NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF DECALIN

(CAS NO. 91-17-8)

IN F344/N RATS AND B6C3F$_1$ MICE

AND A TOXICOLOGY STUDY OF DECALIN IN MALE NBR RATS

(INHALATION STUDIES)

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

January 2005

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

FOREWORD

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

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies, abstracts of all NTP Technical Reports, and full versions of the completed reports are available at the NTP's World Wide Web site: http://ntp.niehs.nih.gov. In addition, printed copies of these reports are available from NTP as supplies last by contacting (919) 541-1371. A listing of all NTP Technical Reports printed since 1982 appears at the end of this Technical Report.

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SUMMARY

Background

Decalin is widely used as a solvent for paints, waxes, resins, oils, and fats. We studied decalin to determine if it caused cancer in rats or mice.

Methods

We exposed groups of 50 male rats to air containing 25, 50, or 100 parts per million (ppm) decalin, 20 male rats to 400 ppm, and 50 female rats and male and female mice to 25, 100, or 400 ppm six hours per day for two years. Similar groups of 50 animals were exposed to clean air in the same inhalation chambers six hours per day as the untreated control groups. Tissues from more than 40 sites were examined for every animal.

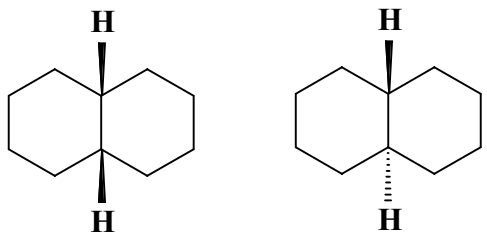
Results

There were no differences in survival of male or female rats or male or female mice exposed to the solvent. Male rats exposed to decalin had higher rates of tumors of the kidney, and female mice exposed to decalin had slightly increased rates of tumors in the liver and uterus.

Conclusions

We conclude that decalin caused cancer of the kidney in male rats. Increases in liver and uterus tumors in female mice may have been related to exposure to decalin. There was no evidence that decalin increased tumor rates in female rats or male mice.

ABSTRACT



***cis*-Decalin** ***trans*-Decalin**

DECALIN

CAS No. 91-17-8

Chemical Formula: $C_{10}H_{18}$ Molecular Weight: 138.2

Synonyms: Bicyclo[4.4.0]decane; dec; decahydronaphthalene; dekalin; naphthalane; napthan; napthane; perhydronaphthalene

Decalin is used as an industrial solvent for naphthalene, fats, resins, oils, and waxes. It is also used as a substitute for turpentine in lacquers, paints, and varnishes; as a solvent and stabilizer for shoe polishes and floor waxes; and as a constituent of motor fuels and lubricants. Other applications include use as a paint thinner and remover, a patent fuel in stoves, a high-density fuel in submarine-launched cruise missile systems, and in stain removal and cleaning machinery. Decalin was nominated for study by the National Cancer Institute because of its chemical structure, its potential for consumer exposure, and a lack of adequate testing of the chemical. Male and female F344/N rats and B6C3F$_1$ mice were exposed to decalin (greater than 99% pure) by inhalation for 2 weeks, 3 months, or 2 years. Groups of male NBR rats were exposed to decalin for 2 weeks. Male NBR rats do not produce α2u-globulin; the NBR rats were included to study the relationship of α2u-globulin and renal lesion induction. Genetic toxicology studies were conducted in *Salmonella typhimurium* and mouse peripheral blood erythrocytes.

2-Week Study in Rats

Groups of five male and five female F344/N rats and five male NBR rats were exposed to 0, 25, 50, 100, 200, or 400 ppm decalin vapor 6 hours per day, 5 days per week for 16 days. All rats survived to the end of the study, and mean body weights of exposed groups were similar to those of the chamber controls. Renal toxicity studies were performed in male F344/N and NBR rats. The numbers of labeled cells and the labeling indices in the left kidney of 200 and 400 ppm F344/N male rats were significantly greater than those in the chamber controls. The α2u-globulin/soluble protein ratios were significantly increased in all exposed groups of F344/N rats. Liver weights of male F344/N and NBR rats exposed to 100 ppm or greater were significantly increased, as were those of all exposed groups of females. Kidney weights of male F344/N rats exposed to 50 ppm or greater were significantly increased. Exposure-related hyaline droplet accumulation, degeneration and regeneration of renal cortical tubules, and granular casts occurred in the kidney of exposed F344/N male rats.

2-Week Study in Mice

Groups of five male and five female B6C3F$_1$ mice were exposed to 0, 25, 50, 100, 200, or 400 ppm decalin vapor 6 hours per day, 5 days per week for 17 days. All mice survived to the end of the study, and mean body weights of exposed groups were similar to those of the chamber

control groups. Liver weights of 200 and 400 ppm males and females and 100 ppm females were significantly increased.

3-Month Study in Rats

Groups of 25 male and 20 female F344/N rats were exposed to 0, 25, 50, 100, 200, or 400 ppm decalin vapor 6 hours per day, 5 days per week for 2 (five male renal toxicity rats), 6 (10 male and 10 female clinical pathology rats), or 14 (10 core study rats) weeks. All rats survived to the end of the study, and mean body weights of exposed groups were similar to those of the chamber control groups.

Urinalysis results indicated that decalin exposure caused increases in urine glucose and protein concentrations and enzyme activities that were consistent with the renal lesions observed microscopically. Renal toxicity studies were performed on rats sacrificed at 2 and 6 weeks and at the end of the study. In kidney tissue examined for cell proliferation, the numbers of PCNA-labeled cells and labeling indices were generally significantly greater than those of the chamber controls in exposed groups of rats at all three time points. Concentrations of α2u-globulin in the kidney as well as the α2u-globulin/soluble protein ratios were significantly increased at week 2 in all exposed groups and in the 200 and 400 ppm groups at week 6 and at the end of the study. Absolute and/or relative kidney and liver weights of male rats exposed to 50 ppm or greater were increased. Incidences of renal tubule regeneration and granular casts in the medulla of the kidney in exposed male rats were increased, and the severities of hyaline droplets generally increased with increasing exposure concentration.

3-Month Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 25, 50, 100, 200, or 400 ppm decalin vapor 6 hours per day, 5 days per week for 14 weeks. All mice survived to the end of the study, and mean body weights of exposed groups were similar to those of the chamber control groups. Liver weights of 200 and 400 ppm males and females were significantly increased. There was a significant exposure concentration-related decrease in the absolute spermatid head count and a significant decrease in absolute head count of the 400 ppm group compared to the chamber controls. Incidences of centrilobular cytomegaly of the liver were increased in exposed male mice.

2-Year Study in Rats

Groups of 50 male and 50 female F344/N rats were exposed to 0, 25, 50 (male rats only), 100, or 400 ppm (female rats only) decalin vapor 6 hours per day, 5 days per week for 105 weeks. A group of 20 male rats was exposed to 400 ppm. Survival of exposed groups was similar to that of the chamber control groups. Mean body weights of 400 ppm males were slightly less than those of the chamber controls during the second year of the study. Incidences of renal tubule adenoma and adenoma or carcinoma (combined) and of benign or malignant pheochromocytoma (combined) of the adrenal medulla in 100 and 400 ppm males were significantly increased. There was a significant association between nephropathy severity and adrenal pheochromocytoma incidence. Nonneoplastic lesions related to decalin exposure occurred in the kidney of male rats.

