cord									+					+		+						+			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, tooth																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Zymbal's gland						+									+										
Carcinoma						X									X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X	X		X	X	X	X			X		X	X	X	X	X	X	
Mesothelioma NOS																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	2 0 8	2 1 5	2 1 7	2 1 8	2 1 9	2 2 3	2 2 4	2 2 6	2 3 2	2 3 5	2 3 9	2 8 5	2 8 8	2 8 9	2 9 1	2 9 2	2 9 7	2 0 1	2 0 5	2 0 9	2 1 1	2 1 4	2 2 7	2 3 4	2 4 0	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											9
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma malignant																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma	X												X														2
Fibroadenoma, multiple											X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																											1
Fibroma							X												X								2
Fibroma, multiple																											1
Keratoacanthoma													X														2
Squamous cell papilloma		X																									1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																		+									5
Spinal cord																		+									5
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, tooth																			X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear									+															+			2
Eye									+																		1
Zymbal's gland																											2
Carcinoma																											2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X	X		X					X	X	X	X	X				X					24
Mesothelioma NOS			X												X						X						3

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

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	11/50 (22%)	13/50 (26%)	12/50 (24%)	9/50 (18%)
Adjusted rate[b]	41.4%	57.0%	37.7%	29.0%
Terminal rate[c]	5/20 (25%)	6/14 (43%)	4/22 (18%)	7/28 (25%)
First incidence (days)	673	585	589	656
Life table test[d]	P=0.057N	P=0.156	P=0.532	P=0.189N
Logistic regression test[d]	P=0.162N	P=0.243	P=0.526	P=0.315N
Cochran-Armitage test[d]	P=0.248N			
Fisher exact test[d]		P=0.408	P=0.500	P=0.402N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	9.3%	14.3%	6.7%	6.7%
Terminal rate	1/20 (5%)	1/14 (7%)	1/22 (5%)	1/28 (4%)
First incidence (days)	720	660	596	686
Life table test	P=0.388N	P=0.371	P=0.669N	P=0.603N
Logistic regression test	P=0.506N	P=0.418	P=0.687N	P=0.661N
Cochran-Armitage test	P=0.544N			
Fisher exact test		P=0.500	P=0.691N	P=0.691N
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	8/50 (16%)	3/50 (6%)	3/50 (6%)
Adjusted rate	11.7%	31.7%	11.6%	10.7%
Terminal rate	1/20 (5%)	3/14 (21%)	2/22 (9%)	3/28 (11%)
First incidence (days)	673	404	646	726 (T)
Life table test	P=0.142N	P=0.059	P=0.644N	P=0.532N
Logistic regression test	P=0.276N	P=0.110	P=0.654N	P=0.623N
Cochran-Armitage test	P=0.276N			
Fisher exact test		P=0.100	P=0.661N	P=0.661N
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	15.0%	10.9%	4.5%	0.0%
Terminal rate	3/20 (15%)	1/14 (7%)	1/22 (5%)	0/28 (0%)
First incidence (days)	726 (T)	678	726 (T)	—[e]
Life table test	P=0.059N	P=0.643N	P=0.268N	P=0.067N
Logistic regression test	P=0.076N	P=0.622N	P=0.268N	P=0.067N
Cochran-Armitage test	P=0.114N			
Fisher exact test		P=0.500N	P=0.309N	P=0.121N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	15.0%	17.7%	4.5%	0.0%
Terminal rate	3/20 (15%)	2/14 (14%)	1/22 (5%)	0/28 (0%)
First incidence (days)	726 (T)	678	726 (T)	—
Life table test	P=0.038N	P=0.508	P=0.268N	P=0.067N
Logistic regression test	P=0.051N	P=0.530	P=0.268N	P=0.067N
Cochran-Armitage test	P=0.084N			
Fisher exact test		P=0.661N	P=0.309N	P=0.121N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	19/49 (39%)	17/49 (35%)	13/50 (26%)	10/50 (20%)
Adjusted rate	57.6%	52.1%	42.7%	27.1%
Terminal rate	7/19 (37%)	2/14 (14%)	6/22 (27%)	5/28 (18%)
First incidence (days)	471	446	631	351
Life table test	P=0.009N	P=0.445	P=0.132N	P=0.017N
Logistic regression test	P=0.033N	P=0.450N	P=0.108N	P=0.033N
Cochran-Armitage test	P=0.034N			
Fisher exact test		P=0.417N	P=0.126N	P=0.033N
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	1/50 (2%)	3/49 (6%)	2/50 (4%)
Adjusted rate	11.1%	7.1%	9.5%	7.1%
Terminal rate	1/20 (5%)	1/14 (7%)	0/21 (0%)	2/28 (7%)
First incidence (days)	471	726 (T)	649	726 (T)
Life table test	P=0.425N	P=0.406N	P=0.658	P=0.391N
Logistic regression test	P=0.572N	P=0.311N	P=0.651	P=0.501N
Cochran-Armitage test	P=0.582N			
Fisher exact test		P=0.309N	P=0.651	P=0.500N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/49 (6%)	2/50 (4%)
Adjusted rate	11.1%	9.1%	9.5%	7.1%
Terminal rate	1/20 (5%)	1/14 (7%)	0/21 (0%)	2/28 (7%)
First incidence (days)	471	492	649	726 (T)
Life table test	P=0.351N	P=0.594N	P=0.658	P=0.391N
Logistic regression test	P=0.492N	P=0.483N	P=0.651	P=0.501N
Cochran-Armitage test	P=0.492N			
Fisher exact test		P=0.500N	P=0.651	P=0.500N
Skin: Fibroma				
Overall rate	5/50 (10%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	15.7%	13.0%	11.8%	10.0%
Terminal rate	1/20 (5%)	1/14 (7%)	2/22 (9%)	2/28 (7%)
First incidence (days)	649	656	656	685
Life table test	P=0.278N	P=0.454N	P=0.359N	P=0.267N
Logistic regression test	P=0.410N	P=0.387N	P=0.346N	P=0.352N
Cochran-Armitage test	P=0.440N			
Fisher exact test		P=0.357N	P=0.357N	P=0.357N
Skin: Squamous Cell Papilloma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	0.0%	16.6%	0.0%	3.6%
Terminal rate	0/20 (0%)	2/14 (14%)	0/22 (0%)	1/28 (4%)
First incidence (days)	—	589	—	726 (T)
Life table test	P=0.516N	P=0.078	—	P=0.567
Logistic regression test	P=0.617N	P=0.106	—	P=0.567
Cochran-Armitage test	P=0.636N			
Fisher exact test		P=0.121	—	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Skin: Keratoacanthoma				
Overall rate	4/50 (8%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	18.7%	18.6%	12.0%	6.8%
Terminal rate	3/20 (15%)	2/14 (14%)	2/22 (9%)	1/28 (4%)
First incidence (days)	713	702	666	692
Life table test	P=0.161N	P=0.627	P=0.459N	P=0.220N
Logistic regression test	P=0.224N	P=0.651	P=0.499N	P=0.274N
Cochran-Armitage test	P=0.330N			
Fisher exact test		P=0.500N	P=0.500N	P=0.339N
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	5.0%	16.6%	0.0%	3.6%
Terminal rate	1/20 (5%)	2/14 (14%)	0/22 (0%)	1/28 (4%)
First incidence (days)	726 (T)	589	—	726 (T)
Life table test	P=0.352N	P=0.206	P=0.481N	P=0.686N
Logistic regression test	P=0.452N	P=0.261	P=0.481N	P=0.686N
Cochran-Armitage test	P=0.487N			
Fisher exact test		P=0.309	P=0.500N	P=0.753N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	4/50 (8%)	5/50 (10%)	3/50 (6%)	4/50 (8%)
Adjusted rate	18.7%	27.4%	12.0%	13.7%
Terminal rate	3/20 (15%)	3/14 (21%)	2/22 (9%)	3/28 (11%)
First incidence (days)	713	589	666	692
Life table test	P=0.304N	P=0.306	P=0.459N	P=0.475N
Logistic regression test	P=0.449N	P=0.378	P=0.499N	P=0.559N
Cochran-Armitage test	P=0.561N			
Fisher exact test		P=0.500	P=0.500N	P=0.643N
Testes: Adenoma				
Overall rate	43/50 (86%)	42/50 (84%)	46/50 (92%)	44/50 (88%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	20/20 (100%)	14/14 (100%)	22/22 (100%)	28/28 (100%)
First incidence (days)	443	404	565	504
Life table test	P=0.022N	P=0.128	P=0.499	P=0.110N
Logistic regression test	P=0.342	P=0.617	P=0.502	P=0.408
Cochran-Armitage test	P=0.452			
Fisher exact test		P=0.500N	P=0.262	P=0.500
Thyroid Gland (C-cell): Adenoma				
Overall rate	1/50 (2%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted rate	3.1%	16.1%	9.9%	3.6%
Terminal rate	0/20 (0%)	1/14 (7%)	0/22 (0%)	1/28 (4%)
First incidence (days)	663	504	646	726 (T)
Life table test	P=0.208N	P=0.141	P=0.307	P=0.706N
Logistic regression test	P=0.296N	P=0.179	P=0.308	P=0.759N
Cochran-Armitage test	P=0.298N			
Fisher exact test		P=0.181	P=0.309	P=0.753N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Thyroid Gland (C-cell): Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	5.0%	0.0%	13.6%	0.0%
Terminal rate	1/20 (5%)	0/14 (0%)	3/22 (14%)	0/28 (0%)
First incidence (days)	726 (T)	—	726 (T)	—
Life table test	P=0.253N	P=0.571N	P=0.337	P=0.433N
Logistic regression test	P=0.253N	P=0.571N	P=0.337	P=0.433N
Cochran-Armitage test	P=0.382N			
Fisher exact test		P=0.500N	P=0.309	P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	4/50 (8%)	6/50 (12%)	1/50 (2%)
Adjusted rate	8.0%	16.1%	22.2%	3.6%
Terminal rate	1/20 (5%)	1/14 (7%)	3/22 (14%)	1/28 (4%)
First incidence (days)	663	504	646	726 (T)
Life table test	P=0.094N	P=0.258	P=0.155	P=0.406N
Logistic regression test	P=0.169N	P=0.325	P=0.140	P=0.482N
Cochran-Armitage test	P=0.184N			
Fisher exact test		P=0.339	P=0.134	P=0.500N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	9.3%	10.9%	4.2%	0.0%
Terminal rate	1/20 (5%)	1/14 (7%)	0/22 (0%)	0/28 (0%)
First incidence (days)	430	678	713	—
Life table test	P=0.081N	P=0.598N	P=0.303N	P=0.110N
Logistic regression test	P=0.114N	P=0.492N	P=0.314N	P=0.106N
Cochran-Armitage test	P=0.114N			
Fisher exact test		P=0.500N	P=0.309N	P=0.121N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	14.0%	10.9%	4.2%	0.0%
Terminal rate	2/20 (10%)	1/14 (7%)	0/22 (0%)	0/28 (0%)
First incidence (days)	430	678	713	—
Life table test	P=0.050N	P=0.454N	P=0.175N	P=0.049N
Logistic regression test	P=0.078N	P=0.340N	P=0.183N	P=0.060N
Cochran-Armitage test	P=0.079N			
Fisher exact test		P=0.339N	P=0.181N	P=0.059N
All Organs: Mesothelioma NOS				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rate	3.7%	3.6%	10.9%	10.7%
Terminal rate	0/20 (0%)	0/14 (0%)	1/22 (5%)	3/28 (11%)
First incidence (days)	698	666	565	726 (T)
Life table test	P=0.422	P=0.715	P=0.201	P=0.406
Logistic regression test	P=0.298	P=0.746	P=0.174	P=0.354
Cochran-Armitage test	P=0.292			
Fisher exact test		P=0.753N	P=0.181	P=0.309

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
All Organs: Mononuclear Cell Leukemia				
Overall rate	33/50 (66%)	21/50 (42%)	26/50 (52%)	24/50 (48%)
Adjusted rate	86.0%	73.3%	66.5%	59.3%
Terminal rate	15/20 (75%)	8/14 (57%)	10/22 (45%)	12/28 (43%)
First incidence (days)	443	533	463	504
Life table test	P=0.034N	P=0.240N	P=0.139N	P=0.017N
Logistic regression test	P=0.243N	P=0.022N	P=0.093N	P=0.052N
Cochran-Armitage test	P=0.265N			
Fisher exact test		P=0.013N	P=0.111N	P=0.053N
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	48/50 (96%)	49/50 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	20/20 (100%)	14/14 (100%)	22/22 (100%)	28/28 (100%)
First incidence (days)	430	404	565	144
Life table test	P=0.022N	P=0.111	P=0.389N	P=0.111N
Logistic regression test	P=0.129	—[f]	P=0.174N	P=0.365
Cochran-Armitage test	P=0.627			
Fisher exact test		P=0.753N	P=0.500N	P=0.753N
All Organs: Malignant Neoplasms				
Overall rate	39/50 (78%)	27/50 (54%)	31/50 (62%)	28/50 (56%)
Adjusted rate	94.9%	84.1%	76.1%	64.5%
Terminal rate	18/20 (90%)	10/14 (71%)	13/22 (59%)	13/28 (46%)
First incidence (days)	443	492	463	504
Life table test	P=0.011N	P=0.316N	P=0.108N	P=0.008N
Logistic regression test	P=0.215N	P=0.016N	P=0.044N	P=0.027N
Cochran-Armitage test	P=0.134N			
Fisher exact test		P=0.010N	P=0.063N	P=0.016N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	49/50 (98%)	49/50 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	20/20 (100%)	14/14 (100%)	22/22 (100%)	28/28 (100%)
First incidence (days)	430	404	463	144
Life table test	P=0.022N	P=0.111	P=0.442N	P=0.111N
Logistic regression test	P=0.101	—	—	P=0.365
Cochran-Armitage test	P=0.691			
Fisher exact test		P=0.753N	P=0.753N	P=0.753N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, 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 dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed 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 a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4a
Historical Incidence of Pituitary Gland (Pars Distalis) Adenoma in Male F344/N Rats Administered Water by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	116/363 (32.0%)
Standard deviation	7.7%
Range	24%-43%

[a] Data as of 17 June 1994

TABLE A4b
Historical Incidence of Mononuclear Cell Leukemia in Male F344/N Rats Administered Water by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	173/367 (47.1%)
Standard deviation	9.2%
Range	34%-56%

[a] Data as of 17 June 1994; includes data for lymphocytic, monocytic, and undifferentiated leukemia

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

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	2	2	1	1
Moribund	23	30	20	17
Natural deaths	5	4	7	4
Survivors				
Terminal sacrifice	20	14	22	28
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)		1 (10%)	1 (10%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan			2 (20%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus			2 (20%)	
Hepatodiaphragmatic nodule		2 (20%)	1 (10%)	2 (20%)
Hyperplasia		1 (10%)		
Mesentery		(2)	(2)	(1)
Fat, necrosis		2 (100%)	2 (100%)	1 (100%)
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy	2 (20%)	2 (20%)	1 (10%)	1 (10%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration	8 (80%)	8 (80%)	8 (80%)	9 (90%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia	1 (10%)	1 (10%)	3 (30%)	
Pituitary gland	(10)	(9)	(10)	(10)
Cyst	1 (10%)	3 (33%)	2 (20%)	2 (20%)
Pars distalis, hyperplasia	5 (50%)	2 (22%)	3 (30%)	3 (30%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia	1 (10%)	1 (10%)		1 (10%)
Follicle, dilatation	2 (20%)			
Genital System				
Preputial gland	(10)	(10)	(9)	(10)
Inflammation, suppurative	1 (10%)			
Testes	(10)	(10)	(10)	(10)
Atrophy	1 (10%)			
Interstitial cell, hyperplasia	1 (10%)	1 (10%)		

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Spleen	(10)	(10)	(10)	(10)
Fibrosis				1 (10%)
Thymus	(9)	(9)	(10)	(10)
Atrophy				1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia	1 (10%)	1 (10%)		1 (10%)
Interstitium, inflammation			1 (10%)	
Special Senses System				
Ear	(3)			
Inflammation, chronic	3 (100%)			
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	9 (90%)	10 (100%)	9 (90%)	8 (80%)
Systems Examined With No Lesions Observed				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Inflammation, chronic			1 (2%)	
Ulcer		1 (2%)		
Periesophageal tissue, inflammation, chronic	1 (2%)			
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	3 (6%)		1 (2%)	1 (2%)
Ulcer				1 (2%)
Intestine large, rectum	(49)	(50)	(50)	(50)
Parasite metazoan	9 (18%)	1 (2%)	2 (4%)	3 (6%)
Intestine large, cecum	(50)	(50)	(49)	(50)
Parasite metazoan				1 (2%)
Ulcer		1 (2%)		1 (2%)
Intestine small, jejunum	(50)	(50)	(49)	(49)
Inflammation, chronic			1 (2%)	
Ulcer		1 (2%)		
Intestine small, ileum	(50)	(50)	(50)	(49)
Inflammation, chronic			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Basophilic focus	4 (8%)	5 (10%)	4 (8%)	5 (10%)
Clear cell focus	1 (2%)	1 (2%)		2 (4%)
Cyst	1 (2%)		1 (2%)	
Degeneration, cystic	9 (18%)	3 (6%)	4 (8%)	
Eosinophilic focus	2 (4%)	3 (6%)	2 (4%)	4 (8%)
Fatty change		2 (4%)	5 (10%)	5 (10%)
Hepatodiaphragmatic nodule	4 (8%)	3 (6%)	6 (12%)	2 (4%)
Inflammation, chronic		1 (2%)		
Mineralization		1 (2%)		
Mixed cell focus	2 (4%)	2 (4%)		
Necrosis	1 (2%)		1 (2%)	1 (2%)
Centrilobular, degeneration	1 (2%)	1 (2%)		1 (2%)
Portal, degeneration				1 (2%)
Sinusoid, congestion, focal	1 (2%)			
Mesentery	(7)	(13)	(22)	(14)
Inflammation, suppurative		1 (8%)		
Artery, thrombosis	1 (14%)			
Fat, inflammation				1 (7%)
Fat, necrosis	6 (86%)	12 (92%)	17 (77%)	12 (86%)
Lymphatic, cyst	1 (14%)			
Pancreas	(50)	(50)	(50)	(50)
Acinus, atrophy	18 (36%)	15 (30%)	9 (18%)	13 (26%)
Arteriole, inflammation, chronic		1 (2%)		
Artery, inflammation, chronic	1 (2%)		1 (2%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperkeratosis				1 (2%)
Inflammation, chronic		1 (2%)		
Ulcer	3 (6%)	6 (12%)	4 (8%)	7 (14%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	1 (2%)			
Mineralization		1 (2%)	1 (2%)	
Ulcer	8 (16%)	6 (12%)	2 (4%)	
Tongue		(1)		
Foreign body		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Atrium, thrombosis	3 (6%)	2 (4%)	5 (10%)	3 (6%)
Myocardium, degeneration	40 (80%)	43 (86%)	40 (80%)	34 (68%)
Valve, inflammation, chronic	1 (2%)			
Valve, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia	7 (14%)	9 (18%)	9 (18%)	7 (14%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	5 (10%)	4 (8%)	2 (4%)
Necrosis		1 (2%)		
Hyperplasia	2 (4%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(50)
Parathyroid gland	(46)	(45)	(46)	(49)
Hyperplasia	1 (2%)			
Pituitary gland	(49)	(49)	(50)	(50)
Angiectasis			1 (2%)	
Cyst	4 (8%)	5 (10%)	3 (6%)	5 (10%)
Pars distalis, hyperplasia	14 (29%)	17 (35%)	9 (18%)	18 (36%)
Pars intermedia, hyperplasia, tubular				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	2 (4%)	2 (4%)	6 (12%)	3 (6%)
C-cell, infiltration cellular		1 (2%)		
Follicle, dilatation				1 (2%)
General Body System				
None				
Genital System				
Preputial gland	(50)	(50)	(49)	(50)
Ectasia		1 (2%)		2 (4%)
Fibrosis			1 (2%)	
Hyperplasia	1 (2%)	2 (4%)		
Inflammation, chronic				1 (2%)
Inflammation, suppurative	5 (10%)	2 (4%)	4 (8%)	3 (6%)
Prostate	(50)	(50)	(50)	(50)
Inflammation			1 (2%)	
Inflammation, chronic		1 (2%)		
Inflammation, suppurative		1 (2%)		1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	
Testes	(50)	(50)	(50)	(50)
Germinal epithelium, atrophy	2 (4%)	4 (8%)	6 (12%)	3 (6%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis				1 (2%)
Hyperplasia	1 (2%)			
Lymph node	(5)	(8)	(5)	(9)
Lumbar, angiectasis				1 (11%)
Mediastinal, angiectasis		1 (13%)		
Mediastinal, pigmentation, hemosiderin			1 (20%)	
Renal, pigmentation, hemosiderin				1 (11%)
Lymph node, mandibular	(50)	(49)	(50)	(49)
Hemorrhage		1 (2%)		
Infiltration cellular, plasma cell				1 (2%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Fibrosis				1 (2%)
Inflammation, suppurative			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(50)	(50)	(50)
Fibrosis	11 (22%)	11 (22%)	6 (12%)	7 (14%)
Hematopoietic cell proliferation	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Necrosis		1 (2%)		
Thymus	(46)	(46)	(48)	(47)
Atrophy	2 (4%)			
Congestion				1 (2%)
Integumentary System				
Mammary gland	(48)	(48)	(49)	(49)
Hyperplasia, cystic	2 (4%)	1 (2%)	1 (2%)	
Lymphatic, ectasia	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis	2 (4%)			
Hyperplasia, basal cell			1 (2%)	
Inflammation, acute	1 (2%)			
Ulcer		1 (2%)		
Dermis, fibrosis, focal		1 (2%)		
Hair follicle, atrophy, focal		1 (2%)		
Subcutaneous tissue, edema			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hypothalamus, hemorrhage	1 (2%)			
Medulla, gliosis				1 (2%)
Ventricle, hydrocephalus			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Ectopic tissue		1 (2%)		
Foreign body	1 (2%)			
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, granulomatous	3 (6%)			1 (2%)
Inflammation, subacute	1 (2%)		1 (2%)	3 (6%)
Alveolar epithelium, hyperplasia		1 (2%)	1 (2%)	
Alveolus, edema				1 (2%)
Pleura, inflammation, chronic	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Foreign body	1 (2%)			
Inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Special Senses System				
Ear	(3)		(1)	(2)
External ear, hyperkeratosis	2 (67%)			
External ear, inflammation, chronic				1 (50%)
Eye	(1)	(1)	(1)	(1)
Degeneration	1 (100%)			
Lens, cataract			1 (100%)	1 (100%)
Harderian gland	(1)		(1)	
Inflammation, suppurative			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Nephropathy	48 (96%)	44 (88%)	48 (96%)	42 (84%)
Renal tubule, pigmentation, hemosiderin			1 (2%)	
Transitional epithelium, hyperplasia				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Inflammation, acute	1 (2%)			
Inflammation, suppurative		1 (2%)		
Ulcer	1 (2%)			
Transitional epithelium, hyperplasia		1 (2%)		

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

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

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10		10	10
Early deaths				
Accidental deaths		18	2	5
Moribund	13	10	6	7
Natural deaths	3	15	16	16
Survivors				
Terminal sacrifice	34	17	26	22
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(10)		(10)	(10)
Pars distalis, adenoma	1 (10%)		1 (10%)	
Genital System				
Uterus	(10)		(10)	(10)
Polyp stromal	1 (10%)			1 (10%)
Integumentary System				
Mammary gland	(10)		(10)	(9)
Fibroadenoma				1 (11%)
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study				
Alimentary System				
Liver	(50)	(60)	(50)	(50)
Hepatocellular adenoma	1 (2%)			
Tongue			(1)	
Squamous cell carcinoma			1 (100%)	
Tooth			(1)	
Gingiva, squamous cell carcinoma			1 (100%)	
Cardiovascular System				
Heart	(50)	(60)	(50)	(50)
Schwannoma NOS	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(60)	(50)	(50)
Adenoma			2 (4%)	1 (2%)
Adrenal medulla	(50)	(60)	(50)	(50)
Pheochromocytoma benign	1 (2%)		1 (2%)	1 (2%)
Bilateral, pheochromocytoma malignant				1 (2%)
Islets, pancreatic	(50)	(60)	(49)	(50)
Adenoma				1 (2%)
Pituitary gland	(50)	(60)	(50)	(50)
Pars distalis, adenoma	20 (40%)	13 (22%)	14 (28%)	10 (20%)
Thyroid gland	(50)	(60)	(50)	(50)
Bilateral, C-cell, adenoma	1 (2%)			
C-cell, adenoma	2 (4%)	1 (2%)	2 (4%)	1 (2%)
C-cell, carcinoma	2 (4%)	1 (2%)		
Follicular cell, adenoma	1 (2%)			3 (6%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(60)	(48)	(50)
Adenoma	3 (6%)	2 (3%)	2 (4%)	1 (2%)
Bilateral, adenoma			1 (2%)	
Uterus	(50)	(60)	(50)	(50)
Adenoma				1 (2%)
Polyp stromal	6 (12%)	1 (2%)	4 (8%)	3 (6%)
Schwannoma NOS	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(60)	(50)	(50)
Pheochromocytoma malignant, metastatic, adrenal medulla				1 (2%)
Lymph node	(2)	(2)	(2)	
Lymph node, mandibular	(50)	(60)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lymph node, mesenteric	(50)	(59)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Spleen	(50)	(60)	(50)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla				1 (2%)
Thymus	(48)	(59)	(50)	(50)
Thymoma malignant			1 (2%)	
Integumentary System				
Mammary gland	(50)	(60)	(50)	(49)
Adenoma			1 (2%)	
Carcinoma	1 (2%)	1 (2%)	1 (2%)	
Fibroadenoma	20 (40%)	8 (13%)	14 (28%)	12 (24%)
Fibroadenoma, multiple	9 (18%)	2 (3%)	5 (10%)	3 (6%)
Skin	(50)	(60)	(50)	(50)
Keratoacanthoma	1 (2%)	1 (2%)		
Sarcoma	1 (2%)			
Sebaceous gland, adenoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle				(1)
Rhabdomyosarcoma				1 (100%)
Nervous System				
Brain	(50)	(60)	(50)	(50)
Peripheral nerve	(5)	(6)	(5)	(2)
Spinal cord	(2)	(4)	(5)	(2)
Respiratory System				
Lung	(50)	(60)	(50)	(50)
Pheochromocytoma malignant, metastatic, adrenal medulla				1 (2%)
Special Senses System				
Eye	(2)	(3)	(2)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(60)	(50)	(50)
Urinary bladder	(50)	(60)	(49)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(60)	(50)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Leukemia mononuclear	20 (40%)	6 (10%)	13 (26%)	4 (8%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2		1	2
2-Year study	48	23	39	31
Total primary neoplasms				
15-Month interim evaluation	2		1	2
2-Year study	92	37	64	43
Total animals with benign neoplasms				
15-Month interim evaluation	2		1	2
2-Year study	37	19	32	28
Total benign neoplasms				
15-Month interim evaluation	2		1	2
2-Year study	66	28	46	37
Total animals with malignant neoplasms				
2-Year study	23	9	16	6
Total malignant neoplasms				
2-Year study	24	9	18	6
Total animals with metastatic neoplasms				
2-Year study				1
Total metastatic neoplasms				
2-Year study				3
Total animals with uncertain neoplasms-benign or malignant				
2-Year study	2			
Total uncertain neoplasms				
2-Year study	2			

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

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

Number of Days on Study	3 7 4	4 3 7	4 6 1	4 6 3	5 6 2	5 6 2	5 8 2	6 1 1	6 1 1	6 2 7	6 5 8	6 6 0	6 6 3	6 7 1	6 8 5	6 9 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6
Carcass ID Number	2 6 7	2 5 3	2 7 2	2 7 9	2 6 2	2 6 8	2 4 7	2 9 1	2 9 7	2 5 4	2 9 3	4 4 9	4 4 5	8 5 5	5 8 7	5 8 0	4 4 2	4 4 3	5 5 2	5 5 9	2 6 0	2 6 5	6 6 9	7 7 4	7 7 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																							X		
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma NOS																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	M	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X							X	X				X			X		X		X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																					X	X	X		
Schwannoma NOS							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 Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	2 7 7	2 8 1	2 8 2	2 8 3	2 8 6	2 8 7	2 8 9	2 9 2	2 9 5	2 9 6	3 0 0	2 4 4	2 4 6	2 4 8	2 5 0	2 5 1	2 5 5	2 6 1	2 6 4	2 6 6	2 7 0	2 7 1	2 9 0	2 9 4	2 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery				+																						1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma NOS														X												1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	M	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X			X	X			X	X						X	X	X		X				X	20
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma														X												1
C-cell, adenoma						X			X																	2
C-cell, carcinoma																						X	X			2
Follicular cell, adenoma																						X				1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Adenoma															X									X		3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X			X										X									6
Schwannoma NOS																										1
Vagina																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	3 7 4	4 3 7	4 6 1	4 6 3	5 6 2	5 6 2	5 8 2	6 1 1	6 1 1	6 2 7	6 5 8	6 6 0	6 6 3	6 7 1	6 8 5	6 9 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6
Carcass ID Number	2 6 7	2 5 3	2 7 2	2 7 9	2 6 2	2 8 8	2 4 7	2 9 1	2 9 7	2 5 4	2 9 3	2 4 9	2 4 5	2 8 5	2 5 7	2 8 0	2 4 2	2 4 3	2 5 2	2 5 9	2 6 0	2 6 5	2 6 9	2 7 4	2 7 5
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+			+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma						X		X	X	X	X					X			X			X			
Fibroadenoma, multiple														X			X				X		X	X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Sarcoma																									
Sebaceous gland, adenoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+		+			+			+			+							
Spinal cord												+						+							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear												+													
Eye										+								+							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	2 7 7	2 8 1	2 8 2	2 8 3	2 8 6	2 8 7	2 8 9	2 9 2	2 9 5	2 9 6	3 0 0	2 0 4	2 4 6	2 4 8	2 5 0	2 5 1	2 5 5	2 6 1	2 6 4	2 6 6	2 7 0	2 7 1	2 9 0	2 9 4	2 9 8	Total Tissues/ Tumors
Hematopoietic System																										
Blood					+																					1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																		X								1
Fibroadenoma						X				X		X		X	X		X	X	X	X	X	X		X		20
Fibroadenoma, multiple	X			X			X																			9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					X																					1
Sarcoma													X													1
Sebaceous gland, adenoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										5
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																						+				2
Eye																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X						X		X						X		X			X		20