2-Year Study in Mice

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed to 0, 25, 100, or 400 ppm decalin vapor 6 hours per day, 5 days per week for 105 weeks. Survival of exposed mice was similar to that of the chamber controls. Mean body weights of exposed groups were generally similar to those of the chamber control groups throughout the study. Increased incidences of hepatocellular neoplasms occurred in 25 and 400 ppm female mice, and the incidences of centrilobular hypertrophy, necrosis, syncytial alteration, and erythrophagocytosis of the liver in 400 ppm males were significantly increased. The incidences of uterine stromal polyp and stromal polyp or stromal sarcoma (combined) occurred with positive trends in female mice.

Pharmacokinetic Model

The rate of metabolism of decalin was the same for males and females in rats and mice. Also in rats and mice, decalin metabolism was saturated at less than 400 ppm. Increased labeling indices in male rats were likely due to changes related to α2u-globulin.

Genetic Toxicology

Decalin was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, or TA1535, with or without induced hamster or rat liver S9 enzymes. A small but significant increase in the frequency of micronucleated normochromatic erythrocytes was noted in male mice exposed to decalin for 3 months; however, no induction of micronuclei was observed in female mice.

Conclusions

Under the conditions of these studies, there was *clear evidence of carcinogenic activity** of decalin in male F344/N rats based on increased incidences of renal tubule neoplasms. The increased incidences of benign or malignant pheochromocytoma (combined) of the adrenal medulla in male rats were also considered to be exposure related. There was *no evidence of carcinogenic activity* of decalin in female F344/N rats exposed to 25, 100, or 400 ppm. There was *no evidence of carcinogenic activity* of decalin in male $B6C3F_1$ mice exposed to 25, 100, or 400 ppm. There was *equivocal evidence of carcinogenic activity* of decalin in female $B6C3F_1$ mice based on marginally increased incidences of hepatocellular and uterine neoplasms.

Exposure of male rats to decalin resulted in nonneoplastic lesions of the kidney characteristic of α2u-globulin accumulation. Nonneoplastic lesions of the liver were observed in male mice exposed to decalin.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 25, 50, 100, or 400 ppm	Chamber control, 25, 100, or 400 ppm	Chamber control, 25, 100, or 400 ppm	Chamber control, 25, 100, or 400 ppm
Body weights	400 ppm group slightly less than the chamber control group	Exposed groups similar to the chamber control group	Exposed groups similar to the chamber control group	Exposed groups similar to the chamber control group
Survival rates	28/50, 23/50, 23/49, 20/50, 14/20	32/50, 35/50, 39/50, 28/50	40/50, 41/50, 36/50, 34/50	37/49, 28/50, 35/50, 36/50
Nonneoplastic effects	Kidney: severity of chronic nephropathy (1.4, 2.3, 2.6, 2.3, 3.0); renal tubule hyperplasia (0/50, 11/50, 11/49, 15/50, 5/20); hyaline droplet accumulation (2/50, 9/50, 7/49, 11/50, 2/20); renal papilla mineralization (1/50, 34/50, 41/49, 43/50, 17/20); pelvic transitional epithelium hyperplasia (1/50, 8/50, 8/49, 10/50, 5/20)	None	Liver: eosinophilic focus (10/50, 9/50, 7/50, 19/50); centrilobular hypertrophy (2/50, 0/50, 4/50, 36/50); necrosis (0/50, 1/50, 3/50, 19/50); syncytial alteration (26/50, 28/50, 36/50, 44/50); erythrophagocytosis (0/50, 0/50, 0/50, 9/50)	None
Neoplastic effects	Kidney: renal tubule adenoma (1/50, 2/50, 6/49, 9/50, 5/20); renal tubule adenoma or carcinoma (1/50, 3/50, 7/49, 12/50, 6/20) Adrenal medulla: benign or malignant pheochromocytoma (8/49, 9/49, 13/49, 16/49, 8/20)	None	None	None

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Equivocal findings	None	None	None	Liver: hepatocellular adenoma (7/49, 13/50, 8/50, 17/50); hepatocellular carcinoma (4/49, 16/50, 6/50, 5/50); hepatocellular adenoma or carcinoma (11/49, 27/50, 14/50, 20/50) Uterus: stromal polyp (0/49, 0/50, 2/50, 3/50); stromal polyp or stromal sarcoma (0/49, 0/50, 2/50, 4/50)
Level of evidence of carcinogenic activity	Clear evidence	No evidence	No evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:		Negative in strains TA97, TA98, TA100, and TA1535 with and without S9		
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo:*		Positive in male mice; negative in 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.

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as “were also related” to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as “may have been” related to chemical exposure.

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 decalin on September 5, 2002, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On September 5, 2002, the draft Technical Report on the toxicology and carcinogenesis studies of decalin 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. P.C. Chan, NIEHS, introduced the report on the toxicology and carcinogenesis studies of decalin by describing the uses of the chemical, the design and dose selection for the inhalation studies, and the nonneoplastic and neoplastic lesions in the 3-month and 2-year studies. The proposed conclusions were *clear evidence of carcinogenic activity* of decalin in male F344/N rats, *no evidence of carcinogenic activity* of decalin in female F344/N rats or in male $B6C3F_1$ mice, and *equivocal evidence of carcinogenic activity* of decalin in female $B6C3F_1$ mice.

Dr. Walker, the first principal reviewer, queried whether the adrenal gland pheochromocytomas in male rats merited a call of some evidence. She also asked about the relevance to humans of the mechanism involving α2u-globulin.

Dr. Thrall, the second principal reviewer, agreed with the proposed conclusions and observed a correlation between pheochromocytoma occurrence and nephropathy severity.

Dr. Boekelheide, the third principal reviewer, inquired about the biologic significance of the benign uterine stromal polyps and the hepatic lesions in female mice as indicators of carcinogenic activity. He also asked about the significance of the effects on the reproductive system in the 3-month male mouse study.

Dr. Chan explained that, while pheochromocytoma occurs commonly as a spontaneous neoplasm in male Fischer rats, the increased incidences in this study were significantly increased and exceeded the historical control range and thus were considered to be related to chemical exposure. Dr. J.K. Haseman, NIEHS, added that the pheochromocytomas were not included in the strongest conclusion statement, *clear evidence of carcinogenic activity*, which was applied to the kidney neoplasms, but the language adopted did indicate that the pheochromocytomas were exposure related. Dr. Chan said that the liver neoplasms in female mice were considered *equivocal evidence* because while increased incidences were seen in two of the three exposed groups, the pattern was not significant by the trend test. Conversely, the uterine stromal polyps were also considered *equivocal evidence*, but because the incidences in the top dose group were not significantly increased relative to the controls despite an overall positive trend. Dr. J.R. Hailey, NIEHS, confirmed that these polyps were indeed neoplasms and not simply an inflammatory response.

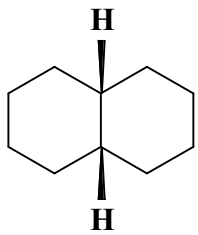
Dr. Elwell observed that decalin has been reported to be an inhaled irritant, but in the present studies no effects on the laryngeal or nasal mucosa were seen. He also asked if the infiltration and fibrosis in the pleura of female rats merited inclusion in the summary table.