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	5 1 9	5 4 1	5 4 4	5 6 2	5 6 2	5 7 2	5 8 1	6 0 3	6 2 4	6 2 8	6 2 8	6 3 5	6 3 5	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	3 5 7	3 5 6	3 4 9	3 0 6	3 3 7	3 4 7	3 5 0	3 3 0	3 5 8	3 3 4	3 4 5	3 3 5	3 5 5	3 4 8	3 5 2	3 5 4	3 0 2	0 0 3	0 0 4	0 0 5	3 3 8	3 3 2	3 3 3	3 4 8	3 4 2	3 4 3	4 4 6	5 3 3	5 5 9	3 6 0	Total Tissues/ Tumors
Alimentary System																														
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Intestine small, ileum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Mesentery																										+					3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Cardiovascular System																														
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	54
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma		X		X					X	X	X						X	X	X	X	X									X	13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma														X																	1
C-cell, carcinoma																											X				1
General Body System																														
None																														
Genital System																														
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Adenoma																				X									X		2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Polyp stromal																															1
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Lymph node							+					+																			2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma																				X											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Histiocytic sarcoma																				X											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma																				X											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	59

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 3 3 3 3 4 4 4 4 4 5 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 3 9 5 5 7 7 7 0 2 6 6 6 1 8 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 9 9 7 8 7 9 9 8 2 3 3 7 7
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 1 1 1 1 1 1 1 1 1 1 2 2 2 2 2 2 2 0 3 3 2 4 0 4 3 4 0 2 2 5 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 1 6 9 0 1 4 9 1 9 7 8 1
Integumentary System	
Mammary gland	+ +
Carcinoma	
Fibroadenoma	
Fibroadenoma, multiple	
Skin	+ +
Keratoacanthoma	
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Peripheral nerve	
Spinal cord	
Respiratory System	
Lung	+ +
Nose	+ +
Trachea	+ +
Special Senses System	
Ear	
Eye	
Urinary System	
Kidney	+ +
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	
Leukemia mononuclear	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	5 1 9	5 4 1	5 4 4	5 6 2	5 6 2	5 7 2	5 8 1	6 0 3	6 2 4	6 2 8	6 2 8	6 3 5	6 3 5	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	3 5 7	3 5 6	3 4 9	3 0 6	3 3 7	3 4 7	3 5 0	3 3 0	3 5 8	3 3 4	3 4 5	3 3 5	3 5 5	3 4 8	3 5 2	3 5 4	3 0 2	3 0 3	3 0 4	3 0 5	3 0 8	3 3 2	3 3 3	3 3 8	3 4 2	3 4 3	3 4 6	3 5 3	3 5 9	3 6 0	Total Tissues/ Tumors
Integumentary System																														
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Carcinoma																												X		1
Fibroadenoma				X			X					X					X	X	X									X	X	8
Fibroadenoma, multiple										X				X																2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Keratoacanthoma	X																													1
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Peripheral nerve									+	+	+	+	+											+						6
Spinal cord											+	+	+											+						4
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Special Senses System																														
Ear															+															1
Eye					+				+			+																		3
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma																				X										1
Leukemia mononuclear	X						X					X	X				X							X						6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	3 6 4	3 7 3	3 8 6	3 9 2	3 9 7	4 0 0	4 0 5	4 1 0	4 1 3	4 1 6	4 1 7	4 3 7	3 6 8	3 6 9	3 7 0	3 7 7	3 8 5	3 8 7	3 9 3	3 9 5	3 9 6	3 9 9	4 0 3	4 1 5	4 1 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																							+			3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue					+																					1
Squamous cell carcinoma					X																					1
Tooth																										1
Gingiva, squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X																								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X			X			X	X								X									14
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X																			X						2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Adenoma											X															2
Bilateral, adenoma													X													1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X		X										X													4
Vagina																										1
Hematopoietic System																										
Blood																								+		1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	2 3 7	3 2 5	3 7 3	4 0 4	4 6 7	4 7 1	5 4 7	5 4 7	5 5 5	6 0 0	6 2 2	6 2 2	6 3 1	6 3 2	6 4 5	6 5 2	6 5 3	6 8 0	6 9 7	7 0 0	7 0 0	7 0 7	7 0 8	7 0 9	7 2 6
Carcass ID Number	3 7 8	3 9 1	4 0 2	4 0 1	3 9 8	3 8 9	3 6 3	3 7 9	4 1 2	3 6 1	3 7 5	4 0 8	4 0 6	4 1 1	4 1 9	3 0 2	4 8 4	4 1 0	3 2 1	3 7 4	3 8 8	4 8 7	3 0 5	3 8 0	3 6 2
Hematopoietic System (continued)																									
Lymph node															+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant																								X	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Carcinoma																									
Fibroadenoma				X					X				X					X							
Fibroadenoma, multiple																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve										+				+	+										
Spinal cord										+				+	+										
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye													+		+										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear									X					X	X		X		X				X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	3 6 4	3 7 3	3 8 6	3 9 2	3 9 7	4 0 0	4 0 5	4 1 0	4 1 3	4 1 6	4 1 7	3 6 7	3 6 8	3 6 9	3 7 0	3 7 7	3 8 5	3 8 7	3 9 3	3 9 5	3 9 6	3 9 9	4 0 3	4 1 5	4 1 8	Total Tissues/ Tumors
Hematopoietic System (continued)																										
Lymph node			+																							2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma					X																					1
Fibroadenoma	X	X	X						X			X			X			X		X			X			14
Fibroadenoma, multiple													X						X					X	X	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve														+					+							5
Spinal cord														+					+							5
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Leukemia mononuclear			X	X		X	X			X									X	X						13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	6 2 9	6 4 7	6 6 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	4 6 8	4 3 0	4 3 8	4 2 5	4 3 1	4 3 9	4 5 8	4 6 4	4 6 5	4 7 2	4 7 4	4 2 7	4 2 8	4 3 4	4 3 6	4 3 7	4 4 0	4 4 9	4 5 3	4 5 7	4 6 2	4 6 6	4 6 9	4 7 0	4 7 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																	+									2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Bilateral, pheochromocytoma malignant					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																								1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma						X		X		X	X							X				X	X			10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X																	1
Follicular cell, adenoma														X						X	X					3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Polyp stromal																		X								3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla					X																					1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	0 4 1	0 5 1	1 7 8	1 9 0	2 5 4	2 9 1	3 3 2	3 3 2	3 3 6	3 4 6	3 7 2	3 9 1	3 9 2	3 9 4	4 7 3	4 8 5	4 9 8	4 9 9	5 0 2	5 2 0	5 7 0	5 7 6	5 9 0	6 0 3	6 0 7
Carcass ID Number	4 7 5	4 6 1	4 5 4	4 4 5	4 2 4	4 5 2	4 4 8	4 7 3	4 2 9	4 5 0	4 6 0	4 7 8	4 4 2	4 4 3	4 5 5	4 6 3	4 5 9	4 8 0	4 2 3	4 5 6	4 4 4	4 4 7	4 2 1	4 3 5	4 3 3
Hematopoietic System (continued)																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Fibroadenoma																						X	X		X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+													
Rhabdomyosarcoma												X													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																						+			
Spinal cord																						+			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X		X										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	6 2 9	6 4 7	6 6 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	4 6 8	4 3 0	4 3 8	4 2 5	4 3 1	4 3 9	4 5 8	4 6 4	4 6 5	4 7 2	4 7 4	4 2 7	4 2 8	4 3 4	4 3 6	4 3 7	4 4 0	4 4 9	4 5 3	4 5 7	4 6 2	4 6 6	4 6 9	4 7 0	4 7 7	Total Tissues/ Tumors
Hematopoietic System (continued)																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla					X																					1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma			X			X		X		X			X	X	X	X									X	12
Fibroadenoma, multiple					X														X	X						3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve														+												2
Spinal cord														+												2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla					X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X						X												4

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

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Clitoral Gland: Adenoma				
Overall rate[a]	3/49 (6%)	2/60 (3%)	3/48 (6%)	1/50 (2%)
Adjusted rate[b]	9.1%	11.8%	10.4%	4.5%
Terminal rate[c]	3/33 (9%)	2/17 (12%)	2/24 (8%)	1/22 (5%)
First incidence (days)	726 (T)	726 (T)	547	726 (T)
Life table test[d]	P=0.337N	P=0.578	P=0.532	P=0.458N
Logistic regression test[d]	P=0.350N	P=0.578	P=0.620	P=0.458N
Cochran-Armitage test[d]	P=0.301N			
Fisher exact test[d]		P=0.404N	P=0.651	P=0.301N
Mammary Gland: Fibroadenoma				
Overall rate	29/50 (58%)	10/60 (17%)	19/50 (38%)	15/50 (30%)
Adjusted rate	70.4%	46.1%	59.9%	57.2%
Terminal rate	22/34 (65%)	6/17 (35%)	14/26 (54%)	11/22 (50%)
First incidence (days)	562	562	404	576
Life table test	P=0.387N	P=0.134N	P=0.242N	P=0.249N
Logistic regression test	P=0.396N	P=0.029N	P=0.061N	P=0.149N
Cochran-Armitage test	P=0.224N			
Fisher exact test		P<0.001N	P=0.036N	P=0.004N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	29/50 (58%)	10/60 (17%)	20/50 (40%)	15/50 (30%)
Adjusted rate	70.4%	46.1%	63.2%	57.2%
Terminal rate	22/34 (65%)	6/17 (35%)	15/26 (58%)	11/22 (50%)
First incidence (days)	562	562	404	576
Life table test	P=0.375N	P=0.134N	P=0.316N	P=0.249N
Logistic regression test	P=0.385N	P=0.029N	P=0.092N	P=0.149N
Cochran-Armitage test	P=0.215N			
Fisher exact test		P<0.001N	P=0.055N	P=0.004N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	20/50 (40%)	13/60 (22%)	14/50 (28%)	10/50 (20%)
Adjusted rate	50.6%	51.0%	38.1%	38.6%
Terminal rate	15/34 (44%)	6/17 (35%)	5/26 (19%)	7/22 (32%)
First incidence (days)	461	408	547	520
Life table test	P=0.207N	P=0.320	P=0.382N	P=0.280N
Logistic regression test	P=0.158N	P=0.493N	P=0.174N	P=0.164N
Cochran-Armitage test	P=0.106N			
Fisher exact test		P=0.030N	P=0.146N	P=0.024N
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	1/60 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	8.8%	5.9%	7.7%	4.5%
Terminal rate	3/34 (9%)	1/17 (6%)	2/26 (8%)	1/22 (5%)
First incidence (days)	726 (T)	726 (T)	726 (T)	726 (T)
Life table test	P=0.448N	P=0.572N	P=0.622N	P=0.470N
Logistic regression test	P=0.448N	P=0.572N	P=0.622N	P=0.470N
Cochran-Armitage test	P=0.409N			
Fisher exact test		P=0.244N	P=0.500N	P=0.309N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	2/60 (3%)	2/50 (4%)	1/50 (2%)
Adjusted rate	14.7%	11.8%	7.7%	4.5%
Terminal rate	5/34 (15%)	2/17 (12%)	2/26 (8%)	1/22 (5%)
First incidence (days)	726 (T)	726 (T)	726 (T)	726 (T)
Life table test	P=0.214N	P=0.557N	P=0.334N	P=0.226N
Logistic regression test	P=0.214N	P=0.557N	P=0.334N	P=0.226N
Cochran-Armitage test	P=0.188N			
Fisher exact test		P=0.151N	P=0.218N	P=0.102N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/50 (2%)	0/60 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	2.9%	0.0%	0.0%	13.6%
Terminal rate	1/34 (3%)	0/17 (0%)	0/26 (0%)	3/22 (14%)
First incidence (days)	726 (T)	—[e]	—	726 (T)
Life table test	P=0.028	P=0.638N	P=0.554N	P=0.164
Logistic regression test	P=0.028	P=0.638N	P=0.554N	P=0.164
Cochran-Armitage test	P=0.037			
Fisher exact test		P=0.455N	P=0.500N	P=0.309
Uterus: Stromal Polyp				
Overall rate	6/50 (12%)	1/60 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rate	17.6%	2.6%	13.5%	10.8%
Terminal rate	6/34 (18%)	0/17 (0%)	3/26 (12%)	1/22 (5%)
First incidence (days)	726 (T)	379	471	502
Life table test	P=0.582N	P=0.218N	P=0.529N	P=0.484N
Logistic regression test	P=0.571N	P=0.138N	P=0.417N	P=0.419N
Cochran-Armitage test	P=0.522N			
Fisher exact test		P=0.033N	P=0.370N	P=0.243N
All Organs: Mononuclear Cell Leukemia				
Overall rate	20/50 (40%)	6/60 (10%)	13/50 (26%)	4/50 (8%)
Adjusted rate	47.7%	26.9%	38.8%	13.9%
Terminal rate	13/34 (38%)	2/17 (12%)	7/26 (27%)	2/22 (9%)
First incidence (days)	374	519	555	392
Life table test	P=0.022N	P=0.138N	P=0.307N	P=0.011N
Logistic regression test	P=0.013N	P=0.013N	P=0.114N	P<0.001N
Cochran-Armitage test	P=0.009N			
Fisher exact test		P<0.001N	P=0.101N	P<0.001N
All Organs: Benign Neoplasms				
Overall rate	38/50 (76%)	19/60 (32%)	32/50 (64%)	29/50 (58%)
Adjusted rate	84.3%	65.7%	83.5%	87.7%
Terminal rate	27/34 (79%)	8/17 (47%)	20/26 (77%)	18/22 (82%)
First incidence (days)	461	379	404	291
Life table test	P=0.176	P=0.486N	P=0.474	P=0.213
Logistic regression test	P=0.168	P=0.025N	P=0.214N	P=0.541
Cochran-Armitage test	P=0.404			
Fisher exact test		P<0.001N	P=0.138N	P=0.044N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	9/60 (15%)	16/50 (32%)	6/50 (12%)
Adjusted rate	55.1%	41.5%	45.7%	20.3%
Terminal rate	16/34 (47%)	5/17 (29%)	8/26 (31%)	3/22 (14%)
First incidence (days)	374	519	555	391
Life table test	P=0.023N	P=0.270N	P=0.362N	P=0.015N
Logistic regression test	P=0.012N	P=0.052N	P=0.133N	P<0.001N
Cochran-Armitage test	P=0.008N			
Fisher exact test		P<0.001N	P=0.109N	P<0.001N
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/50 (96%)	23/60 (38%)	39/50 (78%)	32/50 (64%)
Adjusted rate	96.0%	78.4%	92.7%	88.6%
Terminal rate	32/34 (94%)	11/17 (65%)	23/26 (88%)	18/22 (82%)
First incidence (days)	374	379	404	291
Life table test	P=0.412	P=0.367N	P=0.557N	P=0.520
Logistic regression test	P=0.566N	P<0.001N	P=0.017N	P=0.013N
Cochran-Armitage test	P=0.346N			
Fisher exact test		P<0.001N	P=0.007N	P<0.001N

(T)Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral 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 dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed 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 a dose group is indicated by N.

[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Pituitary Gland (Pars Distalis) Adenoma in Female F344/N Rats Administered Water by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	170/365 (46.6%)
Standard deviation	6.7%
Range	42%-58%

[a] Data as of 17 June 1994

TABLE B4b
Historical Incidence of Mononuclear Cell Leukemia in Female F344/N Rats Administered Water by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	99/368 (26.9%)
Standard deviation	7.6%
Range	16%-40%

[a] Data as of 17 June 1994; includes data for lymphocytic, monocytic, and undifferentiated leukemia

TABLE B4c
Historical Incidence of Thyroid Gland (Follicular Cell) Adenoma in Female F344/N Rats Administered Water by Gavage[a]

	Incidence in Controls
Overall Historical Incidence	
Total	5/367 (1.4%)
Standard deviation	1.9%
Range	0%-4%

[a] Data as of 17 June 1994

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

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10		10	10
Early deaths				
Accidental deaths		18	2	5
Moribund	13	10	6	7
Natural deaths	3	15	16	16
Survivors				
Terminal sacrifice	34	17	26	22
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(10)		(10)	(10)
Parasite metazoan	3 (30%)		3 (30%)	
Liver	(10)		(10)	(10)
Basophilic focus	2 (20%)			2 (20%)
Fatty change				1 (10%)
Hematopoietic cell proliferation	1 (10%)			
Hepatodiaphragmatic nodule	3 (30%)		2 (20%)	4 (40%)
Inflammation, acute, focal	1 (10%)			
Inflammation, granulomatous	1 (10%)			
Pancreas	(10)		(10)	(10)
Acinus, atrophy	1 (10%)			
Cardiovascular System				
Heart	(10)		(10)	(10)
Myocardium, degeneration	9 (90%)		2 (20%)	4 (40%)
Endocrine System				
Pituitary gland	(10)		(10)	(10)
Cyst	6 (60%)		6 (60%)	8 (80%)
Pars distalis, angiectasis	1 (10%)		1 (10%)	1 (10%)
Pars distalis, hyperplasia			4 (40%)	1 (10%)
Thyroid gland	(10)		(10)	(10)
C-cell, hyperplasia				2 (20%)
Follicular cell, hyperplasia			1 (10%)	
Genital System				
Ovary	(10)		(10)	(10)
Cyst				1 (10%)
Respiratory System				
Lung	(10)		(10)	(10)
Alveolar epithelium, hyperplasia			1 (10%)	

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)		(10)	(10)
Nephropathy	2 (20%)		2 (20%)	1 (10%)
Urinary bladder	(10)		(10)	(10)
Calculus, gross observation	1 (10%)			
Transitional epithelium, hyperplasia	1 (10%)			
Systems Examined With No Lesions Observed				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(59)	(47)	(47)
Parasite metazoan	2 (4%)	4 (7%)	2 (4%)	5 (11%)
Intestine large, rectum	(50)	(59)	(47)	(47)
Parasite metazoan	4 (8%)	2 (3%)	1 (2%)	
Intestine small, duodenum	(50)	(60)	(50)	(49)
Inflammation, chronic		1 (2%)		
Intestine small, jejunum	(49)	(56)	(47)	(46)
Inflammation, chronic		1 (2%)		
Liver	(50)	(60)	(50)	(50)
Basophilic focus	20 (40%)	11 (18%)	21 (42%)	21 (42%)
Clear cell focus	1 (2%)	1 (2%)		
Eosinophilic focus	3 (6%)	4 (7%)	4 (8%)	5 (10%)
Fatty change	2 (4%)	1 (2%)		
Hepatodiaphragmatic nodule	11 (22%)	9 (15%)	4 (8%)	7 (14%)
Hyperplasia, adenomatous	1 (2%)			
Mixed cell focus	1 (2%)			
Necrosis			1 (2%)	
Bile duct, inflammation, chronic		1 (2%)		
Serosa, fibrosis				1 (2%)
Mesentery	(1)	(3)	(3)	(2)
Fat, necrosis	1 (100%)	3 (100%)	2 (67%)	2 (100%)
Lymphatic, cyst			1 (33%)	
Pancreas	(50)	(60)	(50)	(50)
Acinus, atrophy	15 (30%)	7 (12%)	8 (16%)	6 (12%)
Artery, inflammation, chronic		1 (2%)		
Duct, concretion				1 (2%)
Salivary glands	(50)	(60)	(50)	(50)
Inflammation, chronic			1 (2%)	
Inflammation, subacute	1 (2%)			
Stomach, forestomach	(50)	(60)	(50)	(48)
Hyperkeratosis	1 (2%)			
Ulcer	2 (4%)	1 (2%)	1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, glandular	(50)	(60)	(50)	(49)
Ulcer	3 (6%)		1 (2%)	1 (2%)
Artery, mineralization	1 (2%)			
Cardiovascular System				
Blood vessel	(50)	(60)	(50)	(49)
Inflammation, granulomatous	1 (2%)			
Mineralization	1 (2%)			
Heart	(50)	(60)	(50)	(50)
Atrium, thrombosis		1 (2%)	1 (2%)	1 (2%)
Myocardium, degeneration	21 (42%)	17 (28%)	29 (58%)	20 (40%)
Myocardium, mineralization	1 (2%)			
Valve, thrombosis			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(60)	(50)	(50)
Degeneration	1 (2%)			
Hyperplasia	11 (22%)	5 (8%)	6 (12%)	4 (8%)
Adrenal medulla	(50)	(60)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Bilateral, hyperplasia				1 (2%)
Pituitary gland	(50)	(60)	(50)	(50)
Cyst	33 (66%)	28 (47%)	31 (62%)	23 (46%)
Pigmentation, hemosiderin	1 (2%)			
Pars distalis, hyperplasia	16 (32%)	11 (18%)	12 (24%)	16 (32%)
Thyroid gland	(50)	(60)	(50)	(50)
C-cell, hyperplasia	5 (10%)	1 (2%)	2 (4%)	
General Body System				
None				
Genital System				
Clitoral gland	(49)	(60)	(48)	(50)
Ectasia	5 (10%)	1 (2%)		
Hyperplasia		2 (3%)		1 (2%)
Inflammation, suppurative	2 (4%)	2 (3%)	1 (2%)	
Ovary	(50)	(60)	(50)	(50)
Cyst	1 (2%)	2 (3%)	1 (2%)	2 (4%)
Uterus	(50)	(60)	(50)	(50)
Decidual reaction			1 (2%)	
Dilatation		1 (2%)		
Hyperplasia, cystic				1 (2%)
Inflammation, chronic		1 (2%)		
Inflammation, suppurative	1 (2%)			
Vagina	(2)		(1)	
Infiltration cellular, polymorphonuclear	1 (50%)			
Epithelium, vacuolization cytoplasmic			1 (100%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(60)	(50)	(50)
Inflammation, granulomatous				1 (2%)
Myelofibrosis				1 (2%)
Myelostromal proliferation		1 (2%)		
Lymph node	(2)	(2)	(2)	
Renal, pigmentation, hemosiderin		1 (50%)		
Lymph node, mandibular	(50)	(60)	(50)	(50)
Inflammation, chronic			1 (2%)	
Lymph node, mesenteric	(50)	(59)	(50)	(50)
Inflammation, subacute	1 (2%)			
Spleen	(50)	(60)	(50)	(50)
Fibrosis	2 (4%)	2 (3%)	2 (4%)	
Hematopoietic cell proliferation	1 (2%)	4 (7%)	1 (2%)	2 (4%)
Necrosis		1 (2%)	1 (2%)	
Lymphoid follicle, atrophy	1 (2%)			2 (4%)
Red pulp, atrophy				1 (2%)
Integumentary System				
Mammary gland	(50)	(60)	(50)	(49)
Edema		1 (2%)		
Hyperplasia, cystic	2 (4%)	1 (2%)	1 (2%)	
Inflammation		1 (2%)		
Skin	(50)	(60)	(50)	(50)
Acanthosis			1 (2%)	
Hyperkeratosis				1 (2%)
Ulcer		2 (3%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(60)	(50)	(50)
Osteopetrosis		2 (3%)	1 (2%)	
Nervous System				
None				
Respiratory System				
Lung	(50)	(60)	(50)	(50)
Erythrophagocytosis	1 (2%)			
Foreign body		1 (2%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)	1 (2%)		
Infiltration cellular, mononuclear cell	1 (2%)	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)		2 (4%)
Inflammation, granulomatous		1 (2%)		
Inflammation, subacute	1 (2%)		1 (2%)	
Alveolar epithelium, hyperplasia	2 (4%)	2 (3%)	3 (6%)	1 (2%)
Alveolus, edema		1 (2%)		
Bronchus, inflammation, acute			1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(50)	(60)	(50)	(50)
Exudate		1 (2%)		
Inflammation, suppurative			2 (4%)	
Special Senses System				
Ear	(2)	(1)		
External ear, ulcer		1 (100%)		
Eye	(2)	(3)	(2)	
Inflammation, chronic		1 (33%)		
Anterior chamber, inflammation			1 (50%)	
Cornea, necrosis	1 (50%)			
Urinary System				
Kidney	(50)	(60)	(50)	(50)
Cyst	1 (2%)			
Hemorrhage			1 (2%)	1 (2%)
Hydronephrosis				1 (2%)
Infarct			1 (2%)	
Nephropathy	33 (66%)	22 (37%)	27 (54%)	13 (26%)
Pelvis, inflammation, chronic			1 (2%)	
Urinary bladder	(50)	(60)	(49)	(50)
Transitional epithelium, hyperplasia				1 (2%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	20	20	20	20
Early deaths				
Accidental deaths			2	2
Moribund	4	7	4	7
Natural deaths	6	4	5	2
Survivors				
Terminal sacrifice	40	39	39	39
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma				1 (10%)
Hepatocellular adenoma	1 (10%)	2 (20%)	1 (10%)	
Hepatocellular adenoma, multiple	1 (10%)	1 (10%)		
Hepatocyte, hepatocellular adenoma		1 (10%)		
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	2 (20%)			1 (10%)
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study				
Alimentary System				
Intestine small, duodenum	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Intestine small, jejunum	(50)	(50)	(49)	(50)
Carcinoma			1 (2%)	
Intestine small, ileum	(49)	(49)	(50)	(48)
Liver	(50)	(50)	(50)	(50)
Carcinoma, multiple			1 (2%)	
Hemangioma	1 (2%)			
Hemangiosarcoma			3 (6%)	
Hemangiosarcoma, multiple			1 (2%)	
Hemangiosarcoma, metastatic, skin	1 (2%)			
Hemangiosarcoma, metastatic, spleen		1 (2%)		
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma	6 (12%)	13 (26%)	5 (10%)	7 (14%)
Hepatocellular carcinoma, multiple		2 (4%)		
Hepatocellular adenoma	10 (20%)	18 (36%)	6 (12%)	8 (16%)
Hepatocellular adenoma, multiple	16 (32%)	4 (8%)	3 (6%)	
Histiocytic sarcoma	3 (6%)			1 (2%)
Ito cell tumor NOS, multiple	1 (2%)			
Mesentery	(4)	(3)	(3)	(2)
Hemangiosarcoma		1 (33%)		
Histiocytic sarcoma				1 (50%)
Pancreas	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Mast cell tumor malignant		1 (2%)		
Squamous cell papilloma			1 (2%)	
Tooth	(14)	(4)	(4)	(2)
Odontoma	1 (7%)	1 (25%)	2 (50%)	1 (50%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Endocrine System				
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	3 (6%)		1 (2%)	1 (2%)
Pituitary gland	(48)	(47)	(46)	(44)
Pars distalis, adenoma				1 (2%)
Pars intermedia, adenoma	1 (2%)		1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma		1 (2%)		1 (2%)
General Body System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Genital System				
Preputial gland	(50)	(50)	(50)	(50)
Sarcoma				1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)	1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, liver			1 (2%)	
Hemangiosarcoma, metastatic, skin	1 (2%)			
Lymph node	(2)		(2)	(3)
Bronchial, carcinoma, metastatic, liver			1 (50%)	
Mediastinal, carcinoma, metastatic, liver			1 (50%)	
Mediastinal, histiocytic sarcoma				1 (33%)
Lymph node, mandibular	(49)	(48)	(47)	(46)
Lymph node, mesenteric	(48)	(46)	(47)	(47)
Carcinoma, metastatic, liver			1 (2%)	
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Histiocytic sarcoma	3 (6%)			1 (2%)
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)	
Hemangiosarcoma, multiple		1 (2%)		
Hemangiosarcoma, metastatic, liver			1 (2%)	
Hemangiosarcoma, metastatic, skin	1 (2%)			
Histiocytic sarcoma	2 (4%)			1 (2%)
Thymus	(42)	(44)	(40)	(40)
Carcinoma, metastatic, liver			1 (3%)	
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Mast cell tumor malignant		1 (2%)		
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Musculoskeletal System				
None				
Nervous System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	11 (22%)	7 (14%)	7 (14%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	4 (8%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)			
Carcinoma, metastatic, harderian gland		2 (4%)		
Carcinoma, metastatic, liver			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	3 (6%)	3 (6%)	1 (2%)	3 (6%)
Histiocytic sarcoma	1 (2%)			1 (2%)
Nose	(50)	(50)	(50)	(50)
Mast cell tumor malignant		2 (4%)		1 (2%)
Special Senses System				
Harderian gland	(16)	(18)	(19)	(13)
Adenoma	3 (19%)	1 (6%)	1 (5%)	2 (15%)
Carcinoma		4 (22%)	1 (5%)	1 (8%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Artery, hepatocellular carcinoma, metastatic, liver				1 (2%)
Renal tubule, adenoma			1 (2%)	
Renal tubule, carcinoma	2 (4%)			
Urinary bladder	(50)	(50)	(50)	(49)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)			1 (2%)
Leukemia lymphocytic	1 (2%)		1 (2%)	1 (2%)
Lymphomá malignant lymphocytic	1 (2%)		1 (2%)	3 (6%)
Lymphoma malignant mixed	3 (6%)	2 (4%)	1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	4	4	1	2
2-Year Study	43	41	31	29
Total primary neoplasms				
15-Month interim evaluation	4	4	1	2
2-Year study	69	66	43	37
Total animals with benign neoplasms				
15-Month interim evaluation	4	4	1	1
2-Year study	36	28	21	18
Total benign neoplasms				
15-Month interim evaluation	4	4	1	1
2-Year study	48	34	26	20
Total animals with malignant neoplasms				
15-Month interim evaluation				1
2-Year study	17	25	16	15
Total malignant neoplasms				
15-Month interim evaluation				1
2-Year study	20	32	17	17
Total animals with metastatic neoplasms				
2-Year study	4	5	4	3
Total metastatic neoplasms				
2-Year study	6	6	10	4
Total animals with uncertain neoplasms-benign or malignant				
2-Year study	1			
Total uncertain neoplasms				
2-Year study	1			

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Ten animals per group received ophthalmic examinations and were discarded without further evaluation
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control

Number of Days on Study	2 9 4	4 4 7	5 4 0	6 4 7	6 8 0	6 8 3	6 9 4	7 0 0	7 0 7	7 2 5	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	0 1 6	0 6 9	0 1 4	0 0 2	0 3 9	0 5 6	0 1 9	0 5 4	0 3 5	0 2 2	0 0 5	0 0 6	0 2 0	0 4 2	0 5 0	0 5 8	0 6 1	0 6 4	0 6 5	0 6 9	0 7 0	0 7 1	0 7 1	0 7 3	0 7 5	0 7 6
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma					X																					
Hemangiosarcoma, metastatic, skin										X																
Hepatocellular carcinoma								X	X		X						X				X					
Hepatocellular adenoma						X								X				X				X				
Hepatocellular adenoma, multiple					X		X			X	X					X			X	X			X	X	X	
Histiocytic sarcoma		X																								
Ito cell tumor NOS, multiple																										
Mesentery																				+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+			+					+							+		
Odontoma																X										
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																						
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma				X																						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																										
None																										

+: 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 Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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	
Carcass ID Number	0 3 2	0 3 3	0 3 7	0 4 0	0 4 5	0 4 7	0 4 8	0 4 9	0 5 5	0 5 7	0 5 9	0 6 6	0 0 3	0 0 7	0 1 5	0 2 7	0 2 9	0 3 0	0 3 6	0 3 8	0 4 1	0 4 6	0 5 2	0 6 3	0 7 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma, metastatic, skin																										1
Hepatocellular carcinoma																					X					6
Hepatocellular adenoma		X																X	X	X	X				X	10
Hepatocellular adenoma, multiple			X		X			X							X		X							X		16
Histiocytic sarcoma												X												X		3
Ito cell tumor NOS, multiple				X																						1
Mesentery	+								+							+										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+		+			+	+	+	+										+			+	+		+	14
Odontoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X		X														3
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	2 9 4	4 4 7	5 4 0	6 4 7	6 8 0	6 8 3	6 9 4	7 0 0	7 0 7	7 2 5	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	0 1 6	0 6 9	0 1 4	0 0 2	0 3 9	0 5 6	0 1 9	0 5 4	0 3 5	0 2 2	0 0 5	0 0 6	0 2 0	0 4 2	0 5 0	0 5 8	0 6 1	0 6 4	0 6 5	0 6 9	0 1 0	0 1 1	0 2 3	0 2 5	0 2 6
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis					+			+																	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin										X															
Lymph node																+									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin										X															
Histiocytic sarcoma		X																							
Thymus	+	+	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X	X									X		X		X			X		
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma					X							X													
Alveolar/bronchiolar carcinoma, multiple								X																	
Hepatocellular carcinoma, metastatic, liver								X	X																
Histiocytic sarcoma		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland	M	M	+	+	M	+	+	M	+	M	M	M	M	M	M	+	+	+	+	M	M	M	M	M	M
Adenoma			X																						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	7 2 9	
Carcass ID Number	0 3 2	0 3 3	0 3 7	0 4 0	0 4 5	0 4 7	0 4 8	0 4 9	0 5 5	0 5 7	0 5 9	0 6 6	0 0 3	0 0 7	0 1 5	0 2 7	0 2 9	0 3 0	0 3 6	0 3 8	0 4 1	0 4 6	0 5 2	0 6 3	0 7 0	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, skin																										1
Lymph node		+																								2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma												X											X			3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, skin																										1
Histiocytic sarcoma												X														2
Thymus	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	42
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	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X		X	X				X									X			11
Alveolar/bronchiolar adenoma, multiple																X										1
Alveolar/bronchiolar carcinoma																										2
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver																					X					3
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland	+	M	+	M	M	M	M	M	+	M	M	+	M	M	M	+	M	M	M	+	M	M	M	M	+	16
Adenoma			X																						X	3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	2 9 4	4 4 7	5 4 0	6 4 7	6 8 0	6 8 3	6 9 4	7 0 0	7 0 7	7 2 5	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	0 1 6	0 6 9	0 1 4	0 0 2	0 3 9	0 5 6	0 1 9	0 5 4	0 3 5	0 2 2	0 0 5	0 0 6	0 2 0	0 4 2	0 5 0	0 5 8	0 6 1	0 6 4	0 6 5	0 0 9	0 1 0	0 1 1	0 2 3	0 2 5	0 2 6
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Renal tubule, carcinoma											X								X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Leukemia lymphocytic						X																			
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed																				X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	
Carcass ID Number	0 3 2	0 3 3	0 3 7	0 4 0	0 4 5	0 4 7	0 4 8	0 4 9	0 5 5	0 5 7	0 5 9	0 6 6	0 6 3	0 7 7	0 1 5	0 2 7	0 2 9	0 3 0	0 3 6	0 3 8	0 4 1	0 4 6	0 5 2	0 6 3	0 7 0	Total Tissues/ Tumors	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	50	
Histiocytic sarcoma																								X		1	
Renal tubule, carcinoma																										2	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma												X												X		3	
Leukemia lymphocytic																										1	
Lymphoma malignant lymphocytic																										1	
Lymphoma malignant mixed		X																		X						3	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	7 2 9	
Carcass ID Number	1 6 8	1 6 9	1 7 2	1 7 8	1 7 9	1 8 3	1 8 4	1 8 7	1 8 9	1 9 3	1 9 9	1 3 1	1 3 3	1 3 5	1 4 8	1 6 3	1 6 7	1 7 1	1 7 5	1 7 6	1 8 0	1 8 2	1 8 8	1 9 4	2 0 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																							X			1
Hepatoblastoma																										1
Hepatocellular carcinoma									X									X			X					13
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma	X		X	X							X	X			X	X	X	X	X							18
Hepatocellular adenoma, multiple														X								X	X		X	4
Mesentery								+										+								3
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth		+																			+					4
Odontoma																					X					1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma							X																			1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																							X			1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	7 2 9	
Carcass ID Number	1 6 8	1 6 9	1 7 2	1 7 8	1 7 9	1 8 3	1 8 4	1 8 7	1 8 9	1 9 3	1 9 9	1 3 1	1 3 3	1 3 5	1 4 8	1 6 3	1 6 7	1 7 1	1 7 5	1 7 6	1 8 0	1 8 2	1 8 8	1 9 4	2 0 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
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
Mast cell tumor malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X		X				X												7
Alveolar/bronchiolar carcinoma					X				X		X															4
Carcinoma, metastatic, harderian gland																										2
Hepatocellular carcinoma, metastatic, liver																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant															X											2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+																3
Harderian gland	M	M	M	M	M	+	M	+	M	+	M	M	+	M	M	M	M	M	M	M	M	M	+	M	M	18
Adenoma										X																1
Carcinoma																										4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed	X																					X				2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	0 5 0	1 3 1	3 7 6	5 2 0	5 6 0	5 9 0	5 9 4	6 0 6	6 9 1	6 9 3	7 0 7	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	2 1 9	2 0 4	2 5 4	2 1 7	2 3 2	2 7 0	2 4 2	2 2 8	2 5 2	2 5 1	2 3 9	2 0 6	2 0 7	2 2 1	2 4 6	2 4 7	2 4 8	2 5 3	2 6 2	2 6 3	2 6 8	2 7 4	2 7 6	2 7 5	2 7 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver					X																				
Lymph node											+								+						
Bronchial, carcinoma, metastatic, liver																			X						
Mediastinal, carcinoma, metastatic, liver																			X						
Lymph node, mandibular	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																			X						
Hemangiosarcoma, metastatic, spleen										X															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Hemangiosarcoma, metastatic, liver					X																				
Thymus	+	+	+	M	M	M	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																			X						
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve				+																					
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X		X							X				X					
Alveolar/bronchiolar adenoma, multiple												X													
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, liver																			X						
Hepatocellular carcinoma, metastatic, liver																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland	+	+	+	M	M	M	+	M	M	+	M	M	+	M	M	M	M	+	M	M	+	M	M	M	+
Adenoma																									X
Carcinoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 3 5	2 3 8	2 4 0	2 4 3	2 4 4	2 4 9	2 6 6	2 6 9	2 0 1	2 0 2	2 0 5	2 1 0	2 1 8	2 2 2	2 2 7	2 3 3	2 3 6	2 4 1	2 5 5	2 5 8	2 5 9	2 6 3	2 6 4	2 6 5	2 6 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver																										1
Lymph node																										2
Bronchial, carcinoma, metastatic, liver																										1
Mediastinal, carcinoma, metastatic, liver																										1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, liver																										1
Hemangiosarcoma, metastatic, spleen																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic, liver																										1
Thymus	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	40
Carcinoma, metastatic, liver																										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	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X	X																	X		7
Alveolar/bronchiolar adenoma, multiple												X														2
Alveolar/bronchiolar carcinoma			X																							1
Carcinoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																	+									1
Harderian gland	M	M	M	+	+	M	M	+	M	+	M	+	M	+	M	M	+	M	M	+	M	M	M	+	+	19
Adenoma																										1
Carcinoma																	X									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	0 5 0	1 3 1	3 7 6	5 2 0	5 6 0	5 9 0	5 9 4	6 0 6	6 9 1	6 9 3	7 0 7	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	2 1 9	2 0 4	2 5 4	2 1 7	2 3 2	2 7 0	2 4 2	2 2 8	2 5 2	2 5 1	2 3 9	2 0 6	2 0 7	2 2 1	2 4 6	2 4 7	2 4 8	2 5 3	2 6 2	2 0 3	2 0 8	2 1 4	2 1 6	2 2 5	2 2 9
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia lymphocytic									X																
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 3 5	2 3 8	2 4 0	2 4 3	2 4 4	2 4 9	2 6 6	2 6 9	2 0 1	2 0 2	2 0 5	2 1 0	2 1 8	2 2 2	2 2 7	2 3 3	2 3 6	2 4 1	2 5 5	2 5 8	2 5 9	2 6 3	2 6 4	2 6 5	2 6 7	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia lymphocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed					X																					1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg

Number of Days on Study	3 0 0	4 0 5	4 0 5	4 3 2	5 8 7	5 9 4	6 2 2	6 2 7	6 9 7	7 0 5	7 0 7	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	3 2 2	2 7 4	3 1 1	2 8 3	3 2 9	3 0 3	3 1 0	3 0 6	2 9 1	3 1 7	3 2 1	2 7 2	2 7 6	2 7 7	2 7 6	2 8 6	3 1 6	3 2 0	3 2 7	3 3 3	3 3 5	3 7 7	2 8 9	2 9 0	2 9 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X											X				X			
Hepatocellular adenoma					X	X														X				X	
Histiocytic sarcoma											X														
Mesentery											+								+						
Histiocytic sarcoma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth													+		+										
Odontoma															X										
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+
Pars distalis, adenoma						X																			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																				X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	
Carcass ID Number	2 9 3	2 9 9	3 0 0	3 0 5	3 0 8	3 1 8	3 2 4	3 3 0	3 3 1	3 3 2	3 3 8	3 7 1	2 7 5	2 8 1	2 9 5	2 9 6	2 9 7	3 0 9	3 1 2	3 1 3	3 1 9	3 2 3	3 2 5	3 3 4	3 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X		X					X													X					7
Hepatocellular adenoma												X				X			X	X						8
Histiocytic sarcoma																										1
Mesentery																										2
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										2
Odontoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	43
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	44
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																		X								1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	3 0 0	4 0 5	4 0 5	4 3 2	5 8 7	5 9 4	6 2 2	6 2 7	6 9 7	7 0 5	7 0 7	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	3 2 2	2 7 4	3 1 1	2 8 3	3 2 9	3 0 3	3 1 0	3 0 6	2 9 1	3 1 7	3 2 1	2 7 2	2 7 6	2 7 7	2 8 6	2 1 6	3 2 0	3 2 7	3 3 3	3 3 5	3 3 7	2 7 9	2 8 9	2 9 0	2 9 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+							+		+														
Mediastinal, histiocytic sarcoma											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Thymus	+	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve				+																					
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver							X																		
Histiocytic sarcoma											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear					+																				
Eye																	+								
Harderian gland	M	M	+	M	M	+	M	M	M	M	M	+	M	M	+	M	+	M	M	M	M	M	M	+	M
Adenoma			X																						
Carcinoma																	X								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	7 2 9	
Carcass ID Number	2 9 3	2 9 9	3 0 0	3 0 5	3 0 8	3 1 8	3 2 4	3 3 0	3 3 1	3 3 2	3 3 8	2 7 1	2 7 5	2 8 1	2 9 5	2 9 6	2 9 7	2 9 9	3 0 9	3 1 2	3 1 3	3 1 9	3 2 3	3 2 5	3 3 4	3 4 0	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											3
Mediastinal, histiocytic sarcoma																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Thymus	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		40
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	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Peripheral nerve																											1
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma				X									X		X						X						5
Alveolar/bronchiolar adenoma, multiple	X																										1
Alveolar/bronchiolar carcinoma																	X		X								2
Hepatocellular carcinoma, metastatic, liver								X														X					3
Histiocytic sarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Mast cell tumor malignant																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																											
Ear																											1
Eye			+																								2
Harderian gland	M	M	+	+	M	M	M	M	+	M	M	M	M	+	M	+	M	+	M	M	+	M	M	M	M		13
Adenoma			X																								2
Carcinoma																											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	3	4	4	4	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	0	3	8	9	2	2	9	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	0	5	5	2	7	4	2	7	7	5	7	6	6	6	6	6	6	6	6	6	6	7	7	7	7
Carcass ID Number	3	2	3	2	3	3	3	3	2	3	3	2	2	2	2	3	3	3	3	3	3	2	2	2	2
	2	7	1	8	2	0	1	0	9	1	2	7	7	7	8	1	2	2	3	3	3	7	8	9	9
	2	4	1	3	9	3	0	6	1	7	1	2	6	7	6	6	0	7	3	5	7	9	9	0	2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Artery, hepatocellular carcinoma, metastatic, liver																									
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Leukemia lymphocytic		X																							
Lymphoma malignant lymphocytic										X															

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	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 2 9	
Carcass ID Number	2 9 3	2 9 9	3 0 0	3 0 5	3 0 8	3 1 8	3 2 4	3 3 0	3 3 1	3 3 2	3 3 8	2 7 1	2 7 5	2 8 1	2 9 5	2 9 6	2 9 7	2 9 9	3 0 2	3 1 3	3 1 9	3 2 3	3 2 5	3 3 4	3 4 0	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Artery, hepatocellular carcinoma, metastatic, liver								X																		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia lymphocytic																										1
Lymphoma malignant lymphocytic														X											X	3

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate[b]	7.0%	2.6%	2.6%	4.6%
Terminal rate[c]	2/40 (5%)	1/39 (3%)	1/39 (3%)	1/39 (3%)
First incidence (days)	540	726 (T)	726 (T)	405
Life table test[d]	P=0.616	P=0.312N	P=0.317N	P=0.511N
Logistic regression test[d]	P=0.640	P=0.317N	P=0.295N	P=0.441N
Cochran-Armitage test[d]	P=0.623			
Fisher exact test[d]		P=0.309N	P=0.309N	P=0.500N
Harderian Gland: Carcinoma				
Overall rate	0/50 (0%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	9.7%	2.6%	2.6%
Terminal rate	0/40 (0%)	2/39 (5%)	1/39 (3%)	1/39 (3%)
First incidence (days)	—[e]	705	726 (T)	726 (T)
Life table test	P=0.467N	P=0.065	P=0.495	P=0.495
Logistic regression test	P=0.477N	P=0.063	P=0.495	P=0.495
Cochran-Armitage test	P=0.459N			
Fisher exact test		P=0.059	P=0.500	P=0.500
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted rate	7.0%	12.1%	5.1%	7.1%
Terminal rate	2/40 (5%)	3/39 (8%)	2/39 (5%)	2/39 (5%)
First incidence (days)	540	705	726 (T)	405
Life table test	P=0.502N	P=0.352	P=0.513N	P=0.649
Logistic regression test	P=0.484N	P=0.352	P=0.499N	P=0.619N
Cochran-Armitage test	P=0.492N			
Fisher exact test		P=0.357	P=0.500N	P=0.661N
Liver: Hepatocellular Adenoma				
Overall rate	26/50 (52%)	22/50 (44%)	9/50 (18%)	8/50 (16%)
Adjusted rate	59.0%	53.5%	21.3%	19.1%
Terminal rate	22/40 (55%)	20/39 (51%)	6/39 (15%)	6/39 (15%)
First incidence (days)	680	705	594	587
Life table test	P<0.001N	P=0.318N	P=0.001N	P<0.001N
Logistic regression test	P<0.001N	P=0.289N	P<0.001N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.274N	P<0.001N	P<0.001N
Liver: Hemangiosarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate	0.0%	0.0%	9.0%	0.0%
Terminal rate	0/40 (0%)	0/39 (0%)	1/39 (3%)	0/39 (0%)
First incidence (days)	—	—	560	—
Life table test	P=0.492N	—	P=0.061	—
Logistic regression test	P=0.461N	—	P=0.078	—
Cochran-Armitage test	P=0.480N			
Fisher exact test		—	P=0.059	—

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Liver: Hepatocellular Carcinoma				
Overall rate	6/50 (12%)	15/50 (30%)	6/50 (12%)	7/50 (14%)
Adjusted rate	14.2%	31.0%	14.9%	17.3%
Terminal rate	4/40 (10%)	6/39 (15%)	5/39 (13%)	6/39 (15%)
First incidence (days)	700	405	693	622
Life table test	P=0.297N	P=0.034	P=0.594	P=0.476
Logistic regression test	P=0.270N	P=0.020	P=0.577	P=0.468
Cochran-Armitage test	P=0.267N			
Fisher exact test		P=0.024	P=0.620N	P=0.500
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma				
Overall rate	30/50 (60%)	33/50 (66%)	14/50 (28%)	15/50 (30%)
Adjusted rate	65.2%	67.3%	32.5%	35.3%
Terminal rate	24/40 (60%)	23/39 (59%)	10/39 (26%)	12/39 (31%)
First incidence (days)	680	405	594	587
Life table test	P=0.003N	P=0.328	P=0.004N	P=0.007N
Logistic regression test	P=0.001N	P=0.348	P=0.002N	P=0.004N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.339	P=0.001N	P=0.002N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	6/50 (12%)	16/50 (32%)	6/50 (12%)	7/50 (14%)
Adjusted rate	14.2%	33.1%	14.9%	17.3%
Terminal rate	4/40 (10%)	7/39 (18%)	5/39 (13%)	6/39 (15%)
First incidence (days)	700	405	693	622
Life table test	P=0.260N	P=0.022	P=0.594	P=0.476
Logistic regression test	P=0.233N	P=0.012	P=0.577	P=0.468
Cochran-Armitage test	P=0.230N			
Fisher exact test		P=0.014	P=0.620N	P=0.500
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	30/50 (60%)	33/50 (66%)	14/50 (28%)	15/50 (30%)
Adjusted rate	65.2%	67.3%	32.5%	35.3%
Terminal rate	24/40 (60%)	23/39 (59%)	10/39 (26%)	12/39 (31%)
First incidence (days)	680	405	594	587
Life table test	P=0.003N	P=0.328	P=0.004N	P=0.007N
Logistic regression test	P=0.001N	P=0.348	P=0.002N	P=0.004N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.339	P=0.001N	P=0.002N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/50 (24%)	7/50 (14%)	9/50 (18%)	6/50 (12%)
Adjusted rate	28.3%	17.9%	21.7%	15.4%
Terminal rate	10/40 (25%)	7/39 (18%)	7/39 (18%)	6/39 (15%)
First incidence (days)	683	726 (T)	594	726 (T)
Life table test	P=0.180N	P=0.170N	P=0.347N	P=0.110N
Logistic regression test	P=0.197N	P=0.158N	P=0.358N	P=0.120N
Cochran-Armitage test	P=0.169N			
Fisher exact test		P=0.154N	P=0.312N	P=0.096N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate	6.8%	9.7%	2.6%	5.1%
Terminal rate	1/40 (3%)	3/39 (8%)	1/39 (3%)	2/39 (5%)
First incidence (days)	680	618	726 (T)	726 (T)
Life table test	P=0.406N	P=0.489	P=0.327N	P=0.519N
Logistic regression test	P=0.404N	P=0.498	P=0.318N	P=0.516N
Cochran-Armitage test	P=0.393N			
Fisher exact test		P=0.500	P=0.309N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/50 (30%)	11/50 (22%)	10/50 (20%)	8/50 (16%)
Adjusted rate	33.8%	27.2%	24.2%	20.5%
Terminal rate	11/40 (28%)	10/39 (26%)	8/39 (21%)	8/39 (21%)
First incidence (days)	680	618	594	726 (T)
Life table test	P=0.133N	P=0.277N	P=0.218N	P=0.096N
Logistic regression test	P=0.142N	P=0.244N	P=0.214N	P=0.098N
Cochran-Armitage test	P=0.119N			
Fisher exact test		P=0.247N	P=0.178N	P=0.077N
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adjusted rate	7.0%	0.0%	2.3%	2.6%
Terminal rate	2/40 (5%)	0/39 (0%)	0/39 (0%)	1/39 (3%)
First incidence (days)	647	—	606	726 (T)
Life table test	P=0.535N	P=0.127N	P=0.330N	P=0.324N
Logistic regression test	P=0.519N	P=0.121N	P=0.292N	P=0.313N
Cochran-Armitage test	P=0.522N			
Fisher exact test		P=0.121N	P=0.309N	P=0.309N
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	2/50 (4%)	5/50 (10%)	0/50 (0%)
Adjusted rate	2.4%	4.3%	11.2%	0.0%
Terminal rate	0/40 (0%)	0/39 (0%)	1/39 (3%)	0/39 (0%)
First incidence (days)	725	405	560	—
Life table test	P=0.200N	P=0.499	P=0.099	P=0.510N
Logistic regression test	P=0.132N	P=0.433	P=0.120	P=0.511N
Cochran-Armitage test	P=0.187N			
Fisher exact test		P=0.500	P=0.102	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	2/50 (4%)	5/50 (10%)	0/50 (0%)
Adjusted rate	4.6%	4.3%	11.2%	0.0%
Terminal rate	0/40 (0%)	0/39 (0%)	1/39 (3%)	0/39 (0%)
First incidence (days)	680	405	560	—
Life table test	P=0.149N	P=0.687	P=0.203	P=0.255N
Logistic regression test	P=0.092N	P=0.650	P=0.331	P=0.240N
Cochran-Armitage test	P=0.135N			
Fisher exact test		P=0.691N	P=0.218	P=0.247N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.9%	0.0%	0.0%	2.5%
Terminal rate	2/40 (5%)	0/39 (0%)	0/39 (0%)	0/39 (0%)
First incidence (days)	447	—	—	707
Life table test	P=0.589N	P=0.126N	P=0.129N	P=0.322N
Logistic regression test	P=0.566N	P=0.138N	P=0.092N	P=0.275N
Cochran-Armitage test	P=0.579N			
Fisher exact test		P=0.121N	P=0.121N	P=0.309N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rate	9.5%	5.1%	5.0%	7.4%
Terminal rate	3/40 (8%)	2/39 (5%)	1/39 (3%)	2/39 (5%)
First incidence (days)	680	726 (T)	707	705
Life table test	P=0.588	P=0.351N	P=0.358N	P=0.519N
Logistic regression test	P=0.577	P=0.337N	P=0.361N	P=0.526N
Cochran-Armitage test	P=0.600			
Fisher exact test		P=0.339N	P=0.339N	P=0.500N
All Organs: Benign Neoplasms				
Overall rate	36/50 (72%)	28/50 (56%)	21/50 (42%)	18/50 (36%)
Adjusted rate	78.2%	68.2%	46.6%	42.3%
Terminal rate	30/40 (75%)	26/39 (67%)	15/39 (38%)	15/39 (38%)
First incidence (days)	540	705	520	405
Life table test	P=0.004N	P=0.104N	P=0.010N	P=0.001N
Logistic regression test	P=0.003N	P=0.063N	P=0.004N	P<0.001N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.072N	P=0.002N	P<0.001N
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	25/50 (50%)	16/50 (32%)	15/50 (30%)
Adjusted rate	36.8%	50.0%	35.5%	34.6%
Terminal rate	11/40 (28%)	14/39 (36%)	10/39 (26%)	11/39 (28%)
First incidence (days)	447	405	560	405
Life table test	P=0.189N	P=0.105	P=0.546N	P=0.464N
Logistic regression test	P=0.130N	P=0.108	P=0.524N	P=0.423N
Cochran-Armitage test	P=0.136N			
Fisher exact test		P=0.078	P=0.500N	P=0.415N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	41/50 (82%)	31/50 (62%)	29/50 (58%)
Adjusted rate	87.8%	82.0%	66.0%	62.8%
Terminal rate	34/40 (85%)	30/39 (77%)	23/39 (59%)	22/39 (56%)
First incidence (days)	447	405	520	405
Life table test	P=0.019N	P=0.490N	P=0.045N	P=0.018N
Logistic regression test	P=0.002N	P=0.388N	P=0.010N	P=0.002N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.393N	P=0.006N	P=0.002N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pancreatic islets; 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 dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed 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 a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Hepatocellular Neoplasms in Male B6C3F$_1$ Mice Administered Water by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	40/315 (12.7%)	39/315 (12.4%)	74/315 (23.5%)
Standard deviation	5.2%	6.1%	7.2%
Range	4%-18%	6%-24%	14%-36%

[a] Data as of 17 June 1994

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	20	20	20	20
Early deaths				
Accidental deaths			2	2
Moribund	4	7	4	7
Natural deaths	6	4	5	2
Survivors				
Terminal sacrifice	40	39	39	39
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Clear cell focus	1 (10%)	1 (10%)	1 (10%)	
Eosinophilic focus	1 (10%)	2 (20%)	1 (10%)	
Fatty change	2 (20%)	4 (40%)		
Mixed cell focus	1 (10%)		2 (20%)	
Bile duct, hyperplasia	1 (10%)	1 (10%)		
Hepatocyte, hypertrophy		1 (10%)		
Mesentery	(1)			
Fat, inflammation, chronic active	1 (100%)			
Pancreas	(10)	(10)	(10)	(10)
Atrophy		1 (10%)		1 (10%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Hyperplasia, focal			1 (10%)	2 (20%)
Tooth			(1)	
Dysplasia			1 (100%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia	4 (40%)	1 (10%)	2 (20%)	2 (20%)
Capsule, hyperplasia, adenomatous	1 (10%)		1 (10%)	3 (30%)
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia	3 (30%)	7 (70%)	4 (40%)	
Pituitary gland	(10)	(9)	(9)	(9)
Cyst	1 (10%)		1 (11%)	
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)		
Preputial gland	(10)	(10)	(9)	(10)
Duct, ectasia	10 (100%)	9 (90%)	8 (89%)	9 (90%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Ten animals per group received ophthalmic examinations and were discarded without further evaluation