Dr. Drinkwater asked whether the proposed conclusion based on kidney neoplasms should carry a qualifying comment that the neoplasms were a secondary effect of α2u-globulin accumulation. Dr. J.R. Bucher, NIEHS, replied that the standard practice had been simply to mention the occurrence of both lesions and permit future readers to draw their own inferences about causality based on the evolving hypotheses and knowledge.

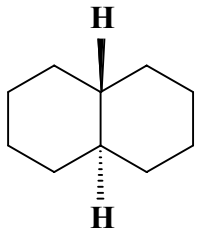
Dr. Boekelheide asked whether the uterine stromal polyps should be considered neoplasms or a nonneoplastic response. Dr. Walker indicated that while sarcomas are irreversible, there was less certainty about stromal polyps. Dr. Hailey said that stromal polyps occasionally progress to sarcomas and generally the two were grouped for purposes of analysis.

Dr. Walker moved that the proposed conclusions be approved as written and Dr. Roberts seconded the motion. Dr. Piegorsch offered an amendment that the proposed conclusion in male mice be changed to *equivocal evidence* based on a marginal increase in liver neoplasms. The amendment failed for lack of a second. The original motion was then accepted unanimously with 10 votes.

INTRODUCTION



***cis*-Decalin**



***trans*-Decalin**

DECALIN

CAS No. 91-17-8

Chemical Formula: $C_{10}H_{18}$ Molecular Weight: 138.2

Synonyms: Bicyclo[4.4.0]decane; dec; decahydronaphthalene; dekalin; naphthalane; napthan; napthane; perhydronaphthalene

Chemical and Physical Properties

Decalin is a clear liquid with a slight odor that resembles menthol; it exists as two isomers, *cis*- and *trans*-decalin. It has a boiling point of 195.7° C (*cis*) or 187.25° C (*trans*) and a melting point of –43.26° C (*cis*) or –30.4° C (*trans*). Decalin is insoluble in water; very soluble in alcohol, methanol, ether, and chloroform; and miscible with propyl and isopropyl alcohol and with most ketones and esters. It is stable at normal temperatures and conditions of storage. Potentially explosive peroxides can form on long-term storage in contact with air (DuPont, 1990a). The *cis* isomer has a density of 0.8963 and the *trans* isomer has a density of 0.8700 at 20°/4° C. Decalin has a vapor pressure of 1 mm at 22.5° C (*cis*) or 10 mm at 47.2° C (*trans*). The flash point of decalin is 58° C (136° F) (closed cup).

While Decalin and Tetralin are tradenames for decahydro- and tetrahydroanaphthalene products, respectively, the names are commonly used for any decahydro- or tetrahydroanaphthalene. This Technical Report follows common usage.

Production, Use, and Human Exposure

Decalin is produced by complete catalytic hydrogenation of naphthalene or tetrahydronaphthalene (tetralin). Hydrogenation of naphthalene in glacial acetic acid in the presence of a platinum catalyst at 15° C and 130 atmospheres yields a mixture of 77% *cis*- and 23% *trans*-decalin. Hydrogenation of tetralin under the same conditions yields almost entirely *cis*-decalin (*Merck Index*, 1989). The commercial decalin product is a mixture of *cis* and *trans* isomers.

Decalin is in high demand, with estimates of annual production/importation in the millions of pounds. Current domestic production volumes for decalin were not found in the literature.

Decalin is widely used as an industrial solvent, primarily for naphthalene, fats, resins, oils, and waxes. It is used as a substitute for turpentine in lacquers, paints, and varnishes; as a solvent and stabilizer for shoe polishes and floor waxes; as a constituent of motor fuels and

lubricants; and as a paint thinner and remover. Decalin is also used as a patent fuel in stoves, as a high-density fuel in submarine-launched cruise missile systems, and in stain removal and cleaning machinery (Sandmeyer, 1981; Longacre, 1987; Sax and Lewis, 1989).

The most probable human exposure to decalin is through dermal contact or inhalation during manufacture or use. Potential occupational exposures are controlled by engineering controls (e.g., the 8-hour time-weighted average permissible exposure limit/threshold limit value for the reactant naphthalene is 10 ppm; ACGIH, 2002) and the routine use of personal protective equipment. DuPont, the major manufacturer, also recommends that the compounds be handled in closed systems where possible, or in work areas with good ventilation (DuPont, 1990a,b). The National Occupational Hazard Survey (1972-1974) estimated that 935 workers were potentially exposed to decalin (NIOSH, 1978). The National Occupational Exposure Survey (1981-1983) reported 28 workers were potentially exposed to decalin (NIOSH, 1990). The latter survey estimate represents actual observations where the surveyor observed use of the specific compound only, whereas the earlier survey estimate consists of actual observations, observations of the use of a tradename product known to contain the compound, and generic observations in which the surveyor saw a product in some type of general use which led NIOSH to suspect the compound might be in that product.

Submarine personnel may be exposed to decalin when it is transferred or transported for cruise missile fueling (Gaworski *et al.*, 1980). Consumers may be exposed to decalin in paints, varnishes, lacquers, waxes, shoe polishes, and finished petroleum products such as gasoline and motor oils. In addition, nonoccupational exposures may occur via urban atmospheres, contaminated drinking water, and recreational activities at contaminated waterways (CRCS, 1984; HSDB, 2002). Krotoszynski and O'Neill (1982) identified decalin in the expired breath of male and female nonsmokers in three study populations (control, diabetic, and prediabetic subjects); no concentrations were reported.

Decalin occurs naturally in petroleum and coal and is expected to be released in emissions from petroleum refining, coal tar distillation, gasoline and diesel engines, and in combustion. It is also expected to be released in wastestreams during the disposal of products containing the compound as a solvent (e.g., paints and waxes) and of crude oil and refined petroleum products (HSDB, 2002).

Decalin has been identified as a component of vehicle exhaust emissions in the Allegheny Mountain Tunnel of the Pennsylvania Turnpike (Hampton *et al.*, 1982). It was also identified in the effluent discharged from the production platforms in the Buccaneer Gas and Oil Field in the Gulf of Mexico (Middleditch, 1982). Decalin was one of 53 chemicals detected at all five indoor sampling sites during an air monitoring study at a Washington, DC, home for the elderly (Ziegenfus, 1987). These studies indicate the widespread presence of decalin in the environment; however, no concentrations were reported. No standards or guidelines have been set for occupational exposures or environmental levels of decalin.

Metabolism and Excretion

Experimental Animals

Urinary metabolites of *cis*-and *trans*-decalin following gavage administration in male and female F344 rats were reported by Olson *et al.* (1986). *Cis,trans*-1-decalol and *cis,cis*-2-decalol were identified as metabolites of *cis*-decalin in males and females; *cis,cis*-1-decalol was identified in males only. *trans,cis*-2-Decalol was identified as a metabolite of *trans*-decalin in males and females. The alcohols were probably present as conjugates in the urine as the urine was treated with glucuronidase/sulfatase prior to analysis by gas chromatography. Extracts of kidney homogenates from male rats administered *cis*-and *trans*-decalin yielded *cis*-2-decalone and *trans*-2-decalone, respectively. The female rats had no detectable decalin metabolites in their kidney extracts; the metabolic pathway is shown in Figure 1. The ketones, also found in male rats after administration of the cruise missile fuel JP-10 (Inman *et al.*, 1982), may play a role in renal damage (Olson *et al.*, 1986).