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
Skeletal muscle		(1)		
Degeneration		1 (100%)		
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia			1 (10%)	1 (10%)
Special Senses System				
Eye				(1)
Degeneration				1 (100%)
Harderian gland	(4)	(2)	(2)	(3)
Inflammation, chronic active			2 (100%)	2 (67%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	10 (100%)	9 (90%)	10 (100%)	6 (60%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Integumentary System				
Nervous System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Periesophageal tissue, inflammation, suppurative	1 (2%)			1 (2%)
Gallbladder	(49)	(49)	(49)	(49)
Inflammation, chronic active		1 (2%)		
Intestine small, jejunum	(50)	(50)	(49)	(50)
Hyperplasia, lymphoid				1 (2%)
Ulcer			1 (2%)	1 (2%)
Intestine small, ileum	(49)	(49)	(50)	(48)
Amyloid deposition				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Amyloid deposition				1 (2%)
Basophilic focus	3 (6%)	4 (8%)	3 (6%)	
Clear cell focus	12 (24%)	4 (8%)	2 (4%)	
Eosinophilic focus	21 (42%)	12 (24%)	7 (14%)	2 (4%)
Fatty change	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	2 (4%)			2 (4%)
Inflammation, chronic active	1 (2%)			1 (2%)
Mixed cell focus	5 (10%)	7 (14%)	7 (14%)	1 (2%)
Necrosis	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Mesentery	(4)	(3)	(3)	(2)
Infiltration cellular, lymphocyte			1 (33%)	
Fat, inflammation, chronic active			1 (33%)	1 (50%)
Fat, necrosis	2 (50%)	2 (67%)	1 (33%)	
Pancreas	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	1 (2%)		1 (2%)
Hyperplasia			1 (2%)	
Necrosis		1 (2%)		
Duct, cyst		1 (2%)		2 (4%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia, focal	3 (6%)	2 (4%)	2 (4%)	6 (12%)
Stomach, glandular	(50)	(50)	(50)	(50)
Inflammation, chronic active, focal		1 (2%)		
Tooth	(14)	(4)	(4)	(2)
Dysplasia	13 (93%)	3 (75%)	2 (50%)	1 (50%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, inflammation, chronic active				1 (2%)
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic active		2 (4%)	1 (2%)	
Mineralization	2 (4%)			
Artery, inflammation, chronic active				1 (2%)
Artery, mineralization			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)		1 (2%)	1 (2%)
Hyperplasia	23 (46%)	17 (34%)	18 (36%)	25 (50%)
Capsule, hyperplasia, adenomatous	7 (14%)	2 (4%)	7 (14%)	3 (6%)
Adrenal medulla	(49)	(45)	(50)	(50)
Hyperplasia		3 (7%)		
Inflammation, chronic active	1 (2%)			
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	29 (58%)	23 (46%)	8 (16%)	2 (4%)
Parathyroid gland	(46)	(41)	(47)	(43)
Hyperplasia			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(48)	(47)	(46)	(44)
Pars distalis, hyperplasia	1 (2%)		1 (2%)	
Pars intermedia, hyperplasia				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, hyperplasia	13 (26%)	15 (30%)	13 (26%)	5 (10%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)	2 (4%)		
Inflammation, chronic active				1 (2%)
Artery, inflammation, chronic active			1 (2%)	
Preputial gland	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Duct, ectasia	47 (94%)	49 (98%)	48 (96%)	45 (90%)
Prostate	(49)	(50)	(50)	(50)
Inflammation, chronic active			2 (4%)	2 (4%)
Artery, inflammation, chronic active			1 (2%)	
Seminal vesicle	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	
Testes	(50)	(50)	(50)	(50)
Atrophy	2 (4%)			
Interstitial cell, hyperplasia				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Thrombosis				1 (2%)
Erythroid cell, hyperplasia		4 (8%)		2 (4%)
Myeloid cell, hyperplasia	1 (2%)	4 (8%)	5 (10%)	5 (10%)
Lymph node	(2)		(2)	(3)
Lumbar, hyperplasia, lymphoid				1 (33%)
Mediastinal, hyperplasia, lymphoid	1 (50%)			
Lymph node, mandibular	(49)	(48)	(47)	(46)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)
Lymph node, mesenteric	(48)	(46)	(47)	(47)
Hematopoietic cell proliferation	2 (4%)			1 (2%)
Hyperplasia, lymphoid	1 (2%)			
Hyperplasia, plasma cell				1 (2%)
Inflammation, chronic active		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Amyloid deposition				1 (2%)
Angiectasis	1 (2%)			
Depletion lymphoid		1 (2%)	1 (2%)	3 (6%)
Hematopoietic cell proliferation	8 (16%)	12 (24%)	14 (28%)	12 (24%)
Hyperplasia, lymphoid	1 (2%)			
Thymus	(42)	(44)	(40)	(40)
Atrophy	6 (14%)	12 (27%)	4 (10%)	7 (18%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Ulcer				1 (2%)
Subcutaneous tissue, inflammation, chronic active		2 (4%)		
Subcutaneous tissue, lymphangiectasis	1 (2%)			
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage, acute			1 (2%)	
Artery, inflammation, chronic active			1 (2%)	
Neuron, necrosis	1 (2%)		1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Embolus	1 (2%)			
Hemorrhage, acute			1 (2%)	
Inflammation, chronic active			2 (4%)	1 (2%)
Inflammation, suppurative	1 (2%)			1 (2%)
Pigmentation, hemosiderin		1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia	8 (16%)	3 (6%)	2 (4%)	1 (2%)
Nose	(50)	(50)	(50)	(50)
Hemorrhage, acute			1 (2%)	
Inflammation, suppurative		1 (2%)		2 (4%)
Trachea	(50)	(50)	(50)	(50)
Peritracheal tissue, hemorrhage, acute			1 (2%)	
Special Senses System				
Eye		(3)	(1)	(2)
Cornea, inflammation, chronic active		1 (33%)	1 (100%)	1 (50%)
Cornea, necrosis		1 (33%)		
Harderian gland	(16)	(18)	(19)	(13)
Hyperplasia	1 (6%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	6 (12%)		2 (4%)	3 (6%)
Hydronephrosis				1 (2%)
Infarct			1 (2%)	
Inflammation, chronic active	2 (4%)		2 (4%)	2 (4%)
Necrosis		1 (2%)		1 (2%)
Nephropathy	48 (96%)	46 (92%)	42 (84%)	37 (74%)
Artery, inflammation, chronic active			2 (4%)	
Glomerulus, amyloid deposition				1 (2%)
Renal tubule, hyperplasia		2 (4%)		
Urinary bladder	(50)	(50)	(50)	(49)
Inflammation, chronic active	2 (4%)		2 (4%)	3 (6%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	19	20	20	19
Early deaths				
Accidental deaths	2		1	
Moribund	9	11	7	7
Natural deaths	7	3	5	6
Survivors				
Terminal sacrifice	33	36	37	38
Animals examined microscopically	61	60	60	61
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular adenoma	1 (10%)			
Endocrine System				
Thyroid gland	(10)	(9)	(10)	(10)
Follicular cell, adenoma				1 (10%)
Genital System				
Ovary	(10)	(10)	(10)	(10)
Cystadenoma	1 (10%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study				
Alimentary System				
Gallbladder	(51)	(50)	(49)	(51)
Intestine large, rectum	(51)	(50)	(50)	(50)
Anus, sarcoma			1 (2%)	
Intestine small, duodenum	(51)	(49)	(50)	(51)
Hemangiosarcoma			1 (2%)	
Intestine small, jejunum	(51)	(49)	(50)	(50)
Carcinoma	1 (2%)			
Liver	(51)	(50)	(50)	(51)
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, multiple	1 (2%)			
Hepatocellular carcinoma	7 (14%)	5 (10%)	5 (10%)	4 (8%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)	3 (6%)	
Hepatocellular adenoma	10 (20%)	13 (26%)	9 (18%)	4 (8%)
Hepatocellular adenoma, multiple	5 (10%)	5 (10%)		2 (4%)
Hepatocholangiocarcinoma	1 (2%)			
Histiocytic sarcoma	1 (2%)	2 (4%)		1 (2%)
Bile duct, carcinoma	1 (2%)			
Mesentery	(7)	(9)	(4)	(5)
Carcinoma, metastatic, liver	1 (14%)			
Histiocytic sarcoma				1 (20%)
Pancreas	(51)	(50)	(50)	(51)
Carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma				1 (2%)
Salivary glands	(51)	(50)	(50)	(51)
Stomach, forestomach	(51)	(50)	(50)	(51)
Mast cell tumor benign			1 (2%)	
Squamous cell papilloma			1 (2%)	2 (4%)
Stomach, glandular	(51)	(50)	(50)	(51)
Cardiovascular System				
Heart	(51)	(50)	(50)	(51)
Carcinoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal cortex	(51)	(50)	(50)	(51)
Capsule, adenoma		1 (2%)		
Adrenal medulla	(51)	(49)	(49)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign		2 (4%)		
Islets, pancreatic	(51)	(50)	(50)	(51)
Adenoma		1 (2%)	1 (2%)	
Pituitary gland	(50)	(47)	(47)	(46)
Pars distalis, adenoma	4 (8%)	3 (6%)	3 (6%)	3 (7%)
Pars intermedia, adenoma		1 (2%)		1 (2%)
Thyroid gland	(51)	(50)	(50)	(51)
Follicular cell, adenoma	3 (6%)			2 (4%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
General Body System				
None				
Genital System				
Ovary	(51)	(49)	(49)	(51)
Cystadenoma	3 (6%)		3 (6%)	1 (2%)
Fibroma		1 (2%)		
Hemangiosarcoma	1 (2%)			
Luteoma				1 (2%)
Uterus	(51)	(50)	(50)	(51)
Adenoma	1 (2%)			
Hemangioma			1 (2%)	
Hemangiosarcoma	1 (2%)			
Hemangiosarcoma, metastatic, ovary	1 (2%)			
Polyp stromal	1 (2%)			
Sarcoma stromal	1 (2%)	1 (2%)		
Hematopoietic System				
Bone marrow	(51)	(50)	(50)	(51)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma	1 (2%)			
Lymph node	(6)	(5)	(4)	(3)
Bronchial, carcinoma, metastatic, harderian gland			1 (25%)	
Bronchial, carcinoma, metastatic, liver	1 (17%)			
Bronchial, hepatocholangiocarcinoma, metastatic, liver	1 (17%)			
Mediastinal, carcinoma, metastatic, liver	1 (17%)			
Mediastinal, hepatocholangiocarcinoma, metastatic, liver	1 (17%)			
Mediastinal, histiocytic sarcoma	1 (17%)			1 (33%)
Lymph node, mandibular	(50)	(46)	(48)	(51)
Lymph node, mesenteric	(50)	(47)	(49)	(48)
Spleen	(51)	(50)	(50)	(51)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Thymus	(48)	(43)	(46)	(45)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Mast cell tumor malignant				1 (2%)
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)	
Integumentary System				
Skin	(51)	(50)	(50)	(51)
Squamous cell carcinoma				1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	1 (2%)	
Subcutaneous tissue, hemangiosarcoma		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Musculoskeletal System				
Bone	(51)	(50)	(50)	(51)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Skeletal muscle	(1)		(1)	
Hepatocholangiocarcinoma, metastatic, liver	1 (100%)			
Rhabdomyosarcoma			1 (100%)	
Nervous System				
None				
Respiratory System				
Lung	(51)	(50)	(50)	(51)
Alveolar/bronchiolar adenoma	3 (6%)	4 (8%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)		1 (2%)	
Carcinoma, metastatic, liver	1 (2%)			
Hemangiosarcoma, metastatic, ovary	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	1 (2%)	2 (4%)	5 (10%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Special Senses System				
Harderian gland	(17)	(14)	(15)	(13)
Adenoma	1 (6%)	3 (21%)	2 (13%)	1 (8%)
Carcinoma	2 (12%)	1 (7%)	1 (7%)	
Urinary System				
Kidney	(51)	(50)	(50)	(51)
Carcinoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Urinary bladder	(50)	(48)	(49)	(51)
Systemic Lesions				
Multiple organs[c]	(51)	(50)	(50)	(51)
Histiocytic sarcoma	1 (2%)	2 (4%)		1 (2%)
Lymphoma malignant lymphocytic	2 (4%)	3 (6%)	2 (4%)	4 (8%)
Lymphoma malignant mixed	7 (14%)	5 (10%)	6 (12%)	3 (6%)
Lymphoma malignant undifferentiated cell			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	1			1
2-Year study	40	36	35	29
Total primary neoplasms				
15-Month interim evaluation	2			1
2-Year study	62	58	45	35
Total animals with benign neoplasms				
15-Month interim evaluation	1			1
2-Year study	24	25	21	18
Total benign neoplasms				
15-Month interim evaluation	2			1
2-Year study	31	34	22	19
Total animals with malignant neoplasms				
2-Year study	26	22	21	14
Total malignant neoplasms				
2-Year study	31	24	23	16
Total animals with metastatic neoplasms				
2-Year study	5	2	7	1
Total metastatic neoplasms				
2-Year study	19	2	8	1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Nine or ten animals per group received ophthalmic examinations and were discarded without further evaluation
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control

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

+: 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 Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	3 5 7	3 5 9	3 6 2	3 6 8	3 7 2	3 7 7	3 8 6	3 9 2	3 9 9	4 0 3	4 0 5	4 0 9	3 4 3	3 4 4	3 4 5	3 5 3	3 6 4	6 6	3 8 1	3 8 2	3 8 3	3 8 9	4 0 2	4 0 6	4 0 7	4 1 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma									X																	1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma			X						X	X										X					X	7
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma		X					X			X					X	X		X						X		10
Hepatocellular adenoma, multiple											X										X		X			5
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma																										1
Bile duct, carcinoma																										1
Mesentery		+					+																			7
Carcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma									X						X		X									4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma											X					X										3
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	0 7 3	3 0 7	4 9 2	5 1 1	5 1 1	5 8 4	6 9 4	6 0 4	6 1 0	6 1 1	6 1 1	6 1 8	6 6 1	6 7 9	7 0 7	7 0 9	7 1 2	7 1 7	7 2 0	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	4 0 0	3 0 8	4 0 4	3 6 7	3 9 3	3 7 5	3 7 3	3 5 1	3 6 5	3 9 5	3 9 5	3 9 6	3 9 0	3 4 2	3 9 4	3 7 6	3 4 7	3 5 5	3 8 0	3 7 8	3 8 7	3 9 8	3 4 6	3 4 8	3 4 9	3 5 4
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma				X								X			X											
Hemangiosarcoma																			X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Hemangiosarcoma																										
Hemangiosarcoma, metastatic, ovary																			X							
Polyp stromal																										
Sarcoma stromal																										
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																							
Lymph node			+				+		+	+								+								
Bronchial, carcinoma, metastatic, liver																		X								
Bronchial, hepatocholangiocarcinoma, metastatic, liver										X																
Mediastinal, carcinoma, metastatic, liver																		X								
Mediastinal, hepatocholangiocarcinoma, metastatic, liver										X																
Mediastinal, histiocytic sarcoma			X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Histiocytic sarcoma			X																							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver										X																
Histiocytic sarcoma			X																							
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma															X											
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver										X																
Skeletal muscle										+																
Hepatocholangiocarcinoma, metastatic, liver										X																

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	3 5 7	3 5 9	3 6 2	3 6 8	3 7 2	3 7 7	3 8 6	3 9 2	3 9 9	4 0 3	4 0 5	4 0 9	3 4 3	3 4 4	3 4 5	3 5 3	3 6 4	3 6 6	3 8 1	3 8 2	3 8 3	3 8 9	4 0 2	4 0 6	4 0 7	4 1 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cystadenoma																											3
Hemangiosarcoma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma														X													1
Hemangiosarcoma								X																			1
Hemangiosarcoma, metastatic, ovary																											1
Polyp stromal													X														1
Sarcoma stromal	X																										1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Lymph node																						+					6
Bronchial, carcinoma, metastatic, liver																											1
Bronchial, hepatocholangiocarcinoma, metastatic, liver																											1
Mediastinal, carcinoma, metastatic, liver																											1
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																											1
Mediastinal, histiocytic sarcoma																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																								X			1
Histiocytic sarcoma																											1
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, fibrosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocholangiocarcinoma, metastatic, liver																											1
Skeletal muscle																											1
Hepatocholangiocarcinoma, metastatic, liver																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	0 7 7	3 3 3	4 9 2	5 1 1	5 8 1	5 9 4	6 0 4	6 1 0	6 1 1	6 1 1	6 1 8	6 6 1	6 7 9	7 0 7	7 0 9	7 1 2	7 1 7	7 2 0	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	4 0 0	3 8 8	4 0 4	3 6 7	3 9 3	3 7 5	3 7 3	3 5 1	3 6 5	3 9 5	3 9 6	3 9 0	3 4 2	3 9 4	3 7 6	3 4 7	3 5 5	3 8 0	3 7 8	3 8 7	3 9 8	3 4 6	3 4 8	3 4 9	3 5 4
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve											+							+							
Spinal cord											+							+							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X				X										
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, harderian gland				X																					
Carcinoma, metastatic, liver																	X								
Hemangiosarcoma, metastatic, ovary																		X							
Hepatocellular carcinoma, metastatic, liver													X												
Hepatocholangiocarcinoma, metastatic, liver										X															
Histiocytic sarcoma			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+																					
Harderian gland	+	M	+	+	M	+	M	+	M	M	M	M	M	+	+	M	M	M	+	M	+	M	+	M	M
Adenoma																									
Carcinoma				X				X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver																	X								
Hepatocholangiocarcinoma, metastatic, liver										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed							X		X									X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: Vehicle Control (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	7 3 0	
Carcass ID Number	3 5 7	3 5 9	3 6 2	3 6 8	3 7 2	3 7 7	3 8 6	3 9 2	3 9 9	4 0 3	4 0 5	4 0 9	3 4 3	3 4 4	3 4 5	3 5 3	3 6 4	3 6 6	3 8 1	3 8 2	3 8 3	3 8 9	4 0 2	4 0 6	4 0 7	4 1 0	Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Peripheral nerve																											2
Spinal cord																											2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma																			X								3
Alveolar/bronchiolar carcinoma			X																								1
Carcinoma, metastatic, harderian gland																											1
Carcinoma, metastatic, liver																											1
Hemangiosarcoma, metastatic, ovary																											1
Hepatocellular carcinoma, metastatic, liver																											1
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye		+																									2
Harderian gland	M	+	M	M	M	M	M	+	M	+	M	M	+	M	+	+	M	M	M	M	+	M	M	M	M	M	17
Adenoma		X																									1
Carcinoma																											2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, liver																											1
Hepatocholangiocarcinoma, metastatic, liver																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Lymphoma malignant lymphocytic																						X					2
Lymphoma malignant mixed							X	X							X								X				7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	7228	7228	7228	7228	7228	7228	7228	7228	7228	7228	7228	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	
Carcass ID Number	4496	4497	5007	5008	5510	5113	5114	5118	5119	5124	5125	4473	4774	4475	4787	5201	5505	5566	5209	5512	5525	5521	5522	5523	5536	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma	X				X													X						X		5
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma									X	X				X		X			X			X	X	X		X	13
Hepatocellular adenoma, multiple								X										X								5
Histiocytic sarcoma																										2
Mesentery							+	+	+			+							+						+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma													X													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	41
Pituitary gland	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma																										3
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Fibroma														X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 1 mg/kg (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	7 3 0	
Carcass ID Number	4 9 6	4 9 7	5 0 7	5 0 8	5 1 0	5 1 3	5 1 4	5 1 8	5 1 9	5 2 4	5 3 5	4 7 3	4 7 4	4 7 5	4 8 7	5 0 1	5 0 5	5 0 6	5 0 9	5 1 2	5 1 5	5 2 1	5 2 2	5 3 3	5 3 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																+				+						5
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										2
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X	X																	X	4
Alveolar/bronchiolar carcinoma											X															3
Hepatocellular carcinoma, metastatic, liver					X																			X		2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																					+					2
Harderian gland	+	+	+	M	+	M	M	M	M	+	M	M	M	M	+	M	M	+	M	M	M	+	M	+	+	14
Adenoma																						X			X	3
Carcinoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic							X		X																	3
Lymphoma malignant mixed										X										X						5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	56 7	56 8	57 2	58 0	58 5	59 1	59 3	59 7	59 8	60 0	60 0	60 0	54 1	54 3	54 9	56 4	56 5	57 4	57 5	57 9	59 0	59 2	60 1	60 6	60 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Anus, sarcoma										X																1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma													X													5
Hepatocellular carcinoma, multiple								X			X															3
Hepatocellular adenoma			X						X								X							X		9
Mesentery													+				+				+					4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor benign					X																					1
Squamous cell papilloma															X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	M	+	+	M	+	M	+	+	M	+	M	+	+	+	+	M	+	M	+	+	+	+	M	37
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Pars distalis, adenoma																			X							3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Cystadenoma												X					X			X						3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	2 4 3	3 0 2	3 5 6	3 7 3	5 1 0	5 7 8	6 0 4	6 1 7	6 4 7	6 7 6	6 7 8	6 8 5	7 0 6	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	5 4 4	5 9 5	5 8 7	6 0 4	5 5 8	6 1 0	6 0 2	5 8 1	5 8 4	5 4 5	5 7 7	5 7 8	5 8 8	5 7 1	5 8 6	5 8 9	5 4 2	5 4 6	5 4 8	5 5 3	5 5 6	5 5 9	5 6 1	5 6 2	5 6 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+				+			+													
Bronchial, carcinoma, metastatic, harderian gland												X													
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle																									X
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									+
Rhabdomyosarcoma																									X
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma													X												
Carcinoma, metastatic, harderian gland												X													
Hepatocellular carcinoma, metastatic, liver								X	X	X	X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye												+					+								
Harderian gland	M	M	M	M	M	M	M	+	+	+	M	+	+	M	+	+	M	+	M	+	M	+	M	M	+
Adenoma										X												X			
Carcinoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed									X						X	X									
Lymphoma malignant undifferentiated cell type																						X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 5 mg/kg (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	5 6 7	5 6 8	5 6 7 2	5 8 0	5 8 5	5 9 1	5 9 3	5 9 7	5 9 8	6 0 0	6 0 5	6 0 8	5 4 1	5 4 3	5 4 9	5 6 4	5 6 5	5 7 4	5 7 5	5 7 9	5 9 0	5 9 2	6 0 1	6 0 6	6 0 9	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node												+													4
Bronchial, carcinoma, metastatic, harderian gland																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M 48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle																									1
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																	X								1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									1
Rhabdomyosarcoma																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X								1
Alveolar/bronchiolar carcinoma																									1
Carcinoma, metastatic, harderian gland																									1
Hepatocellular carcinoma, metastatic, liver											X														5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Eye																									2
Harderian gland	M	+	M	M	M	M	M	+	M	M	M	M	M	+	M	M	M	M	M	M	+	M	M	M	M 15
Adenoma																									2
Carcinoma																									1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																					X				2
Lymphoma malignant mixed								X										X						X	6
Lymphoma malignant undifferentiated cell type																									1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 5 2	6 5 6	6 5 7	6 6 1	6 6 2	6 7 2	6 8 0	6 1 2	6 1 3	6 1 4	6 1 5	6 1 7	6 1 8	6 3 1	6 3 3	6 3 6	6 4 5	6 5 4	6 6 3	6 6 4	6 6 5	6 6 7	6 7 3	6 7 4	6 7 6	6 7 9	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma							X																			X	4
Hepatocellular adenoma											X					X						X					4
Hepatocellular adenoma, multiple																								X			2
Histiocytic sarcoma																											1
Mesentery																						+		+			5
Histiocytic sarcoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma		X																									2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	M	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Pituitary gland	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Pars distalis, adenoma																											3
Pars intermedia, adenoma						X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma								X																			2
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cystadenoma											X																1
Luteoma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	3 5 0	3 9 9	4 3 2	4 6 8	5 4 4	5 5 1	6 0 4	6 3 6	6 7 0	6 7 7	6 8 0	6 9 1	6 9 4	7 2 6	7 2 6	7 2 6	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	6 7 8	6 4 0	6 6 9	6 6 8	6 4 6	6 5 5	6 4 1	6 2 6	6 2 9	6 2 1	6 5 0	6 4 4	6 7 0	6 1 6	6 3 5	6 5 8	6 5 9	6 7 5	6 2 2	6 2 3	6 2 4	6 3 4	6 4 3	6 4 7	6 4 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node										+		+	+												
Mediastinal, histiocytic sarcoma												X													
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Thymus	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Mast cell tumor malignant																									X
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	M																								
Spinal cord	+																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma							X																		
Hepatocellular carcinoma, metastatic, liver																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland	M	+	M	M	M	+	M	M	M	M	+	+	M	M	M	+	M	+	M	+	M	M	M	M	M
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Lymphoma malignant lymphocytic						X		X		X			X												
Lymphoma malignant mixed																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate: 25 mg/kg (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 5 2	6 5 6	6 5 7	6 6 1	6 6 2	6 7 2	6 8 0	6 1 2	6 1 3	6 1 4	6 1 5	6 1 7	6 1 8	6 3 1	6 3 3	6 3 6	6 4 5	6 5 4	6 6 3	6 6 4	6 6 5	6 6 7	6 7 3	6 7 4	6 7 6	6 7 9	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																		X									1
Lymph node																											3
Mediastinal, histiocytic sarcoma																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Mast cell tumor malignant																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell carcinoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Peripheral nerve																											
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma					X																X						2
Alveolar/bronchiolar carcinoma																											1
Hepatocellular carcinoma, metastatic, liver																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Harderian gland	M	+	+	M	+	M	M	+	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	13
Adenoma										X																	1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Lymphoma malignant lymphocytic																											4
Lymphoma malignant mixed	X		X						X																		3

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	1/51 (2%)	3/50 (6%)	2/50 (4%)	1/51 (2%)
Adjusted rate[b]	3.0%	7.5%	5.1%	2.6%
Terminal rate[c]	1/33 (3%)	2/36 (6%)	1/37 (3%)	1/38 (3%)
First incidence (days)	726 (T)	482	676	726 (T)
Life table test[d]	P=0.380N	P=0.328	P=0.532	P=0.730N
Logistic regression test[d]	P=0.402N	P=0.285	P=0.497	P=0.730N
Cochran-Armitage test[d]	P=0.402N			
Fisher exact test[d]		P=0.301	P=0.492	P=0.752N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/51 (6%)	4/50 (8%)	3/50 (6%)	1/51 (2%)
Adjusted rate	7.2%	10.2%	7.5%	2.6%
Terminal rate	1/33 (3%)	3/36 (8%)	1/37 (3%)	1/38 (3%)
First incidence (days)	511	482	676	726 (T)
Life table test	P=0.157N	P=0.522	P=0.642N	P=0.285N
Logistic regression test	P=0.169N	P=0.450	P=0.653	P=0.320N
Cochran-Armitage test	P=0.166N			
Fisher exact test		P=0.489	P=0.652	P=0.309N
Liver: Hepatocellular Adenoma				
Overall rate	15/51 (29%)	18/50 (36%)	9/50 (18%)	6/51 (12%)
Adjusted rate	42.3%	47.1%	22.8%	15.4%
Terminal rate	13/33 (39%)	16/36 (44%)	7/37 (19%)	5/38 (13%)
First incidence (days)	604	676	578	694
Life table test	P=0.004N	P=0.439	P=0.077N	P=0.011N
Logistic regression test	P=0.005N	P=0.368	P=0.119N	P=0.017N
Cochran-Armitage test	P=0.007N			
Fisher exact test		P=0.311	P=0.133N	P=0.024N
Liver: Hepatocellular Carcinoma				
Overall rate	8/51 (16%)	6/50 (12%)	8/50 (16%)	4/51 (8%)
Adjusted rate	21.1%	16.0%	19.1%	10.3%
Terminal rate	5/33 (15%)	5/36 (14%)	4/37 (11%)	3/38 (8%)
First incidence (days)	594	680	617	694
Life table test	P=0.145N	P=0.337N	P=0.542N	P=0.139N
Logistic regression test	P=0.151N	P=0.381N	P=0.571	P=0.170N
Cochran-Armitage test	P=0.167N			
Fisher exact test		P=0.403N	P=0.590	P=0.179N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	22/51 (43%)	21/50 (42%)	16/50 (32%)	9/51 (18%)
Adjusted rate	57.1%	55.0%	37.0%	23.1%
Terminal rate	17/33 (52%)	19/36 (53%)	10/37 (27%)	8/38 (21%)
First incidence (days)	594	676	578	694
Life table test	P=0.001N	P=0.371N	P=0.106N	P=0.002N
Logistic regression test	P=0.002N	P=0.466N	P=0.165N	P=0.003N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.534N	P=0.171N	P=0.005N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/51 (6%)	4/50 (8%)	1/50 (2%)	2/51 (4%)
Adjusted rate	8.0%	11.1%	2.7%	5.3%
Terminal rate	1/33 (3%)	4/36 (11%)	1/37 (3%)	2/38 (5%)
First incidence (days)	618	726 (T)	726 (T)	726 (T)
Life table test	P=0.354N	P=0.535	P=0.286N	P=0.453N
Logistic regression test	P=0.381N	P=0.506	P=0.312N	P=0.493N
Cochran-Armitage test	P=0.387N			
Fisher exact test		P=0.489	P=0.316N	P=0.500N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/51 (2%)	3/50 (6%)	1/50 (2%)	1/51 (2%)
Adjusted rate	3.0%	7.3%	2.6%	2.2%
Terminal rate	1/33 (3%)	1/36 (3%)	0/37 (0%)	0/38 (0%)
First incidence (days)	726 (T)	590	706	604
Life table test	P=0.431N	P=0.326	P=0.748N	P=0.745N
Logistic regression test	P=0.440N	P=0.298	P=0.762N	P=0.760
Cochran-Armitage test	P=0.439N			
Fisher exact test		P=0.301	P=0.748	P=0.752N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/51 (8%)	7/50 (14%)	2/50 (4%)	3/51 (6%)
Adjusted rate	10.8%	17.9%	5.3%	7.4%
Terminal rate	2/33 (6%)	5/36 (14%)	1/37 (3%)	2/38 (5%)
First incidence (days)	618	590	706	604
Life table test	P=0.256N	P=0.302	P=0.313N	P=0.450N
Logistic regression test	P=0.277N	P=0.262	P=0.344N	P=0.496N
Cochran-Armitage test	P=0.280N			
Fisher exact test		P=0.251	P=0.348N	P=0.500N
Ovary: Cystadenoma				
Overall rate	3/51 (6%)	0/49 (0%)	3/49 (6%)	1/51 (2%)
Adjusted rate	7.1%	0.0%	8.3%	2.6%
Terminal rate	0/33 (0%)	0/35 (0%)	3/36 (8%)	1/38 (3%)
First incidence (days)	511	—[c]	726 (T)	726 (T)
Life table test	P=0.406N	P=0.124N	P=0.643N	P=0.289N
Logistic regression test	P=0.426N	P=0.142N	P=0.645	P=0.316N
Cochran-Armitage test	P=0.427N			
Fisher exact test		P=0.129N	P=0.642	P=0.309N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/50 (8%)	3/47 (6%)	3/47 (6%)	3/46 (7%)
Adjusted rate	11.8%	8.8%	7.5%	8.2%
Terminal rate	3/33 (9%)	3/34 (9%)	1/35 (3%)	2/33 (6%)
First incidence (days)	720	726 (T)	604	670
Life table test	P=0.525N	P=0.482N	P=0.475N	P=0.484N
Logistic regression test	P=0.562N	P=0.505N	P=0.537N	P=0.543N
Cochran-Armitage test	P=0.557N			
Fisher exact test		P=0.535N	P=0.535N	P=0.547N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/51 (6%)	0/50 (0%)	0/50 (0%)	2/51 (4%)
Adjusted rate	9.1%	0.0%	0.0%	4.9%
Terminal rate	3/33 (9%)	0/36 (0%)	0/37 (0%)	1/38 (3%)
First incidence (days)	726 (T)	—	—	677
Life table test	P=0.509	P=0.106N	P=0.101N	P=0.442N
Logistic regression test	P=0.488	P=0.106N	P=0.101N	P=0.483N
Cochran-Armitage test	P=0.482			
Fisher exact test		P=0.125N	P=0.125N	P=0.500N
All Organs: Hemangiosarcoma				
Overall rate	4/51 (8%)	2/50 (4%)	1/50 (2%)	1/51 (2%)
Adjusted rate	11.3%	4.5%	2.7%	2.6%
Terminal rate	2/33 (6%)	0/36 (0%)	1/37 (3%)	1/38 (3%)
First incidence (days)	709	562	726 (T)	726 (T)
Life table test	P=0.222N	P=0.322N	P=0.159N	P=0.151N
Logistic regression test	P=0.234N	P=0.344N	P=0.170N	P=0.162N
Cochran-Armitage test	P=0.235N			
Fisher exact test		P=0.348N	P=0.187N	P=0.181N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/51 (8%)	2/50 (4%)	2/50 (4%)	1/51 (2%)
Adjusted rate	11.3%	4.5%	5.1%	2.6%
Terminal rate	2/33 (6%)	0/36 (0%)	1/37 (3%)	1/38 (3%)
First incidence (days)	709	562	678	726 (T)
Life table test	P=0.207N	P=0.322N	P=0.307N	P=0.151N
Logistic regression test	P=0.217N	P=0.344N	P=0.336N	P=0.162N
Cochran-Armitage test	P=0.219N			
Fisher exact test		P=0.348N	P=0.348N	P=0.181N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	9/51 (18%)	8/50 (16%)	9/50 (18%)	7/51 (14%)
Adjusted rate	23.0%	21.6%	22.6%	16.2%
Terminal rate	5/33 (15%)	7/36 (19%)	7/37 (19%)	3/38 (8%)
First incidence (days)	581	708	510	551
Life table test	P=0.312N	P=0.447N	P=0.531N	P=0.332N
Logistic regression test	P=0.355N	P=0.497N	P=0.585	P=0.393N
Cochran-Armitage test	P=0.359N			
Fisher exact test		P=0.518N	P=0.584	P=0.393N
All Organs: Benign Neoplasms				
Overall rate	24/51 (47%)	25/50 (50%)	21/50 (42%)	18/51 (35%)
Adjusted rate	60.9%	62.0%	48.7%	43.8%
Terminal rate	18/33 (55%)	21/36 (58%)	15/37 (41%)	15/38 (39%)
First incidence (days)	511	482	578	670
Life table test	P=0.057N	P=0.518N	P=0.235N	P=0.072N
Logistic regression test	P=0.079N	P=0.512	P=0.373N	P=0.129N
Cochran-Armitage test	P=0.090N			
Fisher exact test		P=0.462	P=0.378N	P=0.157N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	26/51 (51%)	22/50 (44%)	21/50 (42%)	14/51 (27%)
Adjusted rate	54.8%	49.5%	47.7%	31.6%
Terminal rate	12/33 (36%)	14/36 (39%)	14/37 (38%)	8/38 (21%)
First incidence (days)	492	532	510	551
Life table test	P=0.017N	P=0.247N	P=0.185N	P=0.016N
Logistic regression test	P=0.017N	P=0.389N	P=0.425N	P=0.025N
Cochran-Armitage test	P=0.012N			
Fisher exact test		P=0.308N	P=0.240N	P=0.013N
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/51 (78%)	36/50 (72%)	35/50 (70%)	29/51 (57%)
Adjusted rate	83.2%	78.0%	76.1%	64.3%
Terminal rate	25/33 (76%)	26/36 (72%)	26/37 (70%)	22/38 (58%)
First incidence (days)	492	482	510	551
Life table test	P=0.019N	P=0.196N	P=0.131N	P=0.013N
Logistic regression test	P=0.021N	P=0.322N	P=0.229N	P=0.029N
Cochran-Armitage test	P=0.014N			
Fisher exact test		P=0.302N	P=0.229N	P=0.017N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pituitary gland, 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 dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed 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 a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Hepatocellular Neoplasms in Female B6C3F$_1$ Mice Administered Water by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	13/315 (4.1%)	8/315 (2.5%)	21/315 (6.7%)
Standard deviation	3.2%	2.1%	4.2%
Range	2%-10%	0%-6%	2%-12%

[a] Data as of 17 June 1994

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	19	20	20	19
Early deaths				
Accidental deaths	2		1	
Moribund	9	11	7	7
Natural deaths	7	3	5	6
Survivors				
Terminal sacrifice	33	36	37	38
Animals examined microscopically	61	60	60	61
15-Month Interim Evaluation				
Alimentary System				
Esophagus	(10)	(10)	(10)	(10)
Periesophageal tissue, inflammation, suppurative			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus			1 (10%)	
Inflammation				1 (10%)
Mixed cell focus	1 (10%)	1 (10%)		
Necrosis				1 (10%)
Pancreas	(10)	(10)	(10)	(10)
Atrophy	1 (10%)			
Stomach, forestomach	(10)	(10)	(10)	(10)
Hyperplasia, focal	2 (20%)		3 (30%)	2 (20%)
Cardiovascular System				
Blood vessel	(10)	(10)	(10)	(10)
Aorta, inflammation, chronic active			1 (10%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)			
Parathyroid gland	(10)	(7)	(9)	(8)
Cyst	1 (10%)			
Inflammation, chronic active			1 (11%)	
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, hyperplasia	3 (30%)			1 (10%)
Thyroid gland	(10)	(9)	(10)	(10)
Follicular cell, hyperplasia	2 (20%)			

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Nine or ten animals per group received ophthalmic examinations and were discarded without further evaluation

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Duct, ectasia		1 (10%)		
Ovary	(10)	(10)	(10)	(10)
Cyst	1 (10%)	3 (30%)	1 (10%)	2 (20%)
Uterus	(10)	(10)	(10)	(10)
Hyperplasia, cystic	5 (50%)	8 (80%)	4 (40%)	4 (40%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Myelofibrosis	1 (10%)	2 (20%)		
Thymus	(9)	(10)	(10)	(10)
Inflammation, chronic active				1 (10%)
Mineralization	1 (11%)			
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)		
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)			
Alveolar epithelium, hyperplasia	1 (10%)			
Special Senses System				
Harderian gland	(1)	(1)	(1)	(3)
Inflammation, chronic active		1 (100%)		
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	5 (50%)	3 (30%)	1 (10%)	2 (20%)
Artery, inflammation, chronic active		1 (10%)		
Systems Examined With No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study				
Alimentary System				
Esophagus	(51)	(50)	(50)	(50)
Perforation	1 (2%)			
Periesophageal tissue, inflammation, suppurative	3 (6%)	1 (2%)	1 (2%)	
Intestine large, rectum	(51)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Intestine small, duodenum	(51)	(49)	(50)	(51)
Ulcer		1 (2%)		
Intestine small, jejunum	(51)	(49)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)	1 (2%)		3 (6%)
Inflammation, chronic active			1 (2%)	
Ulcer			1 (2%)	
Liver	(51)	(50)	(50)	(51)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Basophilic focus	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Clear cell focus		1 (2%)		
Developmental malformation		1 (2%)		
Eosinophilic focus	17 (33%)	10 (20%)	13 (26%)	9 (18%)
Fatty change		1 (2%)		
Hematopoietic cell proliferation		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)			
Mixed cell focus	6 (12%)	6 (12%)	3 (6%)	3 (6%)
Necrosis		1 (2%)	2 (4%)	1 (2%)
Kupffer cell, pigmentation, hemosiderin			1 (2%)	
Mesentery	(7)	(9)	(4)	(5)
Artery, inflammation, chronic active			1 (25%)	
Fat, necrosis	6 (86%)	8 (89%)	2 (50%)	2 (40%)
Pancreas	(51)	(50)	(50)	(51)
Atrophy	5 (10%)	4 (8%)	4 (8%)	
Hypertrophy	1 (2%)			
Inflammation, chronic active		2 (4%)		
Duct, cyst	2 (4%)	4 (8%)	1 (2%)	
Salivary glands	(51)	(50)	(50)	(51)
Artery, inflammation, chronic active			1 (2%)	
Duct, hyperplasia	1 (2%)			
Stomach, forestomach	(51)	(50)	(50)	(51)
Diverticulum				1 (2%)
Hyperplasia, focal	6 (12%)	3 (6%)	9 (18%)	12 (24%)
Infiltration cellular, plasma cell			1 (2%)	
Stomach, glandular	(51)	(50)	(50)	(51)
Erosion	2 (4%)			
Cardiovascular System				
Blood vessel	(51)	(50)	(50)	(51)
Aorta, inflammation, chronic active	1 (2%)			
Heart	(51)	(50)	(50)	(51)
Inflammation, chronic active	1 (2%)			
Mineralization	2 (4%)		1 (2%)	
Artery, inflammation, chronic active			1 (2%)	2 (4%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(51)	(50)	(50)	(51)
Accessory adrenal cortical nodule			2 (4%)	1 (2%)
Hematopoietic cell proliferation			1 (2%)	
Hyperplasia	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Capsule, hyperplasia, adenomatous		1 (2%)		
Adrenal medulla	(51)	(49)	(49)	(50)
Hyperplasia	3 (6%)		2 (4%)	
Islets, pancreatic	(51)	(50)	(50)	(51)
Hyperplasia	1 (2%)	2 (4%)		1 (2%)
Pituitary gland	(50)	(47)	(47)	(46)
Angiectasis		1 (2%)	1 (2%)	
Pars distalis, hyperplasia	24 (48%)	15 (32%)	11 (23%)	13 (28%)
Pars intermedia, hyperplasia				1 (2%)
Thyroid gland	(51)	(50)	(50)	(51)
Inflammation, chronic active	1 (2%)		5 (10%)	1 (2%)
Follicular cell, hyperplasia	16 (31%)	14 (28%)	10 (20%)	8 (16%)
General Body System				
None				
Genital System				
Clitoral gland	(48)	(46)	(48)	(48)
Duct, ectasia				1 (2%)
Ovary	(51)	(49)	(49)	(51)
Cyst	16 (31%)	14 (29%)	11 (22%)	12 (24%)
Inflammation, suppurative		1 (2%)		1 (2%)
Mineralization		1 (2%)		
Uterus	(51)	(50)	(50)	(51)
Angiectasis		1 (2%)	2 (4%)	
Hyperplasia, cystic	38 (75%)	29 (58%)	30 (60%)	23 (45%)
Inflammation, chronic active	1 (2%)	1 (2%)		
Hematopoietic System				
Bone marrow	(51)	(50)	(50)	(51)
Myelofibrosis	22 (43%)	21 (42%)	15 (30%)	13 (25%)
Erythroid cell, hyperplasia	3 (6%)	3 (6%)	4 (8%)	
Myeloid cell, hyperplasia	9 (18%)	5 (10%)	6 (12%)	3 (6%)
Lymph node	(6)	(5)	(4)	(3)
Mediastinal, hyperplasia, lymphoid			1 (25%)	
Renal, angiectasis		1 (20%)		
Lymph node, mandibular	(50)	(46)	(48)	(51)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)		1 (2%)
Lymph node, mesenteric	(50)	(47)	(49)	(48)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	2 (4%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(51)	(50)	(50)	(51)
Depletion lymphoid	2 (4%)			
Hematopoietic cell proliferation	17 (33%)	11 (22%)	17 (34%)	7 (14%)
Hyperplasia, lymphoid	3 (6%)		2 (4%)	2 (4%)
Hyperplasia, plasma cell	1 (2%)			
Thymus	(48)	(43)	(46)	(45)
Atrophy	3 (6%)	7 (16%)	4 (9%)	3 (7%)
Integumentary System				
Mammary gland	(51)	(49)	(50)	(51)
Hyperplasia	1 (2%)	3 (6%)	2 (4%)	4 (8%)
Skin	(51)	(50)	(50)	(51)
Cyst epithelial inclusion				1 (2%)
Inflammation, chronic active	1 (2%)			
Ulcer	1 (2%)			
Subcutaneous tissue, fibrosis, chronic active		1 (2%)		
Musculoskeletal System				
None				
Nervous System				
Brain	(51)	(50)	(50)	(51)
Infarct	1 (2%)			
Artery, inflammation, chronic active			1 (2%)	
Neuron, necrosis	1 (2%)	1 (2%)		2 (4%)
Peripheral nerve	(2)	(2)		
Degeneration	2 (100%)	1 (50%)		
Spinal cord	(2)	(2)		(1)
White matter, degeneration		1 (50%)		
Respiratory System				
Lung	(51)	(50)	(50)	(51)
Inflammation, chronic active	1 (2%)	2 (4%)		
Alveolar epithelium, hyperplasia		1 (2%)		
Trachea	(51)	(50)	(50)	(51)
Artery, inflammation, chronic active			1 (2%)	
Special Senses System				
Eye	(2)	(2)	(2)	
Degeneration		1 (50%)	1 (50%)	
Cornea, inflammation, chronic active	2 (100%)			
Lens, cataract			1 (50%)	
Retina, atrophy			1 (50%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(51)	(50)	(50)	(51)
Cyst	1 (2%)			
Infarct	1 (2%)			
Inflammation, chronic active				1 (2%)
Nephropathy	23 (45%)	21 (42%)	26 (52%)	10 (20%)
Artery, inflammation, chronic active			1 (2%)	1 (2%)
Renal tubule, necrosis, acute	1 (2%)			
Urinary bladder	(50)	(48)	(49)	(51)
Inflammation, chronic active				1 (2%)
Artery, inflammation, chronic active			2 (4%)	1 (2%)

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1988). Scopolamine hydrobromide trihydrate was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA1535, and 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 at least five doses of scopolamine hydrobromide trihydrate. The selected high dose was 10,000 μg/plate. All negative 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, is 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 was 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). Scopolamine hydrobromide trihydrate was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of 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 scopolamine hydrobromide trihydrate; the high dose was limited by toxicity in the trials conducted without S9; with S9, no toxicity was noted and 5 mg/mL was selected as the high dose. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with scopolamine hydrobromide trihydrate in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing scopolamine hydrobromide trihydrate 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 scopolamine hydrobromide trihydrate, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no scopolamine hydrobromide trihydrate 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 a shift in the pH was noted at doses of 2,000 μg/mL and above in the trials conducted with S9, *N*-(2-hydroxyethyl)- piperazine-*N'*-(2-ethanesulfonic acid) (HEPES) buffer was added to the culture medium to maintain optimum pH in the third trial with S9.

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.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with scopolamine hydrobromide trihydrate for 10.5 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 scopolamine hydrobromide trihydrate and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11 to 11.5 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. As with the SCE test, an alteration in pH was observed in the first trial conducted with S9 and the second trial with S9 was conducted with HEPES buffer present in the medium to stabilize pH.

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

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

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay can be found in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female $B6C3F_1$ mice at the end of the 14-week toxicity study. Smears were immediately prepared and fixed in absolute methanol, stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned at 630 or 1000× magnification with a semi-automated image analysis system to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in each of 10 animals per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 540 nm UV illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell.

The results were tabulated as the mean of the pooled results from all animals within a treatment group, plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups with a

one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (Margolin *et al.*, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test an individual trial was considered positive if the trend test P value was less than or equal to 0.025 or the P value for any single exposure group was less than or equal to 0.025 divided by the number of exposure groups. A final call of positive for micronucleus induction is preferably based on reproducible positive trials (as noted above). Ultimately, the final call was determined by the scientific staff after considering the results of statistical analyses, reproducibility of any effects observed, and the magnitudes of those effects.

RESULTS

Scopolamine hydrobromide trihydrate (100 to 10,000 μg/plate) did not induce mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537, with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1). In cytogenetic tests with cultured CHO cells, no convincing induction of SCEs was noted with scopolamine hydrobromide trihydrate doses up to 500 μg/mL without S9 or 5,000 μg/mL with S9 (Table E2). Results from the first two trials conducted with S9, which appeared to clearly demonstrate a significant increase in SCEs, were called into question by the observation of a pH shift in the culture medium produced by the high doses (2,000 μg/mL and higher) of scopolamine hydrobromide trihydrate which coincided with the increases in SCE. Therefore, a third trial was conducted, in which the pH of the culture medium was adjusted with HEPES buffer. Results of this third trial were negative and the overall assay results were also considered to be negative. The increases in SCEs noted in the presence of S9 were attributed to the alteration in pH produced by high concentrations of scopolamine hydrobromide trihydrate. No induction of Abs was observed in cultured CHO cells treated with scopolamine hydrobromide trihydrate without S9, but with S9, even in the presence of HEPES buffer to maintain optimum pH, increases in the percentage of cells with Abs were noted in each of two trials at the highest dose tested (5,000 μg/mL) (Table E3).

Despite the evidence for induction chromosomal damage in cultured CHO cells *in vitro*, no increase in the frequency of micronucleated NCEs was noted in peripheral blood samples obtained from male and female mice at the termination of the 14-week toxicity studies with scopolamine hydrobromide trihydrate (Table E4).

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 16-Day Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Male						
n	5	5	5	5	5	5
Necropsy body wt	201 ± 2	189 ± 5	189 ± 7	185 ± 4	177 ± 7**	179 ± 5**
Brain						
Absolute	1.804 ± 0.015	1.760 ± 0.016	1.748 ± 0.053	1.738 ± 0.021	1.722 ± 0.036	1.708 ± 0.022
Relative	8.98 ± 0.10	9.35 ± 0.20	9.27 ± 0.20	9.38 ± 0.13	9.75 ± 0.31	9.58 ± 0.22
Heart						
Absolute	0.724 ± 0.027	0.648 ± 0.029	0.664 ± 0.028	0.640 ± 0.016	0.628 ± 0.025	0.616 ± 0.024*
Relative	3.60 ± 0.14	3.43 ± 0.08	3.52 ± 0.08	3.45 ± 0.05	3.54 ± 0.08	3.45 ± 0.13
R. Kidney						
Absolute	0.910 ± 0.036	0.838 ± 0.012	0.794 ± 0.030*	0.848 ± 0.014	0.816 ± 0.031	0.820 ± 0.038
Relative	4.53 ± 0.17	4.45 ± 0.08	4.21 ± 0.10	4.58 ± 0.11	4.60 ± 0.07	4.59 ± 0.14
Liver						
Absolute	9.976 ± 0.354	9.252 ± 0.296	10.128 ± 0.565	8.774 ± 0.231	9.510 ± 0.763	8.912 ± 0.382
Relative	49.62 ± 1.69	49.02 ± 0.56	53.62 ± 2.36	47.39 ± 1.48	53.34 ± 2.51	49.83 ± 1.10
Lung						
Absolute	0.996 ± 0.039	1.024 ± 0.122	1.122 ± 0.198	0.922 ± 0.027	0.932 ± 0.061	0.862 ± 0.051
Relative	4.95 ± 0.17	5.39 ± 0.52	5.88 ± 0.87	4.98 ± 0.17	5.28 ± 0.36	4.81 ± 0.16
R. Testis						
Absolute	1.112 ± 0.038	1.063 ± 0.011	1.058 ± 0.035	1.065 ± 0.066	1.054 ± 0.046	1.051 ± 0.052
Relative	5.54 ± 0.20	5.65 ± 0.15	5.61 ± 0.14	5.73 ± 0.29	5.95 ± 0.21	5.87 ± 0.16
Thymus						
Absolute	0.445 ± 0.024	0.380 ± 0.021	0.424 ± 0.051	0.401 ± 0.026	0.343 ± 0.024*	0.330 ± 0.013*
Relative	2.21 ± 0.12	2.01 ± 0.07	2.22 ± 0.20	2.16 ± 0.11	1.93 ± 0.07	1.85 ± 0.09

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Female						
n	5	5	5	5	5	5
Necropsy body wt	145 ± 5	135 ± 3	139 ± 4	141 ± 5	145 ± 4	135 ± 2
Brain						
Absolute	1.712 ± 0.010	1.662 ± 0.026	1.632 ± 0.029*	1.656 ± 0.024	1.638 ± 0.012	1.648 ± 0.004
Relative	11.84 ± 0.33	12.28 ± 0.12	11.75 ± 0.13	11.82 ± 0.38	11.35 ± 0.32	12.24 ± 0.17
Heart						
Absolute	0.540 ± 0.014	0.488 ± 0.015	0.504 ± 0.012	0.538 ± 0.010	0.530 ± 0.021	0.508 ± 0.025
Relative	3.73 ± 0.08	3.60 ± 0.08	3.64 ± 0.13	3.84 ± 0.12	3.66 ± 0.05	3.77 ± 0.19
R. Kidney						
Absolute	0.662 ± 0.016	0.606 ± 0.023	0.632 ± 0.018	0.652 ± 0.021	0.688 ± 0.024	0.650 ± 0.013
Relative	4.57 ± 0.06	4.47 ± 0.11	4.55 ± 0.09	4.64 ± 0.09	4.75 ± 0.11	4.83 ± 0.14
Liver						
Absolute	6.270 ± 0.224	5.790 ± 0.199	6.168 ± 0.209	6.334 ± 0.298	6.840 ± 0.444	6.194 ± 0.265
Relative	43.21 ± 0.41	42.75 ± 1.24	44.37 ± 0.91	44.95 ± 0.67	47.11 ± 2.04	45.98 ± 1.94
Lung						
Absolute	0.776 ± 0.037	0.688 ± 0.024	0.846 ± 0.050	0.788 ± 0.056[b]	0.864 ± 0.067	0.794 ± 0.056
Relative	5.34 ± 0.15	5.08 ± 0.12	6.11 ± 0.43	5.61 ± 0.21[b]	5.94 ± 0.31	5.89 ± 0.42
Thymus						
Absolute	0.369 ± 0.018	0.336 ± 0.017	0.362 ± 0.021	0.345 ± 0.021	0.346 ± 0.014	0.314 ± 0.014
Relative	2.54 ± 0.05	2.48 ± 0.12	2.60 ± 0.10	2.45 ± 0.10	2.39 ± 0.11	2.33 ± 0.08

* 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).
[b] n=4

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	15 mg/kg	45 mg/kg	135 mg/kg	400 mg/kg	1,200 mg/kg
Male						
n	10	9	10	8	4	1[b]
Necropsy body wt	353 ± 7	327 ± 6**	314 ± 4**	309 ± 6**	312 ± 3**	321
Brain						
Absolute	1.997 ± 0.010	1.978 ± 0.015	1.922 ± 0.013**	1.900 ± 0.020**	1.883 ± 0.024**	1.840
Relative	5.68 ± 0.12	6.05 ± 0.09*	6.14 ± 0.07**	6.17 ± 0.11**	6.03 ± 0.10	5.73
Heart						
Absolute	1.042 ± 0.017	0.973 ± 0.014**	0.935 ± 0.014**	0.904 ± 0.016**	0.898 ± 0.005**	0.870
Relative	2.96 ± 0.03	2.98 ± 0.06	2.98 ± 0.02	2.93 ± 0.03	2.87 ± 0.03	2.71
R. Kidney						
Absolute	1.362 ± 0.025	1.271 ± 0.018**	1.211 ± 0.026**	1.170 ± 0.015**	1.280 ± 0.038**	1.250
Relative	3.86 ± 0.05	3.89 ± 0.08	3.86 ± 0.05	3.80 ± 0.06	4.10 ± 0.13	3.89
Liver						
Absolute	14.438 ± 0.422	13.121 ± 0.487*	12.188 ± 0.192**	12.911 ± 0.260*	13.420 ± 0.347	14.800
Relative	40.90 ± 0.82	40.00 ± 0.99	38.88 ± 0.42	41.84 ± 0.53	42.99 ± 1.46	46.08
Lung						
Absolute	1.513 ± 0.069	1.451 ± 0.045	1.401 ± 0.051	1.381 ± 0.051	1.380 ± 0.104	1.300
Relative	4.28 ± 0.15	4.45 ± 0.18	4.48 ± 0.19	4.48 ± 0.15	4.42 ± 0.36	4.05
R. Testis						
Absolute	1.422 ± 0.018	1.270 ± 0.145	1.441 ± 0.023	1.310 ± 0.107	1.425 ± 0.043	1.405
Relative	4.04 ± 0.08	3.85 ± 0.44	4.60 ± 0.07	4.23 ± 0.33	4.56 ± 0.14	4.37
Thymus						
Absolute	0.314 ± 0.021	0.247 ± 0.011**	0.241 ± 0.014**	0.216 ± 0.012**	0.195 ± 0.011**	0.221
Relative	0.89 ± 0.05	0.75 ± 0.03*	0.77 ± 0.04*	0.70 ± 0.03**	0.62 ± 0.03**	0.69

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	15 mg/kg	45 mg/kg	135 mg/kg	400 mg/kg	1,200 mg/kg
Female						
n	10	10	9	9	9	3
Necropsy body wt	204 ± 2	197 ± 2*	198 ± 2*	192 ± 3**	192 ± 2**	194 ± 4*
Brain						
Absolute	1.830 ± 0.011	1.822 ± 0.013	1.834 ± 0.016	1.782 ± 0.011*	1.782 ± 0.017*	1.723 ± 0.027**
Relative	8.98 ± 0.07	9.26 ± 0.09	9.26 ± 0.10	9.30 ± 0.10	9.28 ± 0.09	8.87 ± 0.06
Heart						
Absolute	0.676 ± 0.012	0.685 ± 0.009	0.693 ± 0.022	0.679 ± 0.023	0.630 ± 0.012	0.653 ± 0.013
Relative	3.32 ± 0.05	3.48 ± 0.05	3.50 ± 0.11	3.54 ± 0.09	3.28 ± 0.06	3.36 ± 0.09
R. Kidney						
Absolute	0.807 ± 0.013	0.791 ± 0.013	0.798 ± 0.012	0.788 ± 0.023	0.757 ± 0.022	0.833 ± 0.026
Relative	3.96 ± 0.07	4.02 ± 0.05	4.03 ± 0.07	4.10 ± 0.10	3.93 ± 0.09	4.29 ± 0.05
Liver						
Absolute	7.062 ± 0.151	7.230 ± 0.124	7.111 ± 0.171	6.827 ± 0.223	7.278 ± 0.176	8.260 ± 0.100**
Relative	34.67 ± 0.73	36.74 ± 0.55	35.90 ± 0.84	35.56 ± 0.94	37.87 ± 0.80**	42.52 ± 0.44**
Lung						
Absolute	1.115 ± 0.038	1.026 ± 0.032	1.032 ± 0.031	1.011 ± 0.038	1.014 ± 0.024	1.010 ± 0.040
Relative	5.47 ± 0.17	5.21 ± 0.14	5.21 ± 0.15	5.26 ± 0.15	5.28 ± 0.13	5.19 ± 0.12
R. Ovary						
Absolute	0.057 ± 0.007	0.058 ± 0.002	0.053 ± 0.003	0.054 ± 0.003	0.059 ± 0.005	0.063 ± 0.010
Relative	0.28 ± 0.03	0.29 ± 0.01	0.27 ± 0.01	0.28 ± 0.02	0.31 ± 0.02	0.32 ± 0.05
Thymus						
Absolute	0.266 ± 0.011	0.229 ± 0.005**	0.223 ± 0.006**	0.213 ± 0.009**	0.204 ± 0.006**	0.171 ± 0.003**
Relative	1.31 ± 0.05	1.17 ± 0.02**	1.13 ± 0.03**	1.11 ± 0.04**	1.07 ± 0.04**	0.88 ± 0.01**
Uterus						
Absolute	0.740 ± 0.099	0.538 ± 0.036	0.631 ± 0.076	0.743 ± 0.086	0.687 ± 0.084	0.453 ± 0.020
Relative	3.63 ± 0.48	2.73 ± 0.18	3.19 ± 0.38	3.84 ± 0.41	3.61 ± 0.48	2.34 ± 0.13

* 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).
[b] n=1; no standard error calculated

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
n	10	10	10	10
Necropsy body wt	493 ± 9	492 ± 11	481 ± 10	448 ± 9**
R. Epididymis				
Absolute	0.423 ± 0.022	0.464 ± 0.012	0.428 ± 0.014	0.441 ± 0.017
Relative	0.86 ± 0.04	0.94 ± 0.02	0.89 ± 0.03	0.99 ± 0.04*
R. Kidney				
Absolute	1.614 ± 0.029	1.565 ± 0.050	1.543 ± 0.047	1.366 ± 0.036**
Relative	3.28 ± 0.07	3.18 ± 0.06	3.20 ± 0.06	3.06 ± 0.08
Liver				
Absolute	18.032 ± 0.477	17.953 ± 0.579	17.382 ± 0.580	15.319 ± 0.481**
Relative	36.65 ± 0.83	36.46 ± 0.71	36.11 ± 0.81	34.21 ± 0.84
R. Testis				
Absolute	1.884 ± 0.229	1.680 ± 0.075	1.777 ± 0.169	1.669 ± 0.142
Relative	3.83 ± 0.47	3.43 ± 0.18	3.67 ± 0.30	3.76 ± 0.37
Female				
n	10		10	10
Necropsy body wt	293 ± 12	—[b]	285 ± 5	274 ± 7
R. Kidney				
Absolute	0.938 ± 0.017	—	0.869 ± 0.014**	0.845 ± 0.021**
Relative	3.23 ± 0.10	—	3.06 ± 0.07	3.09 ± 0.04
Liver				
Absolute	9.198 ± 0.322	—	8.869 ± 0.147	8.392 ± 0.235*
Relative	31.54 ± 0.92	—	31.19 ± 0.43	30.70 ± 0.59

* Significantly ± ($P \leq 0.05$) 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).
[b] Female rats in the 1 mg/kg group were not necropsied at the interim evaluation due to high mortality.