Following intragastric administration of *cis*- and *trans*-decalin to female rabbits, both hydrocarbons were oxidized to racemic secondary alcohols and excreted in urine as ether-linked glucuronides in amounts equal to 60% of the dose administered. The principal

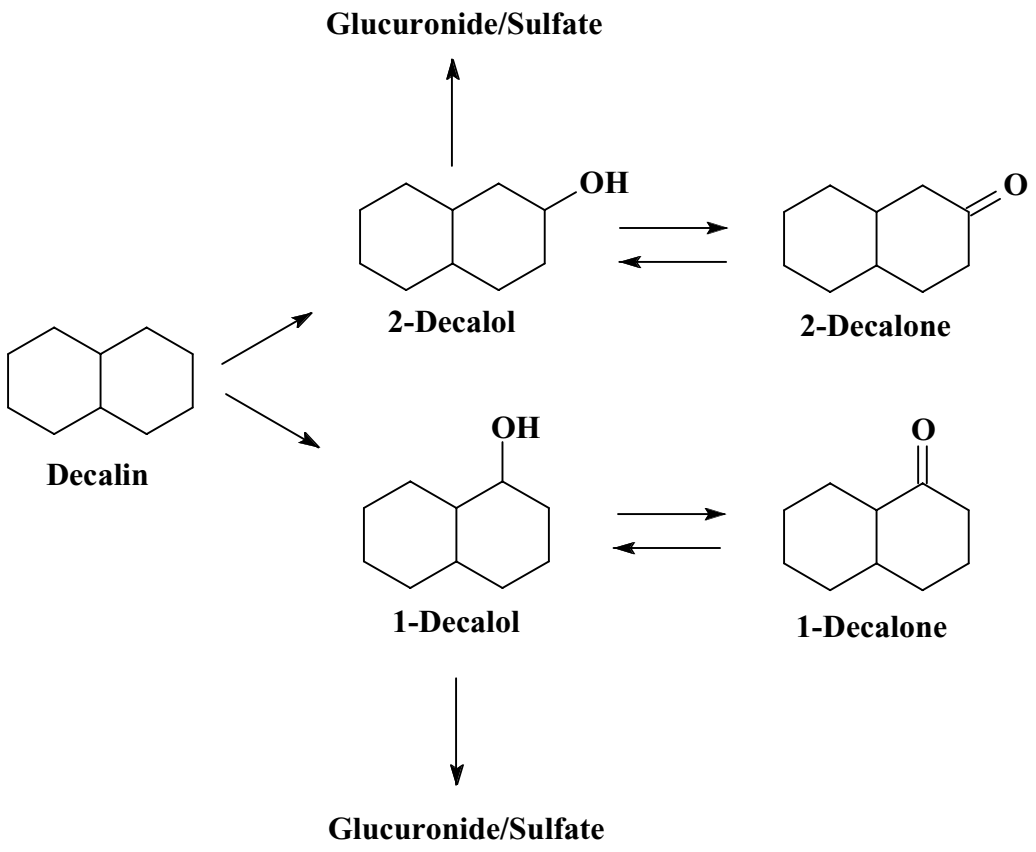


FIGURE 1
Simplified Metabolic Pathway of Decalin (Olson *et al.*, 1986)

glucuronides were isolated as triacetyl methyl esters and as sodium salts. *Cis*-decalin gave rise to *cis,cis*-2 decalol and small amounts of *cis*,*trans*2-decalol. *Trans*-decalin yielded mainly *trans,cis*-2-decalol and small amounts of *trans*,*trans*-2-decalol (Elliott *et al.*, 1966).

Humans

No information on the absorption, metabolism, or excretion of decalin in humans was found in a review of the literature.

TOXICITY

Experimental Animals

The oral LD_{50} of decalin for rats is 4,170 mg/kg and the dermal LD_{50} for rabbits is 5.9 g/kg (Sandmeyer, 1981). The 4-hour inhalation LC_{50} for rats is 710 ppm (Gaworski *et al.*, 1985).

Neat decalin (*cis*- or *trans*-) administered by gavage to Fischer rats (2.5 g/kg to males and 3.0 g/kg to females) on alternate days for 14 days induced hyaline droplet accumulation in the cells of proximal convoluted tubules and multifocal casts of necrotic cells and debris in the tubules near the corticomedullary junction in males. No lesions were found in females (Olson *et al.*, 1986).

Male and female Wistar rats were administered decalin in corn oil by gavage at doses of 0, 10, 100, or 1,000 mg/kg daily for up to 28 days (Read *et al.*, 1988). Body weights and survival were not reported. Increased incidences of hyaline droplets in the renal proximal tubule cells of male rats, increased cell turnover, and focal renal tubule damage were seen in the 100 and 1,000 mg/kg groups. The hyaline droplets were round initially, becoming larger and more numerous as dosing continued, and at 28 days, some appeared rectilinear; the hyaline droplets were acid phosphatase positive.

Decalin administered by gavage in corn oil to male Sprague-Dawley rats at 150 mg/kg for 14 days induced accumulation of α2u-globulin in the kidney (Saito *et al.*,1992). This accumulation appeared to be the result of inhibition of degradation by renal lysosomal cystein proteases. Eurell *et al*. (1990) reported that exfoliated renal tubule epithelial cells could be seen in the tubular lumen 24 hours after three daily gavage administrations of 200 mg/kg decalin to male Sprague-Dawley rats. No inflammatory infiltrate was seen in the tubular epithelium. The exfoliated cells had well-preserved nuclear morphology, cytoplasmic condensation, and enlarged but intact lysosomes-phagolysosomes with reduced acid phosphatase stain intensity.

Female C57BL/6 mice and male and female Fischer rats and beagle dogs were continuously exposed by inhalation to decalin at 0, 5, or 50 ppm 24 hours per day for 90 days (Gaworski *et al.*, 1985). One-third of the animals were necropsied at the end of the exposure period; the remaining animals were held for 19 or 24 months before necropsy. Female mice exposed to 5 or 50 ppm showed no differences in body weight gain or survival compared to the controls. Increased incidences of hepatocellular cytoplasmic vacuolization were seen in both exposed groups of female mice at the end of the 90-day exposure period but not at necropsy 19 months later. However, increased incidences of pituitary gland carcinoma occurred in 50 ppm female mice 19 months after exposure. The survival and body weight gains of male rats did not differ from those of the controls at exposure termination or 19 months after exposure. Toxic tubular nephrosis characterized by hyaline droplets, necrosis, exfoliation, and intratubular casts as well as accentuated tubular degeneration and medullary mineralization were observed in male rats at exposure termination. Increased incidences of chronic progressive nephrosis, mineralization, pelvic urothelial hyperplasia, and pituitary gland adenoma were observed in males 19 months after exposure. No other renal lesions except an increased incidence of chronic progressive nephrosis were observed in the 50 ppm female rats 19 months after exposure. Beagle dogs showed no changes in body weight gain, organ weights, or in blood chemistry compared to the controls; no pathological lesions were observed grossly or microscopically.