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	150 mg/kg	250 mg/kg	450 mg/kg	900 mg/kg	1,800 mg/kg
Male						
n	5	5	5	5	5	4
Necropsy body wt	21.5 ± 0.7	22.1 ± 0.5	21.1 ± 0.6	21.6 ± 1.1	22.0 ± 0.4	22.0 ± 1.0
Brain						
Absolute	0.448 ± 0.002	0.438 ± 0.006	0.446 ± 0.005	0.442 ± 0.007	0.442 ± 0.015	0.428 ± 0.014
Relative	20.92 ± 0.68	19.85 ± 0.39	21.24 ± 0.64	20.63 ± 1.03	20.10 ± 0.65	19.55 ± 1.01
Heart						
Absolute	0.110 ± 0.004	0.118 ± 0.002	0.112 ± 0.008	0.112 ± 0.005	0.102 ± 0.010	0.113 ± 0.009
Relative	5.14 ± 0.27	5.35 ± 0.14	5.37 ± 0.52	5.23 ± 0.34	4.64 ± 0.46	5.16 ± 0.50
R. Kidney						
Absolute	0.208 ± 0.007	0.212 ± 0.007	0.210 ± 0.015	0.202 ± 0.012	0.194 ± 0.007	0.205 ± 0.010
Relative	9.70 ± 0.41	9.59 ± 0.25	10.05 ± 0.97	9.36 ± 0.45	8.84 ± 0.39	9.38 ± 0.63
Liver						
Absolute	1.212 ± 0.051	1.286 ± 0.041	1.306 ± 0.053	1.306 ± 0.084	1.368 ± 0.030	1.420 ± 0.095
Relative	56.41 ± 1.99	58.18 ± 1.21	62.30 ± 3.61	60.26 ± 1.98	62.20 ± 1.27	64.44 ± 1.42*
Lung						
Absolute	0.148 ± 0.005	0.152 ± 0.007	0.145 ± 0.010[b]	0.144 ± 0.005	0.148 ± 0.010	0.153 ± 0.015
Relative	6.92 ± 0.36	6.88 ± 0.31	6.78 ± 0.55[b]	6.72 ± 0.39	6.73 ± 0.45	6.97 ± 0.76
R. Testis						
Absolute	0.099 ± 0.004	0.097 ± 0.004	0.093 ± 0.004	0.091 ± 0.002	0.096 ± 0.004	0.095 ± 0.003
Relative	4.62 ± 0.22	4.40 ± 0.21	4.45 ± 0.22	4.26 ± 0.25	4.38 ± 0.14	4.37 ± 0.30
Thymus						
Absolute	0.060 ± 0.003	0.063 ± 0.003	0.051 ± 0.003	0.059 ± 0.002[b]	0.063 ± 0.002	0.054 ± 0.002
Relative	2.81 ± 0.17	2.83 ± 0.10	2.42 ± 0.13	2.65 ± 0.13[b]	2.89 ± 0.11	2.44 ± 0.08

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	150 mg/kg	250 mg/kg	450 mg/kg	900 mg/kg	1,800 mg/kg
Female						
n	5	4	5	5	5	3
Necropsy body wt	19.7 ± 0.3	19.7 ± 0.3	19.6 ± 0.3	19.4 ± 0.4	19.0 ± 0.4	19.3 ± 0.3
Brain						
Absolute	0.456 ± 0.004	0.453 ± 0.009	0.442 ± 0.005	0.452 ± 0.004	0.432 ± 0.005**	0.433 ± 0.009*
Relative	23.14 ± 0.33	23.00 ± 0.43	22.53 ± 0.52	23.36 ± 0.44	22.76 ± 0.31	22.41 ± 0.09
Heart						
Absolute	0.104 ± 0.004	0.095 ± 0.003	0.098 ± 0.006	0.102 ± 0.002	0.090 ± 0.003*	0.090 ± 0.000
Relative	5.27 ± 0.16	4.83 ± 0.07	5.00 ± 0.34	5.27 ± 0.09	4.74 ± 0.15	4.66 ± 0.08
R. Kidney						
Absolute	0.164 ± 0.005	0.170 ± 0.012	0.156 ± 0.007	0.162 ± 0.006	0.154 ± 0.007	0.153 ± 0.003
Relative	8.32 ± 0.21	8.63 ± 0.53	7.96 ± 0.41	8.36 ± 0.23	8.09 ± 0.21	7.93 ± 0.04
Liver						
Absolute	1.036 ± 0.026	1.160 ± 0.032	1.078 ± 0.032	1.122 ± 0.046	1.118 ± 0.039	1.157 ± 0.041
Relative	52.53 ± 0.94	58.93 ± 0.90*	54.86 ± 1.16*	57.83 ± 1.34**	58.81 ± 1.23**	59.88 ± 2.60**
Lung						
Absolute	0.142 ± 0.006	0.130 ± 0.006	0.154 ± 0.015	0.146 ± 0.004	0.144 ± 0.004	0.133 ± 0.009
Relative	7.20 ± 0.24	6.60 ± 0.19	7.82 ± 0.68	7.55 ± 0.28	7.60 ± 0.28	6.89 ± 0.35
Thymus						
Absolute	0.075 ± 0.003	0.071 ± 0.004	0.079 ± 0.007	0.078 ± 0.003	0.075 ± 0.004	0.067 ± 0.006
Relative	3.80 ± 0.16	3.62 ± 0.22	4.05 ± 0.40	4.01 ± 0.16	3.93 ± 0.17	3.46 ± 0.27

* Significantly different ($P \leq 0.05$) from the control group by 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).
[b] n=4

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	15 mg/kg	45 mg/kg	135 mg/kg	400 mg/kg	1,200 mg/kg
Male						
n	10	10	10	9	10	8
Necropsy body wt	33.8 ± 1.2	30.8 ± 0.4**	30.6 ± 0.4**	30.1 ± 0.6**	28.7 ± 0.6**	29.2 ± 0.7**
Brain						
Absolute	0.458 ± 0.004	0.459 ± 0.003	0.449 ± 0.013	0.452 ± 0.005	0.459 ± 0.005	0.450 ± 0.003
Relative	13.68 ± 0.38	14.93 ± 0.20*	14.70 ± 0.46*	15.04 ± 0.21**	16.05 ± 0.39**	15.49 ± 0.34**
Heart						
Absolute	0.156 ± 0.007	0.141 ± 0.003*	0.146 ± 0.003	0.136 ± 0.003**	0.134 ± 0.003**	0.134 ± 0.006**
Relative	4.63 ± 0.15	4.58 ± 0.08	4.77 ± 0.07	4.51 ± 0.14	4.68 ± 0.14	4.58 ± 0.17
R. Kidney						
Absolute	0.314 ± 0.007	0.292 ± 0.006*	0.282 ± 0.007**	0.263 ± 0.007**	0.262 ± 0.007**	0.258 ± 0.005**
Relative	9.35 ± 0.22	9.49 ± 0.13	9.21 ± 0.19	8.76 ± 0.29	9.14 ± 0.23	8.85 ± 0.18
Liver						
Absolute	1.621 ± 0.076	1.541 ± 0.055	1.490 ± 0.040	1.473 ± 0.049	1.426 ± 0.051	1.474 ± 0.075
Relative	47.94 ± 1.12	50.01 ± 1.41	48.68 ± 1.03	48.87 ± 1.18	49.56 ± 1.05	50.43 ± 1.86
Lung						
Absolute	0.187 ± 0.010	0.160 ± 0.005	0.177 ± 0.006	0.186 ± 0.015	0.170 ± 0.009	0.171 ± 0.010
Relative	5.56 ± 0.25	5.20 ± 0.16	5.78 ± 0.17	6.14 ± 0.45	5.95 ± 0.36	5.86 ± 0.29
R. Testis						
Absolute	0.111 ± 0.002	0.116 ± 0.002	0.118 ± 0.002	0.112 ± 0.003	0.111 ± 0.002	0.109 ± 0.002
Relative	3.31 ± 0.10	3.77 ± 0.05**	3.85 ± 0.05**	3.71 ± 0.10**	3.86 ± 0.08**	3.75 ± 0.10**
Thymus						
Absolute	0.038 ± 0.002	0.036 ± 0.002	0.035 ± 0.002	0.035 ± 0.001	0.036 ± 0.002	0.036 ± 0.002
Relative	1.14 ± 0.04	1.16 ± 0.06	1.14 ± 0.08	1.15 ± 0.03	1.25 ± 0.05	1.22 ± 0.07

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate (continued)

	Vehicle Control	15 mg/kg	45 mg/kg	135 mg/kg	400 mg/kg	1,200 mg/kg
Female						
n	10	10	10	10	10	9
Necropsy body wt	29.2 ± 0.5	27.6 ± 0.4*	27.5 ± 0.5*	26.6 ± 0.5**	26.3 ± 0.5**	25.5 ± 0.3**
Brain						
Absolute	0.471 ± 0.003	0.475 ± 0.005	0.470 ± 0.003	0.473 ± 0.006	0.462 ± 0.006	0.452 ± 0.003**
Relative	16.15 ± 0.23	17.23 ± 0.18**	17.13 ± 0.34**	17.84 ± 0.32**	17.62 ± 0.29**	17.72 ± 0.13**
Heart						
Absolute	0.131 ± 0.004	0.129 ± 0.005	0.127 ± 0.003	0.128 ± 0.004	0.125 ± 0.002	0.114 ± 0.004**
Relative	4.49 ± 0.15	4.67 ± 0.15	4.62 ± 0.10	4.82 ± 0.14	4.78 ± 0.12	4.49 ± 0.15
R. Kidney						
Absolute	0.216 ± 0.003	0.211 ± 0.004	0.200 ± 0.010	0.216 ± 0.005	0.200 ± 0.006	0.190 ± 0.004**
Relative	7.41 ± 0.14	7.65 ± 0.13	7.26 ± 0.33	8.14 ± 0.19	7.62 ± 0.23	7.44 ± 0.13
Liver						
Absolute	1.473 ± 0.042	1.374 ± 0.028	1.402 ± 0.058	1.389 ± 0.051	1.383 ± 0.050	1.393 ± 0.042
Relative	50.38 ± 0.97	49.83 ± 0.96	50.78 ± 1.28	52.44 ± 2.26	52.58 ± 1.34	54.50 ± 1.20
Lung						
Absolute	0.173 ± 0.007	0.168 ± 0.007	0.175 ± 0.007	0.180 ± 0.006	0.172 ± 0.005	0.170 ± 0.005
Relative	5.95 ± 0.31	6.08 ± 0.18	6.37 ± 0.25	6.81 ± 0.30*	6.56 ± 0.19*	6.66 ± 0.19
R. Ovary						
Absolute	0.012 ± 0.001	0.013 ± 0.001	0.011 ± 0.001	0.012 ± 0.001	0.012 ± 0.001	0.010 ± 0.001
Relative	0.42 ± 0.02	0.46 ± 0.02	0.41 ± 0.05	0.45 ± 0.02	0.44 ± 0.03	0.38 ± 0.03
Thymus						
Absolute	0.053 ± 0.003	0.052 ± 0.002	0.046 ± 0.002	0.052 ± 0.001	0.049 ± 0.003	0.044 ± 0.002**
Relative	1.82 ± 0.09	1.87 ± 0.04	1.68 ± 0.06	1.97 ± 0.05	1.86 ± 0.09	1.73 ± 0.08
Uterus						
Absolute	0.167 ± 0.017	0.119 ± 0.010	0.153 ± 0.016	0.156 ± 0.016	0.127 ± 0.013	0.121 ± 0.015
Relative	5.72 ± 0.56	4.32 ± 0.35	5.55 ± 0.54	5.85 ± 0.56	4.85 ± 0.50	4.72 ± 0.56

* 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 F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
n	9	10	10	10
Necropsy body wt	50.2 ± 0.6	51.9 ± 1.1	49.6 ± 1.8	39.0 ± 0.6**
R. Epididymis				
Absolute	0.062 ± 0.003	0.062 ± 0.003	0.059 ± 0.002	0.057 ± 0.003
Relative	1.23 ± 0.05	1.19 ± 0.05	1.20 ± 0.06	1.45 ± 0.06*
R. Kidney				
Absolute	0.376 ± 0.015	0.383 ± 0.009	0.360 ± 0.012	0.325 ± 0.006**
Relative	7.47 ± 0.22	7.38 ± 0.10	7.31 ± 0.22	8.32 ± 0.09**
Liver				
Absolute	2.336 ± 0.122	2.627 ± 0.196	2.374 ± 0.258	2.152 ± 0.353
Relative	46.54 ± 2.34	50.28 ± 3.05	47.39 ± 3.96	55.43 ± 9.41
R. Testis				
Absolute	0.119 ± 0.003	0.123 ± 0.004	0.125 ± 0.002	0.117 ± 0.003
Relative	2.37 ± 0.05	2.38 ± 0.05	2.55 ± 0.08*	2.99 ± 0.04**
Female				
n	10	10	10	10
Necropsy body wt	53.2 ± 1.9	50.6 ± 2.0	48.2 ± 1.5	40.7 ± 1.7**
R. Kidney				
Absolute	0.256 ± 0.005	0.250 ± 0.006	0.241 ± 0.004	0.237 ± 0.008
Relative	4.83 ± 0.10	4.99 ± 0.14	5.04 ± 0.13	5.87 ± 0.16**
Liver				
Absolute	1.915 ± 0.058	1.858 ± 0.073	1.825 ± 0.064	1.820 ± 0.051
Relative	36.09 ± 0.58	36.80 ± 0.56	37.90 ± 0.62	45.15 ± 1.50**

* 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).

APPENDIX G
HEMATOLOGY RESULTS

TABLE G1
Hematology Data for Rats in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	15 mg/kg	45 mg/kg	135 mg/kg	400 mg/kg	1,200 mg/kg
Male						
n	10	9	10	8	4	1[b]
Hematocrit (%)	46.8 ± 0.5	46.2 ± 0.4	48.0 ± 0.3*	48.1 ± 0.3*	49.0 ± 0.4**	48.9
Hemoglobin (g/dL)	15.2 ± 0.2	15.3 ± 0.2	15.7 ± 0.1	15.9 ± 0.1*	16.2 ± 0.1**	16.4
Erythroctes ($10^6/\mu L$)	9.39 ± 0.10	9.38 ± 0.10	9.63 ± 0.08	9.61 ± 0.05	9.72 ± 0.11	9.58
Reticulocytes ($10^6/\mu L$)	0.50 ± 0.03	0.47 ± 0.02	0.52 ± 0.03	0.42 ± 0.03	0.40 ± 0.04	0.46
Nucleated erythrocytes ($10^3/\mu L$)	0.03 ± 0.01	0.04 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.02	0.08
Mean cell volume (fL)	49.9 ± 0.4	49.1 ± 0.1	50.0 ± 0.2	50.0 ± 0.3	50.5 ± 0.3	51.0
Mean cell hemoglobin (pg)	16.2 ± 0.3	16.3 ± 0.1	16.3 ± 0.1	16.6 ± 0.1	16.7 ± 0.1	17.1
Mean cell hemoglobin concentration (g/dL)	32.6 ± 0.5	33.2 ± 0.1	32.8 ± 0.2	33.1 ± 0.2	33.1 ± 0.1	33.5
Platelets ($10^3/\mu L$)	633.4 ± 20.8	638.8 ± 10.6	655.8 ± 28.2[c]	620.6 ± 20.6	621.5 ± 21.3	601.0
Leukocytes ($10^3/\mu L$)	7.35 ± 0.44	6.96 ± 0.31	8.01 ± 0.36	7.59 ± 0.56	6.73 ± 0.57	8.40
Segmented neutrophils ($10^3/\mu L$)	1.14 ± 0.13	1.89 ± 0.28*	2.07 ± 0.17**	1.82 ± 0.20**	1.90 ± 0.12*	2.69
Lymphocytes ($10^3/\mu L$)	5.65 ± 0.35	4.68 ± 0.34	5.67 ± 0.41	5.37 ± 0.37	4.65 ± 0.45	5.38
Atypical lymphocytes ($10^3/\mu L$)	0.12 ± 0.03	0.08 ± 0.03	0.04 ± 0.02	0.08 ± 0.05	0.00 ± 0.00	0.00
Monocytes ($10^3/\mu L$)	0.35 ± 0.09	0.22 ± 0.06	0.17 ± 0.05	0.20 ± 0.04	0.07 ± 0.04*	0.34
Eosinophils ($10^3/\mu L$)	0.08 ± 0.03	0.09 ± 0.03	0.06 ± 0.01	0.11 ± 0.04	0.08 ± 0.02	0.00
Female						
n	9	10	9	9	8	3
Hematocrit (%)	46.9 ± 0.4	47.4 ± 0.6	48.1 ± 0.4	47.7 ± 0.4	49.0 ± 0.4**	49.1 ± 0.9*
Hemoglobin (g/dL)	15.6 ± 0.1	15.5 ± 0.2	15.9 ± 0.1	15.7 ± 0.2	16.2 ± 0.1**	16.4 ± 0.3*
Erythrocytes ($10^6/\mu L$)	8.82 ± 0.07	8.88 ± 0.11	9.09 ± 0.07*	8.98 ± 0.10	9.17 ± 0.08*	9.26 ± 0.17*
Reticulocytes ($10^6/\mu L$)	0.41 ± 0.02	0.38 ± 0.02	0.42 ± 0.03	0.43 ± 0.03	0.43 ± 0.03	0.42 ± 0.05
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.05 ± 0.01	0.03 ± 0.02	0.05 ± 0.02	0.05 ± 0.02	0.07 ± 0.07
Mean cell volume (fL)	53.1 ± 0.3	53.2 ± 0.2	52.7 ± 0.2	53.1 ± 0.2	53.5 ± 0.3	53.0 ± 0.0
Mean cell hemoglobin (pg)	17.7 ± 0.1	17.4 ± 0.1	17.5 ± 0.1	17.5 ± 0.1	17.7 ± 0.1	17.7 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.3 ± 0.2	32.6 ± 0.1*	33.1 ± 0.1	33.0 ± 0.2	33.1 ± 0.1	33.5 ± 0.2
Platelets ($10^3/\mu L$)	759.6 ± 39.6	764.3 ± 31.7	758.4 ± 27.5	807.4 ± 29.8	810.1 ± 44.3	698.7 ± 14.6
Leukocytes ($10^3/\mu L$)	6.37 ± 0.33	6.23 ± 0.40	6.21 ± 0.43	8.57 ± 0.38*	7.39 ± 0.59	5.97 ± 0.91
Segmented neutrophils ($10^3/\mu L$)	1.45 ± 0.11	1.30 ± 0.16	1.45 ± 0.12	2.16 ± 0.29	1.73 ± 0.17	1.68 ± 0.57
Lymphocytes ($10^3/\mu L$)	4.63 ± 0.36	4.68 ± 0.25	4.48 ± 0.42	6.15 ± 0.25*	5.35 ± 0.48	4.10 ± 0.38
Atypical lymphocytes ($10^3/\mu L$)	0.09 ± 0.04	0.03 ± 0.03	0.02 ± 0.01	0.04 ± 0.04	0.04 ± 0.03	0.04 ± 0.02
Monocytes ($10^3/\mu L$)	0.14 ± 0.05	0.15 ± 0.04	0.18 ± 0.06	0.15 ± 0.07	0.20 ± 0.08	0.08 ± 0.03
Eosinophils ($10^3/\mu L$)	0.06 ± 0.01	0.07 ± 0.02	0.07 ± 0.02	0.07 ± 0.03	0.04 ± 0.01	0.07 ± 0.04

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=1; no standard error calculated
[c] n=9

TABLE G2
Hematology Data for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
n	10	10	10	10
Hematocrit (%)	45.5 ± 0.5	46.3 ± 0.3	47.1 ± 0.8	48.5 ± 0.8**
Hemoglobin (g/dL)	15.2 ± 0.2	15.3 ± 0.0	15.4 ± 0.2	15.8 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.61 ± 0.12	9.60 ± 0.12	9.67 ± 0.18	9.91 ± 0.14
Reticulocytes ($10^6/\mu L$)	0.18 ± 0.01[b]	0.16 ± 0.01	0.18 ± 0.01	0.19 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.06 ± 0.03	0.03 ± 0.02	0.01 ± 0.01	0.03 ± 0.02
Mean cell volume (fL)	47.5 ± 0.4	48.2 ± 0.6	48.6 ± 0.8	48.9 ± 0.5
Mean cell hemoglobin (pg)	15.8 ± 0.1	16.0 ± 0.2	16.0 ± 0.2	16.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.6 ± 0.2	33.1 ± 0.2	32.8 ± 0.3	32.7 ± 0.2*
Platelets ($10^3/\mu L$)	533.3 ± 21.9	554.7 ± 19.0	555.8 ± 23.4	537.5 ± 43.0
Leukocytes ($10^3/\mu L$)	4.75 ± 0.18	5.35 ± 0.30	5.13 ± 0.29	4.32 ± 0.24
Segmented neutrophils ($10^3/\mu L$)	1.54 ± 0.10	1.64 ± 0.10	2.03 ± 0.27	1.18 ± 0.12
Lymphocytes ($10^3/\mu L$)	3.09 ± 0.14	3.65 ± 0.25	2.94 ± 0.12	2.98 ± 0.16
Monocytes ($10^3/\mu L$)	0.04 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Eosinophils ($10^3/\mu L$)	0.08 ± 0.02	0.03 ± 0.01	0.12 ± 0.03	0.13 ± 0.03
Female				
n	9		10	10
Hematocrit (%)	44.2 ± 0.7	—[c]	44.7 ± 0.4	45.1 ± 0.5
Hemoglobin (g/dL)	15.2 ± 0.3	—	15.4 ± 0.1	15.6 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.67 ± 0.13	—	8.84 ± 0.05	8.93 ± 0.09
Reticulocytes ($10^6/\mu L$)	0.15 ± 0.01	—	0.13 ± 0.01	0.11 ± 0.01**
Nucleated erythrocytes ($10^3/\mu L$)	0.03 ± 0.01	—	0.04 ± 0.02	0.02 ± 0.01
Mean cell volume (fL)	51.0 ± 0.6	—	50.7 ± 0.4	50.5 ± 0.4
Mean cell hemoglobin (pg)	17.6 ± 0.1	—	17.5 ± 0.1	17.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.5 ± 0.4	—	34.5 ± 0.3	34.5 ± 0.2
Platelets ($10^3/\mu L$)	499.9 ± 30.4	—	527.9 ± 23.4	583.2 ± 20.5
Leukocytes ($10^3/\mu L$)	3.21 ± 0.37	—	3.23 ± 0.31	3.12 ± 0.27
Segmented neutrophils ($10^3/\mu L$)	1.07 ± 0.24	—	1.11 ± 0.14	1.01 ± 0.11
Lymphocytes ($10^3/\mu L$)	2.07 ± 0.13	—	2.05 ± 0.21	2.02 ± 0.18
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	—	0.01 ± 0.01	0.02 ± 0.01
Eosinophils ($10^3/\mu L$)	0.07 ± 0.01	—	0.05 ± 0.01	0.07 ± 0.02

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] Female rats in the 1 mg/kg group were not necropsied at the interim evaluation due to high mortality.

TABLE G3
Hematology Data for Mice in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	15 mg/kg	45 mg/kg	135 mg/kg	400 mg/kg	1,200 mg/kg
Male						
n	9	10	10	9	10	8
Hematocrit (%)	41.8 ± 0.8	41.7 ± 0.8	41.7 ± 0.5	41.7 ± 0.8	42.3 ± 0.9	42.1 ± 0.9
Hemoglobin (g/dL)	15.6 ± 0.2	15.5 ± 0.2	15.5 ± 0.1	15.7 ± 0.2	15.7 ± 0.2	15.8 ± 0.3
Erythrocytes ($10^6/\mu L$)	10.25 ± 0.17	10.05 ± 0.13	10.19 ± 0.10	10.21 ± 0.14	10.06 ± 0.16	9.95 ± 0.21
Reticulocytes ($10^6/\mu L$)	0.29 ± 0.05	0.22 ± 0.03	0.18 ± 0.04	0.28 ± 0.05	0.23 ± 0.06	0.32 ± 0.02
Mean cell volume (fL)	40.8 ± 0.4	41.4 ± 0.4	40.9 ± 0.3	40.8 ± 0.4	42.2 ± 0.3*	42.4 ± 0.4*
Mean cell hemoglobin (pg)	15.3 ± 0.1	15.4 ± 0.1	15.3 ± 0.0	15.3 ± 0.1	15.6 ± 0.1*	15.9 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	37.4 ± 0.3	37.1 ± 0.5	37.2 ± 0.2	37.6 ± 0.4	37.2 ± 0.4	37.6 ± 0.2
Platelets ($10^3/\mu L$)	1,105.1 ± 28.3	1,141.6 ± 55.2[b]	1,104.8 ± 16.1	984.8 ± 52.2	1,016.4 ± 31.0	1,060.5 ± 53.4
Leukocytes ($10^3/\mu L$)	2.08 ± 0.40	2.46 ± 0.33	3.10 ± 0.38	3.30 ± 0.66	3.61 ± 0.73	2.94 ± 0.50
Segmented neutrophils ($10^3/\mu L$)	0.39 ± 0.12	0.37 ± 0.08	0.68 ± 0.13*	0.78 ± 0.12*	0.84 ± 0.14*	0.77 ± 0.12*
Lymphocytes ($10^3/\mu L$)	1.67 ± 0.29	2.05 ± 0.27	2.33 ± 0.25	2.45 ± 0.54	2.61 ± 0.55	2.11 ± 0.39
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.03	0.02 ± 0.02	0.08 ± 0.04	0.04 ± 0.02
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01	0.02 ± 0.01	0.04 ± 0.01	0.03 ± 0.02	0.07 ± 0.02	0.01 ± 0.01
Female						
n	10	10	9	9	10	8
Hematocrit (%)	41.3 ± 0.8	41.2 ± 0.7	42.1 ± 0.4	42.2 ± 0.7	42.2 ± 0.7	40.8 ± 0.5
Hemoglobin (g/dL)	15.3 ± 0.2	15.4 ± 0.2	15.5 ± 0.1	15.8 ± 0.2	15.7 ± 0.2	15.5 ± 0.1
Erythrocytes ($10^6/\mu L$)	9.86 ± 0.16	9.97 ± 0.13	10.00 ± 0.14	10.13 ± 0.10	10.20 ± 0.15	9.80 ± 0.09
Reticulocytes ($10^6/\mu L$)	0.22 ± 0.03	0.23 ± 0.04	0.24 ± 0.06	0.26 ± 0.05	0.30 ± 0.06[b]	0.20 ± 0.06
Mean cell volume (fL)	41.9 ± 0.3	41.3 ± 0.5	42.1 ± 0.5	41.7 ± 0.3	41.4 ± 0.3	41.8 ± 0.4
Mean cell hemoglobin (pg)	15.5 ± 0.1	15.4 ± 0.1	15.5 ± 0.1	15.6 ± 0.1	15.4 ± 0.1	15.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	37.0 ± 0.5	37.3 ± 0.5	36.9 ± 0.2	37.3 ± 0.4	37.3 ± 0.3	38.0 ± 0.4
Platelets ($10^3/\mu L$)	955.8 ± 45.8	979.1 ± 37.8	983.8 ± 32.5	1,080.0 ± 35.3	975.0 ± 39.4	977.3 ± 80.5
Leukocytes ($10^3/\mu L$)	3.39 ± 0.48	3.20 ± 0.43	3.50 ± 0.47	3.07 ± 0.40	3.23 ± 0.63	3.01 ± 0.44
Segmented neutrophils ($10^3/\mu L$)	0.43 ± 0.08	0.68 ± 0.11	0.63 ± 0.12	0.60 ± 0.17	0.72 ± 0.17	0.53 ± 0.09
Lymphocytes ($10^3/\mu L$)	2.89 ± 0.41	2.41 ± 0.30	2.78 ± 0.38	2.39 ± 0.32	2.42 ± 0.48	2.41 ± 0.35
Atypical lymphocytes ($10^3/\mu L$)	0.01 ± 0.01	0.03 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Monocytes ($10^3/\mu L$)	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.02	0.06 ± 0.03	0.05 ± 0.03	0.02 ± 0.01
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.06 ± 0.02	0.03 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.04 ± 0.01

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

TABLE G4
Hematology Data for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
n	10	10	10	10
Hematocrit (%)	46.8 ± 0.9	47.7 ± 1.0	47.0 ± 0.9	45.7 ± 0.8
Hemoglobin (g/dL)	14.7 ± 0.2	15.1 ± 0.2	14.8 ± 0.2	14.4 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.82 ± 0.17	10.23 ± 0.24	9.86 ± 0.24	9.66 ± 0.16
Reticulocytes ($10^6/\mu L$)	0.15 ± 0.01	0.18 ± 0.01	0.16 ± 0.01	0.18 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.6 ± 0.5	46.6 ± 0.8	47.8 ± 0.5	47.3 ± 0.6
Mean cell hemoglobin (pg)	14.9 ± 0.1	14.8 ± 0.2	15.0 ± 0.2	14.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)	31.4 ± 0.3	31.7 ± 0.3	31.4 ± 0.3	31.5 ± 0.3
Platelets ($10^3/\mu L$)	1,315 ± 41	1,216 ± 59	1,272 ± 26	1,357 ± 61
Leukocytes ($10^3/\mu L$)	7.69 ± 0.70	7.61 ± 0.77	7.14 ± 0.47	5.88 ± 0.52
Segmented neutrophils ($10^3/\mu L$)	1.88 ± 0.22	1.49 ± 0.23	1.43 ± 0.21	1.63 ± 0.22
Lymphocytes ($10^3/\mu L$)	5.66 ± 0.48	5.98 ± 0.53	5.45 ± 0.41	4.15 ± 0.33
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.02 ± 0.02	0.00 ± 0.00	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.14 ± 0.04	0.11 ± 0.04	0.26 ± 0.06	0.09 ± 0.02
Female				
n	10	10	10	10
Hematocrit (%)	48.4 ± 0.4	48.2 ± 0.5	48.4 ± 0.3	46.5 ± 0.4*
Hemoglobin (g/dL)	15.0 ± 0.1	15.0 ± 0.2	14.9 ± 0.1	14.5 ± 0.1**
Erythrocytes ($10^6/\mu L$)	9.96 ± 0.08	9.83 ± 0.12	9.88 ± 0.10	9.57 ± 0.07*
Reticulocytes ($10^6/\mu L$)	0.19 ± 0.01	0.18 ± 0.01	0.19 ± 0.01	0.17 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	48.6 ± 0.3	49.0 ± 0.3	49.0 ± 0.5	48.5 ± 0.4
Mean cell hemoglobin (pg)	15.0 ± 0.1	15.2 ± 0.1	15.1 ± 0.1	15.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	31.0 ± 0.2	31.0 ± 0.2	30.8 ± 0.2	31.2 ± 0.2
Platelets ($10^3/\mu L$)	928 ± 20	971 ± 22[b]	1,005 ± 57	1,019 ± 29
Leukocytes ($10^3/\mu L$)	4.84 ± 0.50	4.35 ± 0.43	4.46 ± 0.44	5.10 ± 0.46
Segmented neutrophils ($10^3/\mu L$)	1.20 ± 0.17	1.01 ± 0.08	1.09 ± 0.13	1.51 ± 0.20
Lymphocytes ($10^3/\mu L$)	3.57 ± 0.37	3.25 ± 0.35	3.30 ± 0.36	3.48 ± 0.34
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.07 ± 0.03	0.09 ± 0.03	0.07 ± 0.02	0.11 ± 0.01

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

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	45 mg/kg	135 mg/kg	400 mg/kg
Male				
n	10	10	8	4
Weights (g)				
Necropsy body wt	341 ± 6	302 ± 4**	300 ± 7**[b]	304 ± 3**
R. cauda	0.196 ± 0.004	0.196 ± 0.007	0.190 ± 0.013	0.202 ± 0.005
R. epididymis	0.417 ± 0.004	0.427 ± 0.005	0.394 ± 0.026	0.424 ± 0.006
R. testis	1.422 ± 0.018	1.441 ± 0.023	1.310 ± 0.107	1.425 ± 0.043
Epididymal spermatozoal parameters				
Concentration (10^6/g cauda epididymal tissue)	428.7 ± 36.4	458.1 ± 26.6	395.0 ± 57.7	403.2 ± 33.0
Motility (%)	77.94 ± 1.10	76.10 ± 1.65	67.09 ± 9.85	76.93 ± 0.99
Abnormal sperm (%)	1.200 ± 0.231	1.040 ± 0.206	0.714 ± 0.194[c]	1.100 ± 0.265
Female				
n	10	9	9	9
Necropsy body wt (g)	203 ± 2	196 ± 2*	190 ± 2**	189 ± 2**
Estrous cycle length (days)	4.67 ± 0.17[d]	5.11 ± 0.26	4.43 ± 0.20[e]	4.56 ± 0.24
Estrous stage (% of cycle)				
Diestrus	24.3	30.2	14.3	25.4
Proestrus	20.0	15.9	19.0	15.9
Estrus	34.3	34.9	42.9	34.9
Metestrus	21.4	19.0	22.2	23.8
Uncertain diagnoses	0.0	0.0	1.6	0.0

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
** $P \leq 0.01$
[a] Necropsy weights, organ weights, epididymal spermatozoal parameters, and estrous cycle length are presented as mean ± standard error. Differences from the control group for organ weights, epididymal spermatozoal parameters, and estrous cycle stages are not significant by Dunn's test. By multivariate analysis of variance, exposed frmales did not differ significantly from the control females in relative length of time spent in the estrous stages.
[b] n=9
[c] n=7
[d] Estrous cycle longer than 12 days or unclear in 1 of 10 animals
[e] Estrous cycle longer than 12 days or unclear in 2 of 9 animals

TABLE H2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 14-Week Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	135 mg/kg	400 mg/kg	1,200 mg/kg
Male				
n	9	9	10	8
Weights (g)				
Necropsy body wt	32.7 ± 1.0[b]	29.3 ± 0.6**	28.7 ± 0.8**	28.9 ± 0.6**
R. cauda	0.017 ± 0.001	0.016 ± 0.000	0.015 ± 0.000*	0.015 ± 0.000**
R. epididymis	0.040 ± 0.002	0.038 ± 0.001	0.037 ± 0.001	0.036 ± 0.001
R. testis	0.111 ± 0.002[b]	0.112 ± 0.003	0.111 ± 0.002	0.109 ± 0.002
Epididymal spermatozoal parameters				
Concentration (10^6/g cauda epididymal tissue)	997.4 ± 51.2	1,008.7 ± 74.4	1,077.2 ± 54.6	1,131.6 ± 91.7
Motility (%)	75.18 ± 0.72	74.31 ± 0.82	75.30 ± 1.14	76.66 ± 1.14
Abnormal sperm (%)	1.42 ± 0.08	1.31 ± 0.14	1.64 ± 0.12	1.53 ± 0.17
Female				
n	10	10	10	9
Necropsy body wt (g)	28.0 ± 0.5	26.1 ± 0.4**	26.2 ± 0.5**	25.5 ± 0.4**
Estrous cycle length (days)	4.00 ± 0.00	4.20 ± 0.13	4.00 ± 0.00[c]	4.63 ± 0.18*[d]
Estrous stage (% of cycle)[e]				
Diestrus	28.6	22.9	20.0	19.0
Proestrus	20.0	18.6	11.4	15.9
Estrus	22.9	34.3	45.7	44.4
Metestrus	28.6	24.3	22.9	20.6

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
** $P \leq 0.01$
[a] Necropsy weights, organ weights, epididymal spermatozoal parameters, and estrous cycle length are presented as mean ± standard error. Differences from the control group for epididymal spermatozoal parameters are not significant by Dunn's test.
[b] n=10
[c] Estrous cycle longer than 12 days or unclear in 1 of 10 animals
[d] Estrous cycle longer than 12 days or unclear in 1 of 9 animals
[e] Evidence shows that female mice exposed to 135 mg/kg or 1,200 mg/kg differed significantly (Wilk's Crition, $P \leq 0.05$) from the control females in the relative length of time spent in the estrous stages.

APPENDIX I
NEUROBEHAVIORAL STUDIES

NEUROBEHAVIORAL STUDIES

METHODS

Motor Activity: Motor activity was measured using a Figure 8 Photobeam Activity System (San Diego Instruments; San Diego, CA) with rearing detection attached. Measurements were made under relatively stress free conditions. Speakers placed next to the measurement chambers delivered white noise to mask noise which could have potentially affected behavior. Movement was measured as interruption of photobeams. Motor activity was determined over five 3-minute periods. Measurements of total activity were obtained and compensations were made for normal decreases in activity over the course of the session.

Grip Strength: Forelimb and hindlimb grip strength were measured using a device similar to that described by Meyer *et al.* (1979), and data were entered directly into a Xybion® electronic data collection system. Rats were allowed to grip a triangular ring with their forepaws and were pulled back along a platform until the grip was broken. As the backward motion continued, the rat's hindpaws reached a t-shaped hindlimb grip bar, which it was allowed to grasp and then forced to release by continued pulling. Chatillon push-pull strain gauges (Kew Gardens, NY) were used to record the maximum strain required to break the forelimb and hindlimb grip. Five trials were conducted on each rat with less than 1 minute between trials so that measure of degree of habituation or fatigue could be observed. The body weight of each rat was recorded at the end of the grip strength evaluation.

Thermal Sensitivity: A model 550 Analgesia Meter (Omnitech Electronics, Inc.; Columbus, OH) was used for the test and data were entered directly into a Xybion® system. The device consisted of a square acrylic arena with a clear acrylic cover mounted on a heat source. The rat was placed on the heat source and the arena was covered. The independent variable was rodent reaction time to the heat stimulus (55° C). The response most often observed was a vigorous licking of the hindpaws. Latency was measured manually by a built-in timer. Measurement began when the rat touched the plate and ended at the onset of the pain-sensing response. Rats failing to respond in 30 seconds were removed and assigned a maximum score of 30 seconds.

Startle Responsiveness: Startle responsiveness was measured using an SR-LAB Startle Response System (San Diego Instruments; San Diego, CA), composed of four isolation chambers, a computer control unit and connection box, four startle chambers, and four test station control boxes. The computer controlled the presentation of all stimuli for four chambers simultaneously. The startle enclosure in which the test animal was placed was constructed of transparent acrylic and permitted testing of the animal with minimal restraint. The sensitivity of each enclosure could be individually and reproducibly adjusted. Response measurement took place within a sound-isolated cubicle equipped with a light, a ventilation fan, a small viewing port, and a small mini-max thermometer.

Startle reflex was determined over 80 repeated trials. An acclimation period of 3 minutes was followed by 20 startle trials with a tactile air puff (15 to 20 psi, 20 msec duration per trial). This was followed by 40 prepulse trials in which an 80 to 90 dB(A) white noise prepulse preceded the tactile stimulus by 100 msec. The final 20 trials were identical to the first 20 trials. Startle response for each rat for each trial was recorded following termination of the initial startle stimulus in order to avoid stimulus interference. With this method, the 20 msec wait time was added to all latencies. All trials were separated by an 8 second intertrial interval. A background noise level of 70 dB(A) was used. Each session took approximately 15 minutes to complete. The average response amplitude of each trial presentation was selected as the dependant variable for this study.

Passive Avoidance: Rats were tested using a passive avoidance system (San Diego Instruments; San Diego, CA) consisting of a computer control unit, control cabinets, and test enclosures. A computer unit controlled the presentation of stimuli for four chambers simultaneously and data were directly written to disk. The test enclosure was a two-compartment chamber, one brightly lit and the other dark. The lighted chamber was the smaller of the two (5 in. wide × 7.75 in. high × 8 in. long). The darkened or shock chamber was 8 in. × 7.75 in. × 10 in. A guillotine-type door (Lafayette Instrument Co., Lafayette, IN) blocked a 3.5-inch square opening between the two chambers. A photocell was placed 5 inches into the darkened area. The floor of the unit consisted of a series of 1/8-inch rods. The floor of the shock area consisted of 21 of these rods spaced 1/2 inch apart. Shock was delivered to the rat's feet through the rods by a solid state shocker/distributer (Coulbourn Instruments).

To begin the training sessions, rats were placed in the smaller of the two enclosures, with the gate closed and the cue light off. A start/stop switch was pressed which began the timing of a 10-second adaptation period. At the end of the adaptation period, the cue light was illuminated, the gate was automatically opened and the timing of the session began. Rats were started on a staggered basis. When the subjects interrupted the photobeam in the shock compartment, the autogate closed and the shock (1 milliamp) was turned on for 3 seconds. The breaking of the photobeam indicated the end of the session. The maximum trial duration for the training sessions was 300 seconds. After shock had been administered, rats were immediately removed from the apparatus and returned to their respective cages. Retention test sessions were similar to the training sessions except that no shock was delivered when an animal broke the photobeam in the shock compartment. Maximum trial duration was 600 seconds, and an animal that stayed in the lighted compartment for the entire time received a maximum score of 600 seconds.

Passive avoidance trials were begun on day 90, followed 24 hours later by a retention testing session. Subsequent passive avoidance sessions (days 180, 270, 360, and 720) were limited to retention sessions. Due to the schedule of testing, animals administered scopolamine hydrobromide trihydrate prior to passive avoidance testing as well as prior to retention testing. This was different from protocols in which treatment was given immediately following training so that the animal was not performing the task for the first time while under the influence of an acute drug injection. A modification of the dosing and testing schedule was required to accommodate the gavage administration and retention test session during day 91 for each group of animals since the retention test session (day 91) for a certain set of animals fell on the same day as the initial session (day 90) for another set of animals. This modification was needed because dosing was staggered from the beginning of the study. Animals tested on day 91 were gavaged at approximately the same time as they were on day 90. In addition, attempts were made to keep the time that the animals were placed into the apparatus on day 91 similar to the time that it occurred on the previous day.

RESULTS

Horizontal activity in males was not significantly altered by scopolamine administration; however, horizontal activity of 25 mg/kg females was significantly greater than that of the control group on days 90, 180, and 360. Forelimb grip strength of 1 mg/kg males was significantly greater than that of the controls on day 360. In the 1 mg/kg female group, forelimb grip strength was significantly lower than that of the control group on day 90. Hindlimb grip strength of males and females was not significantly affected by scopolamine hydrobromide trihydrate administration. Pawlick latencies and startle responses of dosed males were not significantly different from those of the control group. In the 25 mg/kg female group at day 90, both pawlick latency and startle response were significantly lower than those of the control group. The startle response of 5 mg/kg females was also significantly lower than that of the control group. Passive avoidance in 25 mg/kg males was significantly lower than that of the control group at day 180; passive avoidance in females was not significantly affected by scopolamine hydrobromide trihydrate administration.

TABLE I1
Neurobehavioral Data for Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate[a]

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male				
n	10	10	10	10
Body weight (g)				
Prestudy	114 ± 4	114 ± 4	113 ± 4	117 ± 4
Day 1	122 ± 4	122 ± 4	121 ± 5	125 ± 5
Day 90	338 ± 7	350 ± 8	326 ± 7	318 ± 6
Day 180	385 ± 9	405 ± 7	379 ± 9	366 ± 6
Day 270	430 ± 10	452 ± 7	429 ± 14	403 ± 8
Day 360	455 ± 10	479 ± 9	448 ± 12	421 ± 10[b]
Day 720	448 ± 8[c]	575[d]	443 ± 24[e]	420 ± 15[e]
Total horizontal activity count (15 minutes)				
Prestudy	146.0 ± 7.8[b]	151.2 ± 6.2[b]	131.3 ± 11.4[b]	127.0 ± 9.8[b]
Day 1	128.6 ± 12.5	126.5 ± 7.9	107.2 ± 10.7	131.1 ± 14.0
Day 90	171.0 ± 13.3	144.7 ± 15.7	144.3 ± 12.0	170.9 ± 11.6
Day 180	77.8 ± 13.9	50.0 ± 11.3	77.9 ± 13.1	98.8 ± 6.8
Day 270	71.5 ± 7.1	61.6 ± 11.9	59.6 ± 6.7	80.3 ± 10.1
Day 360	60.7 ± 8.8	45.4 ± 9.1	58.8 ± 10.2	91.8 ± 18.3
Day 720	92.6 ± 19.4[c]	1.0[d]	118.0 ± 11.0[e]	134.5 ± 29.3[e]
Total vertical activity count (15 minutes)				
Prestudy	27.7 ± 5.3[b]	31.2 ± 4.7[b]	23.8 ± 4.5[b]	29.2 ± 6.7[b]
Day 1	26.3 ± 4.8	30.4 ± 4.3	15.7 ± 2.7	19.1 ± 3.9
Day 90	25.8 ± 5.8	30.6 ± 4.6	26.1 ± 3.5	29.5 ± 4.7
Day 180	13.9 ± 3.2	11.5 ± 4.0	10.6 ± 4.0	17.3 ± 4.3
Day 270	6.8 ± 1.4	11.3 ± 3.3	5.7 ± 1.8	5.8 ± 2.5
Day 360	5.3 ± 1.8	5.0 ± 1.3	4.5 ± 1.2	6.8 ± 2.0[b]
Day 720	3.8 ± 1.7[c]	0.0[d]	2.2 ± 0.9[e]	2.7 ± 1.1[e]
Forelimb grip strength (kg)				
Prestudy	0.460 ± 0.023	0.433 ± 0.011	0.430 ± 0.013	0.437 ± 0.011
Day 1	0.448 ± 0.017	0.436 ± 0.020	0.410 ± 0.019	0.403 ± 0.015
Day 90	1.451 ± 0.033	1.440 ± 0.015	1.376 ± 0.055	1.397 ± 0.022
Day 180	1.124 ± 0.044	1.152 ± 0.060	1.049 ± 0.050	1.162 ± 0.044
Day 270	1.297 ± 0.073	1.310 ± 0.066	1.253 ± 0.073	1.364 ± 0.082
Day 360	0.995 ± 0.059	1.165 ± 0.052*	0.966 ± 0.037	0.998 ± 0.040[b]
Day 720	0.628 ± 0.022[c]	0.350[d]	0.688 ± 0.073[e]	0.625 ± 0.064[e]
Hindlimb grip strength (kg)				
Prestudy	0.214 ± 0.009	0.211 ± 0.008	0.198 ± 0.012	0.209 ± 0.012
Day 1	0.200 ± 0.008	0.205 ± 0.007	0.201 ± 0.012	0.198 ± 0.009
Day 90	0.812 ± 0.026	0.818 ± 0.017	0.769 ± 0.024	0.784 ± 0.023
Day 180	0.775 ± 0.029	0.745 ± 0.030	0.724 ± 0.031	0.701 ± 0.017
Day 270	0.830 ± 0.046	0.892 ± 0.029	0.817 ± 0.026	0.843 ± 0.032
Day 360	0.771 ± 0.030	0.779 ± 0.029	0.742 ± 0.026	0.759 ± 0.044[b]
Day 720	0.632 ± 0.067[c]	0.450[d]	0.572 ± 0.025[e]	0.637 ± 0.037[e]

TABLE I1
Neurobehavioral Data for Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate
(continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Male (continued)				
n	10	10	10	10
Pawlick latency (seconds)				
Prestudy	5.48 ± 0.24	6.20 ± 0.67	5.83 ± 0.29	5.27 ± 0.25
Day 1	4.60 ± 0.19	5.19 ± 0.26	5.92 ± 0.70	5.10 ± 0.32
Day 90	6.07 ± 0.45	6.98 ± 0.67	5.71 ± 0.36	6.47 ± 0.60
Day 180	5.16 ± 0.28	5.83 ± 0.39	5.37 ± 0.26	5.40 ± 0.35
Day 270	3.86 ± 0.34	4.10 ± 0.20	3.96 ± 0.20	4.09 ± 0.29
Day 360	4.23 ± 0.15	4.51 ± 0.29	4.38 ± 0.18	4.79 ± 0.20[b]
Day 720	4.26 ± 0.27[c]	5.90[d]	5.05 ± 0.46[e]	5.15 ± 0.49[e]
Startle response (milliseconds)				
Prestudy	43.80 ± 5.66	35.73 ± 5.28	44.03 ± 8.66	46.97 ± 5.80
Day 1	37.17 ± 6.38	30.01 ± 2.81	35.03 ± 4.37	36.79 ± 5.40
Day 90	33.97 ± 5.55	32.76 ± 3.45	31.29 ± 3.86	32.18 ± 3.08
Day 180	20.19 ± 3.57	20.02 ± 2.16	19.24 ± 1.89	22.22 ± 2.33
Day 270	17.99 ± 1.90	13.99 ± 1.24	14.28 ± 1.72	17.81 ± 1.66
Day 360	27.78 ± 1.99	27.78 ± 3.39	27.85 ± 3.38	30.20 ± 4.17[b]
Day 720	28.75 ± 4.32[c]	22.04[d]	35.74 ± 11.93[e]	31.79 ± 3.39[e]
Passive avoidance (seconds)				
Day 90	41.91 ± 29.13	21.91 ± 5.41	59.36 ± 33.54	23.12 ± 6.17
Day 91	529.8 ± 57.1	535.3 ± 61.3	481.4 ± 69.8	472.7 ± 78.7
Day 180	557.7 ± 52.7	558.6 ± 49.8	564.8 ± 30.7	355.6 ± 87.0*
Day 270	460.3 ± 75.4	583.5 ± 62.0	460.4 ± 88.2	488.9 ± 77.3
Day 360	485.4 ± 80.6	563.9 ± 60.1	561.7 ± 50.6	391.5 ± 110.0[b]
Day 720	507.9 ± 133.2[c]	260.2[d]	178.2 ± 135.8[e]	373.1 ± 151.6[e]

TABLE I1
Neurobehavioral Data for Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate
(continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Female				
n	10	10	10	10
Body weights (g)				
Prestudy	97 ± 3	97 ± 3	97 ± 3	98 ± 3
Day 1	105 ± 3	105 ± 3	105 ± 3	107 ± 4
Day 90	190 ± 5	194 ± 4	188 ± 3	188 ± 2
Day 180	207 ± 3	211 ± 4	209 ± 4	204 ± 2[b]
Day 270	229 ± 5	234 ± 5	227 ± 7[b]	223 ± 3[b]
Day 360	262 ± 6	261 ± 9[b]	255 ± 11[b]	238 ± 5[f]
Day 720	313 ± 10[g]	311 ± 25[g]	320 ± 14[g]	295 ± 19[c]
Total horizontal activity count (15 minutes)				
Prestudy	149.6 ± 14.8	136.7 ± 16.1	136.3 ± 14.9	134.9 ± 19.0
Day 1	128.9 ± 15.2	116.3 ± 16.6	117.0 ± 14.6	151.7 ± 10.0
Day 90	158.1 ± 13.1	155.8 ± 10.6	148.5 ± 10.3	204.7 ± 14.8*
Day 180	115.2 ± 17.9	122.2 ± 17.9	139.9 ± 18.7	178.0 ± 13.4[b]*
Day 270	91.1 ± 9.1	85.5 ± 10.1	103.0 ± 16.6[b]	117.9 ± 14.5[b]
Day 360	80.5 ± 8.1	101.2 ± 14.8[b]	89.2 ± 13.7[b]	134.6 ± 14.3[f]*
Day 720	61.8 ± 6.8[g]	72.3 ± 15.9[g]	65.0 ± 10.2[g]	92.2 ± 7.1[c]
Total vertical activity count (15 minutes)				
Prestudy	23.7 ± 3.5	23.3 ± 4.3	21.1 ± 4.8	19.4 ± 3.9
Day 1	21.2 ± 3.7	20.3 ± 4.6	23.6 ± 3.5	25.3 ± 8.4
Day 90	25.3 ± 4.5	31.9 ± 4.9	38.2 ± 8.3	27.1 ± 5.2
Day 180	16.0 ± 4.1	18.3 ± 4.2	30.6 ± 8.3	25.6 ± 5.4[b]
Day 270	13.4 ± 3.0	14.7 ± 3.8	22.7 ± 6.6[b]	11.3 ± 3.0[b]
Day 360	7.7 ± 1.8	9.2 ± 1.4[b]	12.4 ± 3.5[b]	16.8 ± 4.9[f]
Day 720	2.8 ± 1.1[g]	3.5 ± 2.1[g]	1.5 ± 1.2[g]	4.6 ± 2.3c
Forelimb grip strength (kg)				
Prestudy	0.455 ± 0.018	0.456 ± 0.013	0.404 ± 0.020	0.432 ± 0.015
Day 1	0.475 ± 0.018	0.479 ± 0.017	0.453 ± 0.009	0.430 ± 0.023
Day 90	1.218 ± 0.025	1.213 ± 0.026*	1.183 ± 0.020	1.162 ± 0.021
Day 180	0.994 ± 0.040	1.008 ± 0.023	0.966 ± 0.034	0.972 ± 0.032[b]
Day 270	0.919 ± 0.033	0.993 ± 0.054	0.949 ± 0.028[b]	0.922 ± 0.049[b]
Day 360	0.817 ± 0.047	0.869 ± 0.059[b]	0.872 ± 0.056[b]	0.878 ± 0.041[f]
Day 720	0.634 ± 0.116[g]	0.640 ± 0.069[g]	0.554 ± 0.046[g]	0.625 ± 0.084[c]
Hindlimb grip strength (kg)				
Prestudy	0.182 ± 0.008	0.191 ± 0.009	0.172 ± 0.010	0.183 ± 0.007
Day 1	0.203 ± 0.013	0.193 ± 0.009	0.187 ± 0.012	0.191 ± 0.014
Day 90	0.697 ± 0.011	0.690 ± 0.013	0.649 ± 0.021	0.647 ± 0.020
Day 180	0.666 ± 0.015	0.635 ± 0.022	0.651 ± 0.030	0.604 ± 0.015[b]
Day 270	0.626 ± 0.016	0.626 ± 0.019	0.603 ± 0.018[b]	0.576 ± 0.009[b]
Day 360	0.643 ± 0.024	0.599 ± 0.018[b]	0.612 ± 0.021[b]	0.611 ± 0.021[f]
Day 720	0.625 ± 0.049[g]	0.616 ± 0.046[g]	0.563 ± 0.033[g]	0.523 ± 0.030[c]

TABLE I1
Neurobehavioral Data for Rats in the 2-Year Gavage Study of Scopolamine Hydrobromide Trihydrate
(continued)

	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Female (continued)				
n	10	10	10	10
Pawlick latency (seconds)				
Prestudy	5.91 ± 0.45	6.04 ± 0.39	5.85 ± 0.36	5.44 ± 0.26
Day 1	5.34 ± 0.42	5.30 ± 0.33	4.64 ± 0.28	6.82 ± 1.15
Day 90	5.82 ± 0.23	5.69 ± 0.33	6.32 ± 0.66	8.20 ± 0.70**
Day 180	6.06 ± 0.16	5.72 ± 0.49	5.69 ± 0.28	6.56 ± 0.37[b]
Day 270	5.62 ± 0.36	5.65 ± 0.43	4.71 ± 0.30[b]	6.31 ± 0.42[b]
Day 360	4.97 ± 0.40	4.96 ± 0.30[b]	5.01 ± 0.31[b]	5.80 ± 0.51[f]
Day 720	4.47 ± 0.41[h]	5.30 ± 1.10[g]	5.08 ± 0.92[g]	5.73 ± 0.93[h]
Startle response (milliseconds)				
Prestudy	34.47 ± 2.65	29.01 ± 2.31	38.11 ± 3.86	42.05 ± 7.57
Day 1	36.72 ± 4.02	33.65 ± 6.52	42.27 ± 5.15	36.66 ± 4.36
Day 90	38.51 ± 3.79	32.87 ± 3.79	26.69 ± 2.54*	22.70 ± 1.98**
Day 180	27.09 ± 3.64	24.42 ± 2.51	24.52 ± 2.79	23.38 ± 2.91[b]
Day 270	21.71 ± 2.54	21.39 ± 2.97	18.75 ± 2.12[b]	18.03 ± 1.96[b]
Day 360	31.61 ± 2.45	28.82 ± 2.71[b]	33.01 ± 4.20[b]	28.24 ± 3.08[f]
Day 720	34.52 ± 5.95[g]	29.78 ± 3.02[g]	29.26 ± 4.57[g]	35.20 ± 3.76[c]
Passive avoidance (seconds)				
Day 90	28.96 ± 9.61	18.13 ± 3.88	45.53 ± 28.92	31.59 ± 13.93
Day 91	496.5 ± 82.0	536.6 ± 51.4	396.5 ± 80.6	465.7 ± 48.3
Day 180	444.8 ± 66.5	499.6 ± 57.8	369.6 ± 69.9	361.1 ± 78.6[b]
Day 270	579.0 ± 63.4	520.2 ± 82.7	419.4 ± 93.8[b]	343.9 ± 71.0[b]
Day 360	386.3 ± 88.7	352.3 ± 105.2[b]	525.9 ± 74.9[b]	589.1 ± 77.3[f]
Day 720	279.8 ± 119.4[g]	38.2 ± 11.4[g]	255.7 ± 116.9[g]	200.3 ± 88.7[c]

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test.
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=5
[d] n=1; no standard error calculated
[e] n=6
[f] n=8
[g] n=4
[h] n=3

APPENDIX J
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF SCOPOLAMINE HYDROBROMIDE TRIHYDRATE

Scopolamine hydrobromide trihydrate was obtained in two lots from Rebeco Chemicals, Inc. (New York, NY) (lot 14188) and from Henley and Company, Inc. (New York, NY) (lot 283). Lot 14188 was used during the 16-day studies, and lot 283 was used during the 14-week and 2-year studies. Identity, purity, and stability were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the scopolamine hydrobromide trihydrate studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a white powder, were identified as scopolamine hydrobromide trihydrate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with that expected for the structure, and the infrared and nuclear magnetic resonance spectra were consistent with the literature spectra (*Sadtler Standard Spectra*; Feeney, 1978) of scopolamine hydrobromide trihydrate (Figures J1 and J2). The observed melting point of 192° to 194° C and the specific optical activity ($[\alpha]_D^{25} = -24.5° \pm 0.1°$) for lot 14188 were consistent with the literature reference (*Merck Index*, 1983).

The purity of both lots was determined by elemental analysis, Karl Fisher water analysis, functional group titration, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). Weight loss on drying was determined for lot 14188. Functional group titration was performed by dissolving samples of the test chemical in glacial acetic acid containing excess mercury (II) acetate and then titrating with 0.1 N perchloric acid in glacial acetic acid. The titrations were monitored potentiometrically using a combination pH/mV electrode filled with aqueous 4 M potassium chloride. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) chloroform:acetone:diethylamine (50:40:10) and 2) toluene:ethyl acetate:diethylamine (70:20:10) with caffeine as a reference standard. Plates were examined under ultraviolet light (254 nm) and with a spray of equal parts 0.3% hexachloroplatinic acid and 6% potassium iodide solution. HPLC was performed with a Waters μBondapak C_{18} column, a solvent system of 0.005 M sodium heptanesulfonic acid in water:0.005 M sodium heptanesulfonic acid in methanol (62:38) with 10% phosphoric acid added to adjust the pH, a flow rate of 1.0 mL/minute, and ultraviolet detection at 229 nm. Lot 14188 and a solution of dried United States Pharmacopeia XX (USP) reference standard scopolamine hydrobromide were concomitantly analyzed with the same HPLC methods used for the purity analysis of lot 14188 but with acetanilide as a reference standard. Lot 283 was concomitantly analyzed with a solution of dried USP reference standard scopolamine hydrobromide and with lot 14188 with the same HPLC methods as the concomitant analysis of lot 14188.

For lot 14188, elemental analyses for carbon, hydrogen, nitrogen, and bromine were in agreement with the theoretical values for scopolamine hydrobromide trihydrate. Karl Fisher water analysis indicated 10.8% ± 0.3% water. Weight loss on drying indicated 10.8% ± 0.02% water. Functional group titration indicated a purity of 101.9% ± 0.1% scopolamine hydrobromide trihydrate, equivalent to 89.3% ± 0.1% anhydrous scopolamine hydrobromide. TLC with system 1 indicated a major spot, two trace impurities, and one slight trace impurity. TLC with system 2 indicated a major spot and one trace impurity. HPLC indicated a major peak and one impurity with a peak area of 0.1% relative to the major peak. Major peak comparisons of lot 14188 with a solution of dried USP reference standard scopolamine hydrobromide indicated that lot 14188 contained 88.8% ± 0.2% scopolamine hydrobromide relative to the USP reference. Lot 14188 was determined to contain 89% scopolamine hydrobromide and 11% water.

The theoretical values for scopolamine hydrobromide trihydrate are 87.7% scopolamine hydrobromide and 12.3% water.