Male rats and guinea pigs and female mice exposed to 0, 50, or 200 ppm decalin by inhalation 6 hours a day, 5 days a week for 22 exposure days exhibited respiratory tract irritation and kidney changes (male rats only) similar to those observed by Gaworski *et al.* (1985) (MacEwen and Vernot, 1978).

Comparable body weights and survival rates were observed among groups of male Fischer rats and C57BL/6 mice exposed to decalin by inhalation at 0, 25, 62.5, or 125 ppm 22 hours per day, 7 days per week for 20, 28, or 35 days (Stone *et al.*, 1987a). At necropsy,

hyaline droplets in proximal convoluted tubule cells, granular casts at the outer zone of the medulla, and chronic nephrosis were seen in male rats, and the incidences increased in a dose- and time-related manner from as early as 20 days. These lesions were not seen in male mice.

Humans

Decalin is an irritant to the eyes, skin, and mucous membranes and has been reported to cause dermatitis in painters. The lowest concentration to have an effect in humans exposed by inhalation was 100 ppm (Sandmeyer, 1981). Decalin has been associated with the development of vesicular eczema accompanied by intense pruritus in a man who had used solvent to clean paving stones. Traces of albumin and urobilin in the urine and a few leukocytes in the sediment suggested possible involvement of the kidneys (Sandmeyer, 1981; *Merck Index,* 1989; HSDB, 2002). No hyaline droplets have been reported in the kidneys of patients exposed to decalin.

CARCINOGENICITY

Experimental Animals

Increased incidences of pituitary gland tumors were noted in male F344 rats and female C57BL/6 mice 19 months after exposure to 5 or 50 ppm decalin continuously by inhalation for 90 days (Gaworski *et al.*, 1985). The incidences of pituitary gland adenoma in male rats were five of 50 in the controls, 16 of 49 in the 5 ppm group, and 16 of 48 in the 50 ppm group ($P<0.05$). The incidences of pituitary gland carcinoma in female mice were zero of 77 in the controls, three of 81 in the 5 ppm group, and eight of 80 in the 50 ppm group. The authors felt that the increased incidences of pituitary gland tumors were due to unusually low incidences of these tumors in the control groups.

Decalin has been used as a vehicle in studies of cutaneous tumorigenesis in mice. No skin tumors in C3H mice were found when benzo[a]pyrene (0.02%) in decalin was applied dermally (Bingham and Falk, 1969); however, skin tumors were observed after dermal application of benzo[a]pyrene (0.00002%) in *n*-dodecane. Male C3H mice were administered topical applications of chrysene, fluoranthene, pyrene, triphenylene, perylene, or benzo[b]triphenylene for 80 weeks (Horton and Christian, 1974). When applied in decalin, only benzo[b]triphenylene produced malignant tumors. Crysene, triphenylene, and pyrene, but not benzo[b]triphenylene, produced malignant tumors when applied in a 50:50 mixture of decalin and n-decane.

Humans

No epidemiology studies of decalin were found in a review of the literature.

DEVELOPMENTAL TOXICITY

Experimental Animals

Pregnant CD-1 mice administered 2,700 mg/kg decalin on days 6 through 13 of gestation were allowed to deliver litters (Hardin *et al.*, 1987). Litter size, birth weight, and neonatal growth and survival to day 3 were recorded as indices of potential developmental toxicity. Decalin had no effect in the offspring for the parameters tested. Decalin administration produced 10% maternal mortality and was associated with a significant increase in maternal body weight gain.

Humans

No developmental toxicity studies of decalin in humans were found in a review of the literature.

STRUCTURE/ACTIVITY RELATIONSHIPS

Tetralin and decalin are structurally related compounds and are produced by hydrogenation of naphthalene. Tetralin and decalin each contain 10 carbons and are composed of two fused six-membered rings (Serve, 1989). Tetralin marketed by DuPont contains 2.0% deca-hydronaphthalene (decalin) (DuPont, 1990b) and decalin supplied by DuPont has a maximum tetrahydronaphthalene (tetralin) content of 3.0% (DuPont, 1990a).

Tetralin, like decalin, occurs naturally in petroleum and coal and is expected to be released in emissions from petroleum refining, coal tar distillation, gasoline and diesel engines, and in combustion. They are both widely used as solvents and substitutes for turpentine in the manufacture of paints, lacquers, waxes, and polishes. They are also expected to be released in wastestreams in the disposal of products containing the compounds as solvents (e.g., paints and waxes), and of crude oil and refined petroleum products (Hampton *et al.*, 1982; Middleditch, 1982; Ziegenfus, 1987).

However, the structural and electronic characteristics of tetralin and decalin differ. Structurally, the aromatic ring of tetralin causes that part of the molecule to be planar while the aliphatic portion of the molecule remains nonplanar. Both of the decalin isomers are composed of two fused cyclohexane rings that exist in nonplanar chair configurations. Electronically, the aromatic ring of tetralin activates the alpha carbons toward oxidation. These structural and/or electronic differences may preclude the metabolism of tetralin to potentially toxic intermediates by forming water-soluble metabolites that are eliminated by the kidneys (Serve, 1989). Kidney lesions produced by tetralin are not as severe as those produced by decalin, as evidenced by the lack of intratubular casts or significant inflammation (Serve *et al.*, 1989). No epidemiology studies or case reports associating tetralin with a cancer risk in humans were found in the literature.

The NTP conducted 2-year inhalation studies of naphthalene at exposure concentrations of 0, 10, 30, or 60 ppm in rats (NTP, 2000) and at 0, 10, or 30 ppm in mice (NTP, 1992). There was no evidence of carcinogenicity in male mice. There was some evidence of carcinogenicity in female mice based on the incidences of alveolar/bronchiolar adenoma (chamber control, 5/69; 10 ppm, 2/65; 30 ppm, 28/135). There was clear evidence of carcinogenicity in male and female rats based on increased incidences of respiratory epithelial adenoma (males: chamber control, 0/49; 10 ppm, 6/49; 30 ppm, 8/48; 60 ppm, 15/48; females: 0/49, 0/49, 4/49, 2/49) and olfactory epithelial neuroblastoma (males: 0/49, 0/49, 4/48, 3/48; females: 0/49, 2/49, 3/49, 12/49) of the nose.

Genetic Toxicity

No genetic toxicity studies of decalin were found in a review of the literature.

Study Rationale

Decalin is produced in large volumes and is widely used as a solvent and as a substitute for turpentine in the manufacture of paints, lacquers, waxes, and polishes. It also has specific secondary uses in fuel and for stain removal. Decalin has been found in indoor and outdoor air, in workplaces and homes, in fuel and in exhaust air, in waterways and drinking water, and in recreational facilities. The potential for human exposure to decalin by workers and consumers is high. Humans may potentially be exposed to decalin as a result of contact with naturally occurring crude oil, by inhalation of cigarette smoke or other combustion products, during the manufacture or use of solvents, or by exposure following environmental releases.

Little is known about the toxicity and carcinogenicity of decalin. The National Cancer Institute nominated decalin for study because of its chemical structure, its potential for consumer exposure, and a lack of adequate testing of the chemical, and to explore the possible risk of adverse health effects of exposure to decalin.