For lot 283, elemental analyses for carbon, hydrogen, nitrogen, and bromine were in agreement with the theoretical values for scopolamine hydrobromide trihydrate. Karl Fisher water analysis indicated 11.2% ± 0.2% water. Functional group titration indicated a purity of 101.7% ± 0.6% scopolamine hydrobromide trihydrate, equivalent to 89.2% ± 0.5% anhydrous scopolamine hydrobromide. TLC indicated a major spot and one trace impurity by each system. HPLC indicated a major peak and one impurity with a peak area of 0.2% relative to the major peak. Major peak comparisons of lot 283 with a solution of dried USP reference standard scopolamine hydrobromide indicated that lot 283 contained 89.2% ± 0.3% scopolamine hydrobromide relative to the USP reference. Major peak comparisons of lot 283 with lot 14188 indicated a purity of 100.0% ± 0.4% relative to lot 14188. Lot 283 was also determined to contain 89% scopolamine hydrobromide and 11% water.

Reanalyses to determine the purity of lot 283 were conducted by the analytical chemistry laboratory using functional group titration and HPLC. Functional group titration was performed as previously described except that the combination pH/mV electrode was filled with aqueous 3 M potassium chloride. Frozen reference samples of lots 14188 and 283 were concomitantly analyzed using the same HPLC methods as in the original purity analysis of lot 283 and using those same HPLC methods but with acetanilide as an internal standard and a solvent ratio of 65:35. Functional group titration indicated a purity of 102.0% ± 0.6%. Major peak comparisons lot 283 with lot 14188 by the first HPLC system indicated no additional impurity peaks. Major peak comparisons of lot 283 with lot 14188 by the second HPLC system indicated a purity of 100.3% ± 0.5% relative to lot 14188.

Stability studies of lot 14188 of the bulk chemical were performed by the analytical chemistry laboratory. Analyses were performed using the same HPLC protocol described for the purity analysis but with acetanilide as an internal standard. These studies indicated that bulk scopolamine hydrobromide trihydrate was stable when stored for up to 2 weeks in sealed containers, protected from light, under a nitrogen headspace, and at temperatures up to 25° C. To ensure stability, the bulk chemical was stored in amber glass jars at approximately 25°C under a nitrogen headspace. Stability of the bulk chemical was monitored at the beginning of the 16-day studies and at the beginning and end of the 14-week studies using HPLC. For the 2-year studies, stability of the bulk chemical was monitored at the beginning and end of the studies and every 4 months during the studies using HPLC and potentiometric titration. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations for the 16-day and 14-week studies were prepared every two weeks. For the 2-year rat study, dose formulations were prepared weekly during the first four months of the study and every two weeks for the remainder of the study. Dose formulations for the 2-year mouse study were prepared every two weeks throughout the study. Dose formulations were prepared by mixing the appropriate quantities of scopolamine hydrobromide trihydrate with deionized water to give the required concentrations (Table J1) and were stored at room temperature in amber glass bottles capped with Teflon®-lined lids in the dark for up to 3 weeks.

Stability studies of the 11 and 0.2 mg/mL dose formulations were conducted by the analytical chemistry laboratory. For the 11 mg/mL formulation, samples were prepared by dissolving scopolamine hydrobromide trihydrate in deionized water and diluting to volume. Aliquots (5 mL) were mixed with internal standard solution (0.4 mg/mL acetophenone in acetonitrile) and were further diluted with 0.007 M aqueous sodium heptanesulfonic acid. The samples were then analyzed by HPLC using a

Waters C_{18} Nova Pak column, with a mobile phase of water:acetonitrile (70:30), at a flow rate of 1.0 mL/minute, and with ultraviolet detection at 229 nm. For the 0.2 mg/mL formulation, samples were prepared by dissolving scopolamine hydrobromide trihydrate in deionized water and diluting to volume. Aliquots (7 mL) were mixed with internal standard solution (0.04 mg/mL propiophenone in acetonitrile) and were analyzed by HPLC with the same system used to analyze the 11 mg/mL formulation but with a mobile phase ratio of 75:25. The stability of the dose formulations was confirmed for at least 3 weeks at room temperature when stored in the dark or for at least 3 hours at room temperature and open to air and light.

Periodic analyses of the dose formulations of scopolamine hydrobromide trihydrate were conducted at the study laboratory using ultraviolet/visible spectrometry for the 16-day and 14-week studies and by HPLC for the 2-year studies. During the 16-day studies, dose formulations were analyzed at the beginning of the studies (Table J2). During the 14-week and 2-year studies, dose formulations were analyzed every 6 to 8 weeks (Tables J3 and J4). During the 16-day studies, 70% (7/10) of the dose formulations were within 10% of the target concentration with no value exceeding 16% of the target concentration. All of the dose formulations analyzed during the 14-week studies were within 10% of the target concentration. During the 2-year studies, 92% (72/78) of the dose formulations were within 10% of the target concentration with no value differing more than 20% from the target concentration. For the 14-week and 2-year studies, results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results of the study laboratory (Table J5).

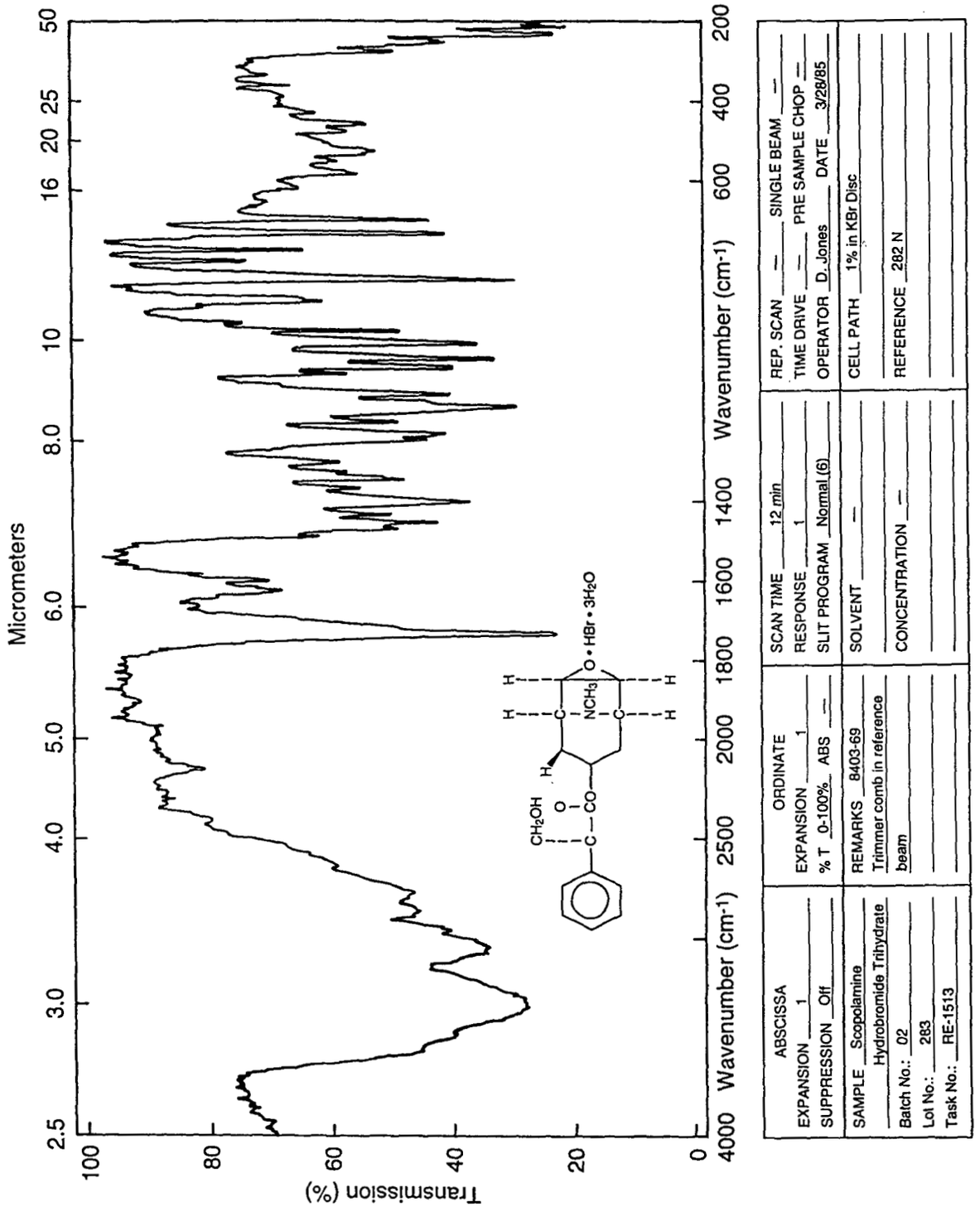

FIGURE J1
Infrared Absorption Spectrum of Scopolamine Hydrobromide Trihydrate

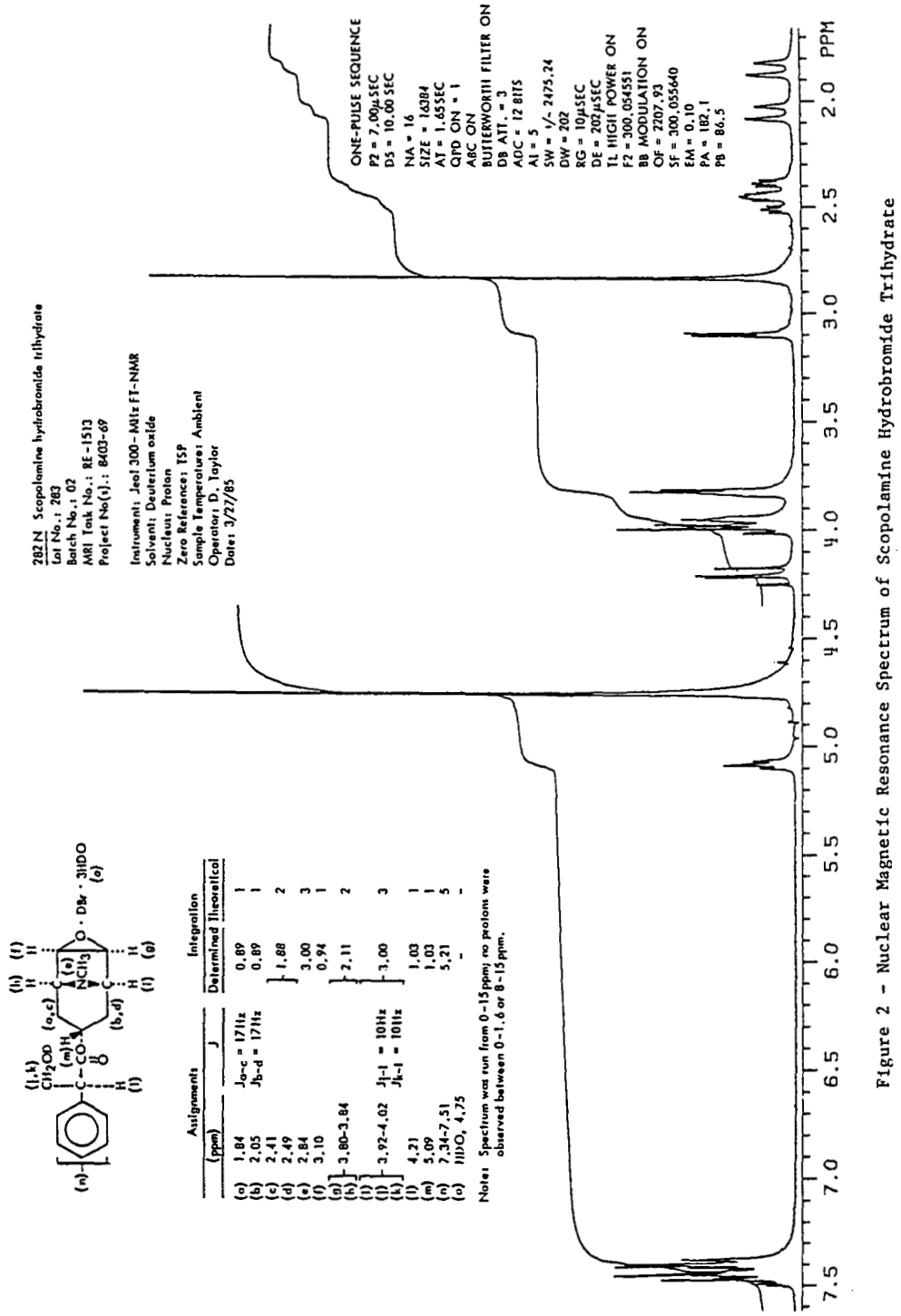

Figure 2 - Nuclear Magnetic Resonance Spectrum of Scopolamine Hydrobromide Trihydrate

FIGURE J2
Nuclear Magnetic Resonance Spectrum of Scopolamine Hydrobromide Trihydrate

TABLE J1
Preparation and Storage of Dose Formulations in the Gavage Studies of Scopolamine Hydrobromide Trihydrate

16-Day Studies	14-Week Studies	2-Year Studies
Preparation		
Scopolamine hydrobromide trihydrate was dissolved in approximately one third of the required volume of deionized water and diluted to the desired concentrations	Same as 16-day studies	Same as 16-day studies
Chemical Lot Number		
14188	283	283
Maximum Storage Time		
3 weeks	3 weeks	3 weeks
Storage Conditions		
Stored in sealed containers at room temperature and protected from light	Stored in amber glass bottles with Teflon®-lined lids at room temperature and protected from light	Same as 14-week studies
Study Laboratory		
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Battelle Columbus Laboratories (Columbus, OH)
Referee Laboratory		
Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE J2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 16-Day Gavage Studies of Scopolamine Hydrobromide Trihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)[a]	Difference from Target (%)
Rats				
27 June 1985	27 June 1985	15	15.2	+1
		30	30.1	0
		60	59.7	−1
		120	114.4	−5
		240	209.2	−13
	9 July 1985[b]	15	15.0	0
		30	29.7	−1
		60	60.0	0
		120	114.4	−5
1 July 1985[c]	1 July 1985	240	210.6	−12
	9 July 1985[b]	240	214.0	−11
Mice				
2 July 1985	3 July 1985	15	13.9	−7
		25	22.9	−8
		45	41.4	−8
		90	78.2	−13
		180	150.8	−16
	12 July 1985[b]	15	14.0	−7
		25	23.0	−8
		45	41.3	−8
4 July 1985[c]	5 July 1985	90	79.8[d]	−11
		180	153.0[d]	−15
	12 July 1985	90	88.0	−2
		180	166.7	−7
	12 July 1985[b]	90	88.6	−2
		180	166.6	−7

[a] Results of duplicate analyses. Dosing volume = 0.5 mL/100 g (rats); 15 mg/mL = 75 mg/kg, 30 mg/mL = 150 mg/kg, 60 mg/mL = 300 mg/kg, 120 mg/mL = 600 mg/kg, 240 mg/mL = 1,200 mg/kg. Dosing volume = 0.1 mL/10 g (mice); 15 mg/mL = 150 mg/kg, 25 mg/mL = 250 mg/kg, 45 mg/mL = 450 mg/kg, 90 mg/mL = 900 mg/kg, 180 mg/mL = 1,800 mg/kg.
[b] Animal room sample
[c] Results of remix
[d] Trial for new dose formulation procedure; formulation not used for dosing

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Week Gavage Studies of Scopolamine Hydrobromide Trihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)[a]	Difference from Target (%)
Rats				
7 March 1986	10 March 1986	3.0	2.92	−3
		9.0	8.88	−1
		27.0	26.8	−1
		80.0	80.2	0
		240.0	241.7	+1
	28 March 1986[b]	3.0	3.00	0
		9.0	9.06	+1
		27.0	26.9	0
		80.0	80.2	0
		240.0	238	−1
18 April 1986	18 April 1986	3.0	2.96	−1
		9.0	8.70	−3
		27.0	26.9	0
		80.0	79.0	−1
		240.0	239	0
	9 May 1986[b]	3.0	2.91	−3
		9.0	8.78	−2
		27.0	27.1	0
		80.0	79.3	−1
		240.0	240	0
30 May 1986	2 June 1986	3.0	3.04	+1
		9.0	8.98	0
		27.0	26.2	−3
		80.0	79.0	−1
		240.0	237	−1
	19 June 1986[b]	3.0	2.95	−2
		9.0	8.80	−2
		27.0	26.0	−4
		80.0	77.6	−3
		240.0	239	0
Mice				
7 March 1986	10 March 1986	1.5	1.46	−3
		4.5	4.45	0
		13.5	13.4	−1
		40.0	39.6	−1
		120.0	119.3	−1
	28 March 1986[b]	1.5	1.54	+3
		4.5	4.70	+4
		13.5	13.5	0
		40.0	39.8	−1
		120.0	119	−1

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Week Gavage Studies of Scopolamine Hydrobromide Trihydrate (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
18 April 1986	18 April 1986	1.5	1.44	−4
		4.5	4.32	−4
		13.5	12.8	−5
		40.0	39.0	−3
		120.0	118	−2
	9 May 1986[b]	1.5	1.51	+1
		4.5	4.38	−3
		13.5	12.9	−4
		40.0	38.7	−3
		120.0	118	−2
13 June 1986	16 June 1986	1.5	1.54	+3
		4.5	4.52	+1
		13.5	13.5	0
		40.0	40.0	0
		120.0	122	+2
	27 June 1986[b]	1.5	1.54	+3
		4.5	4.48	0
		13.5	13.2	−2
		40.0	39.6	−1
		120.0	122	+2

[a] Results of duplicate analyses. Dosing volume = 0.5 mL/100 g (rats); 3.0 mg/mL = 15 mg/kg, 9.0 mg/mL = 45 mg/kg, 27.0 mg/mL = 135 mg/kg, 80 mg/mL = 400 mg/kg, 240 mg/mL = 1,200 mg/kg. Dosing volume = 0.1 mL/10 g (mice); 1.5 mg/mL = 15 mg/kg, 4.5 mg/mL = 45 mg/kg, 13.5 mg/mL = 135 mg/kg, 40 mg/mL = 400 mg/kg, 120 mg/mL = 1,200 mg/kg.
[b] Animal room sample

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Scopolamine Hydrobromide Trihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)[a]	Difference from Target (%)
Rats				
11 October 1988	14 October 1988	0.2	0.203	+2
		1.0	0.990	−1
		5.0	5.053	+1
	28 October 1988[b]	0.2	0.195	−3
		1.0	0.995	−1
		5.0	4.853	−3
21 November 1988	21 November 1988	0.2	0.203	+2
		1.0	0.956	−4
		5.0	4.928	−1
17 January 1989	18-19 January 1989	0.2	0.202	+1
		1.0	1.025	+3
		5.0	4.958	−1
14 March 1989	15 March 1989	0.2	0.201	+1
		1.0	0.962	−4
		5.0	4.839	−3
	28-29 March 1989[b]	0.2	0.205	+3
		1.0	1.081	+8
		5.0	5.047	+1
9 May 1989	11 May 1989	0.2	0.201	+1
		1.0	0.936	−6
		5.0	4.895	−2
6 July 1989	7-8 July 1989	0.2	0.239	+20
		1.0	1.201	+20
		5.0	5.617	+12
29 August 1989	31 August-1 September 1989	0.2	0.210	+5
		1.0	1.024	+2
		5.0	5.328	+7
	13-14 September 1989[b]	0.2	0.209	+5
		1.0	1.101	+10
		5.0	5.035	+1
24 October 1989	27 October 1989	0.2	0.210	+5
		1.0	1.039	+4
		5.0	5.115	+2
19 December 1989	20 December 1989	0.2	0.207	+4
		1.0	1.050	+5
		5.0	4.864	−3

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Scopolamine Hydrobromide Trihydrate (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Rats (continued)				
13 February 1990	16 February 1990	0.2	0.204	+2
		1.0	0.998	0
		5.0	4.994	0
	6 March 1990[b]	0.2	0.159	−21
		1.0	0.999	0
		5.0	5.006	0
16 April 1990	18 April 1990	0.2	0.205	+3
		1.0	0.999	0
		5.0	5.061	+1
	2 May 1990[b]	0.2	0.179	−11
11 June 1990	12 June 1990	0.2	0.205	+3
		1.0	1.062	+6
		5.0	5.250	+5
6 August 1990	8 August 1990	0.2	0.204	+2
		1.0	0.995	−1
		5.0	5.047	+1
	31 August 1990[b]	0.2	0.116	−42
		1.0	1.039	+4
		5.0	4.982	0
Mice				
13 September 1988	15 September 1988	0.1	0.097	−3
		0.5	0.498	0
		2.5	2.49	0
	30 September 1988[b]	0.1	0.094	−6
		0.5	0.494	−1
		2.5	2.46	−2
21 November 1988	21 November 1988	0.1	0.100	0
		0.5	0.507	+1
		2.5	2.534	+1
17 January 1989	18-19 January 1989	0.1	0.100	0
		0.5	0.489	−2
		2.5	2.435	−3

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Scopolamine Hydrobromide Trihydrate (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
14 March 1989	15 March 1989	0.1	0.095	−5
		0.5	0.499	0
		2.5	2.522	+1
	28-29 March 1989[b]	0.1	0.106	+6
		0.5	0.494	−1
		2.5	2.511	0
9 May 1989	11 May 1989	0.1	0.093	−7
		0.5	0.508	+2
		2.5	2.518	+1
6 July 1989	7-8 July 1989	0.1	0.114	+14
		0.5	0.575	+15
		2.5	2.907	+16
29 August 1989	31 August-1 September 1989	0.1	0.102	+2
		0.5	0.539	+8
		2.5	2.563	+3
	13-14 September 1989[b]	0.1	0.112	+12
		0.5	0.511	+2
		2.5	2.582	+3
24 October 1989	27 October 1989	0.1	0.104	+4
		0.5	0.523	+5
		2.5	2.554	+2
19 December 1989	20-21 December 1989	0.1	0.103	+3
		0.5	0.498	0
		2.5	2.480	−1
13 February 1990	16 February 1990	0.1	0.101	+1
		0.5	0.500	0
		2.5	2.530	+1
	6 March 1990[b]	0.1	0.085	−15
		0.5	0.442	−12
		2.5	2.411	−4
16 April 1990	18 April 1990	0.1	0.105	+5
		0.5	0.516	+3
		2.5	2.480	−1
	2 May 1990[b]	0.1	0.058	−42
		0.5	0.470	−6

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Scopolamine Hydrobromide Trihydrate (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
11 June 1990	12 June 1990	0.1	0.106	+6
		0.5	0.511	+2
		2.5	2.574	+3
6 August 1990	8 August 1990	0.1	0.101	+1
		0.5	0.507	+1
		2.5	2.492	0
	31 August 1990[b]	0.1	0.040	−60
		0.5	0.450	−10
		2.5	2.525	+1

[a] Results of duplicate analyses. Dosing volume = 0.5 mL/100 g (rats); 0.2 mg/mL = 1.0 mg/kg, 1.0 mg/mL = 5 mg/kg, 5.0 mg/mL = 25 mg/kg. Dosing volume = 1 mL/100 g (mice); 0.1 mg/mL = 1.0 mg/kg, 0.5 mg/mL = 5 mg/kg, 2.5 mg/mL = 25 mg/kg.
[b] Animal room sample

TABLE J5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 14-Week and 2-Year Gavage Studies of Scopolamine Hydrobromide Trihydrate

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
14-Week Studies (Southern Research Institute)			
Rats			
7 March 1986	3.0	2.92	3.00 ± 0.01
Mice			
13 June 1986	120.0	122	119.00 ± 1.00
2-Year Studies (Battelle Columbus Laboratories)			
Rats			
11 October 1988	0.2	0.203	0.201 ± 0.001
14 March 1989	1.0	0.962	1.010 ± 0.01
13 February 1990	5.0	4.994	4.92 ± 0.04
Mice			
13 September 1988	2.5	2.49	2.48 ± 0.02
29 August 1989	0.5	0.539	0.508 ± 0.01

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

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)	23.17 ± 0.71	21.80 — 24.30	37
Crude fat (% by weight)	5.27 ± 0.21	4.60 — 5.70	37
Crude fiber (% by weight)	3.55 ± 0.41	2.60 — 4.30	37
Ash (% by weight)	6.47 ± 0.24	6.11 — 7.30	37
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 — 1.390	10
Cystine	0.306 ± 0.075	1.181 — 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	0.233 ± 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)	6,798 ± 1,866	4,180 — 12,140	37
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 — 6,300	4
α-Tocopherol (ppm)	36.92 ± 2.20	22.5 — 48.9	9
Thiamine (ppm)	18.60 ± 2.19	15.0 — 28.0	37
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 (%)	1.21 ± 0.11	1.00 — 1.54	37
Phosphorus (%)	0.94 ± 0.03	0.85 — 1.00	37
Potassium (%)	0.887 ± 0.067	0.772 — 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 — 0.635	8
Sodium (%)	0.315 ± 0.034	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[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.29 ± 0.19	0.06 — 0.70	37
Cadmium (ppm)	0.09 ± 0.05	0.05 — 0.2	37
Lead (ppm)	0.27 ± 0.20	0.10 — 1.00	37
Mercury (ppm)	0.03 ± 0.02	0.02 — 0.11	37
Selenium (ppm)	0.38 ± 0.22	0.05 — 1.27	37
Aflatoxins (ppb)[c]	<5.0		37
Nitrate nitrogen (ppm)[d]	14.82 ± 4.80	5.70 — 24.0	37
Nitrite nitrogen (ppm)[d]	0.21 ± 0.17	0.10 — 0.07	37
BHA (ppm)[e]	1.78 ± 1.62	1.00 — 10.00	37
BHT (ppm)[e]	1.54 ± 1.35	1.00 — 8.00	37
Aerobic plate count (CFU/g)	43,275 ± 27,682	4,100 — 120,000	37
Coliform (MPN/g)	4.05 ± 4.36	3.00 — 23.00	37
Escherichia coli (MPN/g)	3.00	<3.00	38
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[f]	7.57 ± 2.60	3.60 — 16.50	37
N-Nitrosodimethylamine (ppb)[f]	5.67 ± 2.26	2.60 — 13.00	37
N-Nitrosopyrrolidine (ppb)[f]	1.92 ± 1.06	1.00 — 4.30	37
Pesticides (ppm)			
α-BHC	<0.01		31
β-BHC	<0.02		31
γ-BHC	<0.01		31
δ-BHC	<0.01		31
Heptachlor	<0.01		31
Aldrin	<0.01		31
Heptachlor epoxide	<0.01		31
DDE	<0.01		31
DDD	<0.01		31
DDT	<0.01		31
HCB	<0.01		31
Mirex	<0.01		31
Methoxychlor	<0.05		31
Dieldrin	<0.01		31
Endrin	<0.01		31
Telodrin	<0.01		31
Chlordane	<0.05		31
Toxaphene	<0.1		31
Estimated PCBs	<0.2		31
Ronnel	<0.01		31
Ethion	<0.02		31
Trithion	<0.05		31
Diazinon	<0.1		31
Methyl parathion	<0.02		31
Ethyl parathion	<0.02		31
Malathion	0.24 ± 0.24	0.05 — 1.00	37
Endosulfan I	<0.01		31
Endosulfan II	<0.01		31
Endosulfan sulfate	<0.03		31

[a] CFU = colony-forming units, MPN = most probable number, BHC = hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] No aflatoxin measurement was recorded for the lot milled on 2 October 1989.
[d] Sources of contamination: alfalfa, grains, and fish meal.
[e] Sources of contamination: soy oil and fish meal.
[f] All values were corrected for percent recovery.

APPENDIX 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 all subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

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

Method and Test	Time of Analysis
RATS	
14-Week Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
M. arthritidis	24 months
M. pulmonis	24 months
PVM	Quarantine, 6, 12, 18, and 24 months
RCV/SDA	Quarantine, 6, 12, 18, and 24 months
Sendai	Quarantine, 6, 12, 18, and 24 months
Immunofluorescence Assay	
RCV/SDA	24 months
Hemagglutination Inhibition	
H-1	Quarantine, 6, 12, 18, and 24 months
KRV	Quarantine, 6, 12, 18, and 24 months

MICE

14-Week Study

Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA	
Ectromelia virus	Quarantine, 6, 12, 18, and 24 months
EDIM	24 months
GDVII	Quarantine, 6, 12, 18, and 24 months
LCM	12, 18, and 24 months
MVM	Quarantine, 6, and 12 months
Mouse adenoma virus	Quarantine, 6, 12, and 24 months
MHV	Quarantine, 6, 12, 18, and 24 months
M. arthritidis	24 months
M. pulmonis	24 months
PVM	Quarantine, 6, 12, 18, and 24 months
Reovirus 3	Quarantine, 6, 12, 18, and 24 months
Sendai	Quarantine, 6, 12, 18, and 24 months
Immunofluorescence Assay	
EDIM	Quarantine, 6, 12, 18, and 24 months
GDVII	24 months
LCM	Quarantine and 6 months
MVM	18 months
Mouse adenoma virus	18 and 24 months
MHV	6 and 12 months
Reovirus 3	24 months

MICE (continued)
2-Year Study (continued)
Hemagglutination Inhibition

K	Quarantine, 6, 12, 18, and 24 months
MVM	24 months
Polyoma virus	Quarantine, 6, 12, 18, and 24 months

Results of serology tests are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for Rats and Mice in the 14-Week and 2-Year Gavage Studies of Scopolamine Hydrobromide Trihydrate

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
14-Week Studies		
Rats		
Study termination	0/10	None positive
Mice		
Study termination	0/10	None positive
2-Year Studies		
Rats		
Quarantine	0/10	None positive
6 Months	0/10	None positive
12 Months	0/10	None positive
18 Months	0/10	None positive
24 Months	3/10	*M. arthritidis*[a]
Mice		
Quarantine	0/10	None positive
6 Months	9/10	MHV[b]
12 Months	6/10	MHV
18 Months	6/10	MHV
24 Months	10/10	MHV
	1/10	Reovirus 3
	1/10	*M. arthritidis*

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may be due to cross reaction with antibiotics of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical findings or histopathic changes of *M. athritidis* infection in mice with positive titers. Accordingly, sporadic *M. arthritidis*-positive titers were considered to be false positive.
[b] MHV was positive by ELISA in 8 of 10 animals and positive by immunofluorescence assay in 9 of 10 animals

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