The NTP has conducted inhalation studies of naphthalene (NTP, 1992, 2000) and tetralin (ongoing) in rats and mice. For comparative purposes, and because inhalation is the major route of exposure to humans, inhalation was recommended as the route of exposure for the decalin studies.

The NBR rat has no detectable level of hepatic α2u-globulin in mRNA, although it is present in the preputial gland (Chatterjee *et al.*, 1989). α2u-Globulin is not produced in the liver of NBR rats, and α2u-globulin-related kidney toxicity has not occurred in NBR rats. In the current toxicity and carcinogenicity studies of decalin, male NBR and F344/N rats were exposed to similar concentrations of decalin for 2 weeks, and F344/N rats and B6C3F$_1$ mice were exposed for 3 months and 2 years for comparison of renal lesion development. Initially, the highest concentration of 400 ppm was selected based on the LC$_{50}$ of 710 ppm reported by Gaworski *et al.* (1985). Toxicokinetic studies were conducted in F344/N rats and B6C3F$_1$ mice to evaluate the metabolism of decalin and to provide information for exposure selection for the current NTP studies.

MATERIALS AND METHODS

Procurement and Characterization of Decalin

Decalin was obtained in three lots [07347LG and 12426EN (Sigma Aldrich Fluka Bulk Chemicals, St. Louis, MO) and 00334HR (Aldrich Chemical Company, Inc., Milwaukee, WI)]. Lots 07347LG and 12426EN were combined, assigned a new lot number (13359), and used in the 2-week and 3-month studies; lot 00334HR was used during the 2-year studies. Identity and purity analyses on lots 07347LG and 12426EN were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC), and on the combined lot and lot 00334HR by the study laboratory. Reports on analyses performed in support of the decalin studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a colorless liquid, was identified as decalin by infrared and nuclear magnetic resonance spectroscopy and gas chromatography/mass spectrometry. The moisture content of lot 00334HR was determined by Karl Fischer titration; the purities of lots 13359 and 00334HR were determined by elemental analyses. Potentiometric titration was used to assess the purity of lots 07347LG, 12426EN, and 00334HR. The purities of all lots were also determined by gas chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for decalin. Karl Fischer titration indicated 73 ± 3.6 ppm water. Potentiometric titration detected no peroxides in lots 07347LG and 12426EN and 0.57 mEq/kg peroxides in lot 00334HR. Gas chromatography indicated two major peaks and up to seven impurities; the total area of the impurities did not exceed 0.59% of the total major peak areas. The overall purity was determined to be greater than 99%.

The bulk chemical was stored at room temperature, in metal drums under a nitrogen headspace. Stability was monitored using gas chromatography. No degradation of the bulk chemical was detected.

Vapor Generation and Exposure System

Decalin was pumped through a preheater and then into the top of a heated glass column filled with glass beads to increase the surface area for evaporation. Heated nitrogen entering the column from below vaporized the chemical as it conveyed it out of the generator. The vapor was transported to the exposure room at an elevated temperature to prevent condensation.

In the exposure room, the vapor was mixed with additional heated air before it entered a short vapor distribution manifold. The pressure in the distribution manifold was kept fixed to ensure constant flows through the manifold and into the chambers. Electronically actuated metering valves controlled flow to each chamber. Metering valves in the chambers automatically opened to the established setting and allowed vapor to flow through individual temperature-controlled delivery lines to each exposure chamber. The vapor was then injected into the chamber inlet duct where it was diluted with conditioned chamber air to achieve the desired exposure concentration.

The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that decalin vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

Vapor Concentration Monitoring

The decalin concentrations in the exposure chambers were monitored by an on-line gas chromatograph. Samples were drawn from each exposure chamber approximately every 24 minutes using a 12-port stream

select valve. The on-line gas chromatograph was checked throughout the day for instrument drift against an on-line standard of decalin in nitrogen supplied by a diffusion tube standard generator. The on-line gas chromatograph was calibrated monthly by a comparison of chamber concentration data to data from grab samples, which were collected with charcoal sampling tubes, extracted with toluene containing 1-phenylhexane as an internal standard, and analyzed by an off-line gas chromatograph. The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of decalin containing 1-phenylhexane as an internal standard in toluene.

Chamber Atmosphere Characterization

Buildup and decay rates for chamber vapor concentration were determined with animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. Based on experimental data, a T_{90} value of 12 minutes was selected for the studies.

Evaluations of chamber uniformity and persistence and monitoring for decalin degradation impurities were conducted periodically throughout the studies by gas chromatography. Chamber uniformity was maintained; no degradation was detected.

2-Week Studies

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY); male NCI Black Reiter (NBR) rats were obtained from Charles River Laboratory, Inc. (Frederick Cancer Research and Development Center; Frederick, MD). On receipt, the F344/N rats and the mice were approximately 4 weeks old; the NBR rats were approximately 5 weeks old. Rats were quarantined for 34 days and were approximately 9 (F344/N) or 10 (NBR) weeks old on the first day of the studies. Mice were quarantined for 13 days and were approximately 6 weeks old on the first day of the studies. Groups of five male and five female F344/N rats and mice and five male NBR rats were exposed to decalin at concentrations of 0, 25, 50, 100, 200, or 400 ppm, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 16 (rats) or 17 (mice) days. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded on days 6 and 13 and at the end of the studies. The animals were weighed initially, on days 6 and 13, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Concentrations of α2u-globulin and *cis*- and *trans*-2-decalone in the right kidney were measured in male F344/N rats from each exposure group. The right kidney was removed, frozen in liquid nitrogen, and stored at –70° C until analysis. One half of each right kidney was thawed. A volume of 67 mM sodium/potassium phosphate buffer (pH 7.2) equivalent to twice the recorded fresh weight of the sample was added, and the sample was homogenized for 30 to 60 seconds using a tissue homogenizer (Tekmar Co., Cincinnati, OH). Approximately 300 µL of the kidney homogenate were removed and stored at –70° C in 1.5-mL plastic screw-cap vials for analysis of *cis*- and *trans*-2-decalone. The remainder of the homogenate was centrifuged at 3,000 g for 15 minutes and the supernatant was drawn off and stored at –70° C in 1.5-mL plastic screw-cap vials. The protein content of each supernatant was measured in a 1:50 dilution in phosphate-buffered saline-Tween using a Pyrogallol Red Assay.

Homogenates diluted to 1:50,000 were analyzed for α2u-globulin using a competitive indirect ELISA technique. The amount of α2u-globulin was measured by comparing the relative fluorescent signal intensity in the study samples to that observed with known amounts of α2u-globulin present in calibration standards. Calibration standards and ELISA control standards (negative and positive) were plated in predetermined wells on 96-well microtiter plates. Calibration standards were assayed in triplicate. Each study sample was assayed in quadruplicate and randomized with respect to its relative position on the ELISA plate.

For quantitation of *cis*- and *trans*-2-decalone, kidney homogenates were thawed on ice; 100 mg were transferred to 2-mL automated liquid sample vials. Approximately 64 ng 2-decalone-1,1,3,3-d_4 (2-decalone-d_4) were added as an internal standard. Samples were extracted with 0.5 mL cyclohexane and the organic

layers were removed for gas chromatography/mass spectrometry analysis. A Hewlett-Packard Model 5971 mass selective detector was used for the analysis. Separations were carried out on a fused silica capillary column (DB-1701, 30 m × 0.25 m, 0.25-µm film, helium carrier gas at 10 psi, 70 eV ionization source; J&W Scientific). After being held at 70° C for 30 seconds, the column temperature was increased 20° C per minute to 270° C, where it was held for 5 minutes. To enhance sensitivity, ions at m/z 152 and 156 were monitored for 2-decalone and 2-decalone-d_4, respectively. Linear calibration curves were generated using a series of standards prepared by spiking decalones into kidney homogenates from unexposed animals. Amounts of *cis*- and *trans*-2-decalone were then determined by comparison of the internal standard corrected response of the samples with that obtained from the matrix-spiked calibration standards.

For cell proliferation analyses, the left kidney (bisected longitudinally) and a piece of duodenum were removed from all male rats and fixed in 10% neutral buffered formalin for 24 hours. The tissues were then processed, embedded in paraffin, and sectioned to a thickness of 5 µm. Kidneys from the male F344/N rats and the chamber control and 400 ppm NBR rats were stained with Mallory-Heidenhain for protein and proliferating cell nuclear antigen (PCNA; PC-10 clone, Dako, Carpinteria, CA). Tissues from the remaining NBR rat groups were stained with hemotoxylin and eosin (H&E) and PCNA. The duodenum and kidney were assessed qualitatively for adequate labeling. Approximately 2,000 proximal tubule nuclei were counted from all kidneys stained with PCNA, and counts of labeled and total nuclei were recorded.

Necropsies were performed on all rats and mice. The right kidney, liver, and lung were weighed. Histopathologic examinations were performed on all chamber control and 400 ppm rats and mice. Table 1 lists the tissues and organs examined.

3-Month Studies

The 3-month studies were conducted to evaluate the cumulative toxic effects of repeated exposure to decalin and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services. On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 12 (males) or 13 (females) days and were approximately 6 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 four (mice) or five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and 10 male and 10 female mice were exposed to decalin at concentrations of 0, 25, 50, 100, 200, or 400 ppm, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 14 weeks. Additional groups of 10 male and 10 female rats were exposed to the same concentrations for 6 weeks for clinical pathology analyses; additional groups of five male rats were exposed to the same concentrations for 2 weeks for renal toxicity analyses. Feed was available *ad libitum* except during exposure and urine collection periods; water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded weekly 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 1.

Animals were anesthetized with carbon dioxide, and blood was collected from the retroorbital (rats) or supraorbital (mice) sinus of clinical pathology rats on days 3 and 23 and from core study rats and mice at the end of the studies for hematology and clinical chemistry (rats only) analyses. Blood samples for hematology analyses were placed in tubes containing potassium EDTA. Packed cell volume; hemoglobin concentration; erythrocyte, platelet, and leukocyte counts; mean cell volume; mean cell hemoglobin; and mean cell hemoglobin concentration were determined using a Roche Cobas Helios (Roche Diagnostics, Branchburg, NJ). Manual hematocrit value was determined using a Damon/IEC MB microcentrifuge (International Equipment Company, Needham Heights, MA) and a Damon/IEC capillary reader for comparison to Cobas values for packed cell volume. Blood smears were stained with Wright/Giemsa stain in a Wescor 1700 aerospray slide stainer (Wescor, Inc., Logan, UT). Leukocyte

differential counts were based on classifying a minimum of 100 white cells. Reticulocytes were stained with new methylene blue and enumerated as a reticulocyte:erythrocyte ratio using the Miller disc method (Brecher and Schneiderman, 1950). Blood samples for clinical chemistry analyses were placed in tubes without anticoagulant, allowed to clot, and centrifuged. During week 12, core study male and female rats were placed in metabolism cages, and urine was collected over ice for 16 hours. Table 1 lists the parameters measured.

At the end of the 3-month studies, samples were collected for sperm count and motility and vaginal cytology evaluations on rats and mice exposed to 0, 100, 200, or 400 ppm. The parameters evaluated are listed in Table 1. For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

Renal toxicity studies were performed on male and female rats. Urine was collected during a 16-hour period from five renal toxicity study males and five clinical pathology females at week 2 and from five male and five female clinical pathology rats at week 6. The 2- and 6-week samples were analyzed for volume and creatinine and then stored at –70° C pending decalin urinary metabolite analyses. To determine levels of α2u-globulin, *cis*- and *trans*-decalin, and *cis*- and *trans*-2-decalone in the kidney, the right kidney was collected from five renal toxicity study males at 2 weeks, five clinical pathology males at 6 weeks, and 10 male and 10 female core study rats at terminal sacrifice. Each kidney was cut in half, weighed, and stored at –70° C pending analysis.

For decalin urinary metabolite analyses, aliquots of approximately 10 µL thawed urine were added to 15-mL, conical-bottom, disposable glass centrifuge tubes (Fisher Scientific; Pittsburgh, PA). To the samples were added 10 µL β-glucuronidase/arylsulfatase (from *Helix pomatia*; β-*D*-glucuroniside glucuronoso-hydrolase, EC 3.2.1.31; and arylsulfate sulfohydrolase, EC 3.1.6.1; Boehringer Mannheim, GmbH, Germany); 100 µL 0.2 M acetate buffer (pH 5.4); and 3.27 µg 1,2,3,4-tetrahydro-1-naphthol. The samples were incubated overnight at 37° ± 2° C, mixed with 2.0 mL cyclohexane (Baxter Healthcare Corp., Muskegon, MI) the following day, and then vortexed for 30 seconds. After centrifugation at 1,000 g for 5 minutes, 1.5 mL of the organic (top) layer was transferred to 2-mL automated liquid sampler vials for gas chromatography/mass spectrometry.

Separation of the decalols was carried out on a fused silica capillary column similar to that described for decalone analyses in the 2-week studies. The column temperature was held at 70° C for 30 seconds, increased to 200° C at a rate of 5° C per minute, then increased from 200° to 250° C at a rate of 30° C per minute, where it was held for 1 minute, for a total run time of 29 minutes.

The kidney homogenate for determination of α2u-globulin, *cis*- and *trans*-2-decalone, and *cis*- and *trans*-decalin was prepared as described for the 2-week studies. Analysis of α2u-globulin levels was performed in the supernatants that had been diluted 1:10,000 to 1:50,000 with PBS-Tween as described for the 2-week studies.

Quantitation of *cis*- and *trans*-2-decalone in the kidney homogenates was conducted using gas chromatography/mass spectrometry similar to that described for

the 2-week studies, except 320 ± 32 ng 2-decalone-1,1,3,3-d_4 (2-decalone-d_4) was added as an internal standard.

Quantitation of the *cis* and *trans* isomers of decalin in the kidney homogenates was conducted using gas chromatography/mass spectrometry similar to that previously described for *cis*- and *trans*-2-decalone, except 160 ± 13 ng (*cis* + *trans*)-decahydronaphthalene-d_{18} (decalin d_{18}) were added as an internal standard. The column temperature was held at 50° C for 30 seconds, increased to 165° C, and then raised at a rate of 50° C per minute to 300° C for a total run time of approximately 9 minutes. For the calibration curves, response values were calculated as the ratio of peak area for *cis*- or *trans*-decalin at m/z 138 to peak area of *trans*-decalin-d_{18} at m/z 156.

The left kidney and duodenum were collected from five male renal toxicity rats at 2 weeks, five male clinical pathology rats at 6 weeks, and 10 male core study rats at terminal sacrifice and prepared as described for the 2-week cell proliferation analyses. Sections from each kidney were stained with Mallory-Heidenhain for protein and with PCNA (PC-10 clone, Dako) for determination of cell proliferation indices. The duodenum and kidney were qualitatively assessed for adequate labeling as described for the 2-week study.

Necropsies were performed on all core study animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on the 0 and 400 ppm core study rats and mice, and the kidney was examined in all male rats. Table 1 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats and mice were exposed to decalin by inhalation at concentrations of 0, 25, 50 (male rats only), 100, or 400 ppm (female rats and male and female mice), 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 105 weeks. A group of 20 male rats was exposed to 400 ppm.

Source and Specification of Animals

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Taconic Laboratory Animals and Services for use in the 2-year studies. Animals were quarantined for 16 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. 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 and mice were housed individually. Feed was available *ad libitum* except during exposure periods. Water was available *ad libitum*. Cages and racks were changed weekly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights were recorded initially, and clinical findings and body weights were recorded approximately every 4 weeks through week 89 and every 2 weeks beginning week 92.

Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

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

all tumors and all potential target organs, which included the adrenal medulla, kidney, and testis in male rats, and the lung, pleura, and thyroid gland (C-cell) in female rats. Additionally, specific diagnoses in the pituitary gland and skin of male and female rats, prostate and peritoneum of male rats, and kidney of female rats were reviewed. The liver of male and female mice, testis of male mice, and specific diagnoses in the uterus of female mice were also reviewed.

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

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Decalin

2-Week Studies	3-Month Studies	2-Year Studies
Study Laboratory		
Battelle Toxicology Northwest (Richland, WA)	Battelle Toxicology Northwest (Richland, WA)	Battelle Toxicology Northwest (Richland, WA)
Strain and Species		
F344/N rats NBR rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice
Animal Source		
F344/N rats and $B6C3F_1$ mice: Taconic Laboratory Animals and Services (Germantown, NY) NBR rats: Charles River Laboratories, Inc. (Frederick Cancer Research and Development Center; Frederick, MD)	Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies		
Rats: 34 days Mice: 13 days	Rats and mice: 12 days (males) or 13 days (females)	16 days
Average Age When Studies Began		
F344/N rats: 9 weeks NBR rats: 10 weeks Mice: 6 weeks	6 weeks	Rats: 7 weeks Mice: 6 weeks
Date of First Exposure		
May 13, 1996	September 16 (males) or 17 (females), 1996	Rats: August 14, 1997 Mice: August 28, 1997
Duration of Exposure		
6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 (rats) or 17 (mice) days	6 hours per day plus T_{90} (12 minutes), 5 days per week, for 14 weeks, plus one additional exposure day (December 15, 1996)	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks
Date of Last Exposure		
Rats: May 28, 1996 Mice: May 29, 1996	Rats: December 16 (males) or 17 (females), 1996 Mice: December 18 (males) or 19 (females), 1996	Rats: August 13, 1999 Mice: August 27, 1999
Necropsy Dates		
Rats: May 29, 1996 Mice: May 30, 1996	Core study rats: December 17 (males) or 18 (females), 1996 Mice: December 19, (males) or 20 (females), 1996	Rats: August 16-19, 1999 Mice: August 30-September 3, 1999
Average Age at Necropsy		
F344/N rats: 11 weeks NBR rats: 13 weeks Mice: 8 weeks	19 weeks	111 weeks

Table 1
Experimental Design and Materials and Methods in the Inhalation Studies of Decalin

2-Week Studies	3-Month Studies	2-Year Studies
Size of Study Groups		
F344/N rats: 5 males and 5 females NBR rats: 5 males Mice: 5 males and 5 females	Core Study: 10 male and 10 female rats Clinical Pathology: 10 male and 10 female rats Renal Toxicity Analysis: 5 male rats	Rats: 20 or 50 males and 50 females Mice: 50 males and 50 females
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 2-week studies	Same as 2-week studies
Animals per Cage		
1	1	1
Method of Animal Identification		
Tail tattoo	Tail tattoo	Tail tattoo
Diet		
NTP-2000 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods, changed weekly	Same as 2-week studies, except irradiated. Available *ad libitum* except during exposure and urine collection periods.	Same as 3-month studies
Water		
Tap water (City of Richland municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI) and softened by Battelle, available *ad libitum*	Same as 2-week studies	Same as 2-week studies, except not softened
Cages		
Stainless-steel wire bottom (Hazleton System, Inc., Aberdeen, MD), changed weekly	Same as 2-week studies	Stainless steel wire-bottom (Lab Products, Inc., Seaford, DE), changed weekly
Chamber Air Supply Filters		
Single HEPA (Northland Filter System International, Mechanicville, NY); charcoal (RSE, New Baltimore, MI); Purafil (Environmental Systems, Lynnwood, WA)	Same as 2-week studies	Single HEPA (Environmental Filter, Santa Rosa, CA); charcoal (RSE, New Baltimore, MI); Purafil (Environmental Systems, Lynnwood, WA)
Chambers		
Stainless steel with excreta pan suspended below each cage unit (Lab Products, Inc., Aberdeen, MD) changed weekly	Same as 2-week studies	Same as 2-week studies (Lab Products, Inc., Seaford, DE)
Chamber Environment		
Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour
Exposure Concentrations		
0, 25, 50, 100, 200, or 400 ppm	0, 25, 50, 100, 200, or 400 ppm	0, 25, 50 (male rats only), 100, or 400 ppm

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Decalin

2-Week Studies	3-Month Studies	2-Year Studies
Type and Frequency of Observation		
Observed twice daily; animals were weighed initially, on days 6 and 13, and at the end of the studies; clinical findings were recorded on days 6 and 13 and at the end of the studies.	Observed twice daily; core study animals were weighed initially, weekly, and at the end of the studies. Clinical findings were recorded weekly.	Observed twice daily; animals were weighed and clinical findings were recorded initially (body weight), every 4 weeks for weeks 5 through 89 (rats) and weeks 4 through 89 (mice), and every 2 weeks beginning week 92.
Method of Sacrifice		
Carbon dioxide asphyxiation	Same as 2-week studies	Same as 2-week studies
Necropsy		
Necropsy was performed on all animals. Organs weighed were the right kidney, liver, and lung.	Necropsy was performed on all core study animals. Organs weighed were the heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all animals.
Clinical Pathology		
None	Blood was collected from the retroorbital sinus of clinical pathology rats on days 3 and 23 and from core study rats and mice at the end of the studies for hematology and clinical chemistry (rats only). Core study rats were placed in metabolism cages for 16-hour urine collection during week 12. ***Hematology:*** hematocrit; packed red cell volume; hemoglobin; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts, mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, globulin, albumin/globulin ratio, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile acids ***Urinalysis:*** creatinine, glucose, glucose/creatinine ratio, protein, protein/creatinine ratio, alkaline phosphatase, alkaline phosphatase/creatinine ratio, aspartate aminotransferase, aspartate aminotransferase/creatinine ratio, lactate dehydrogenase, lactate dehydrogenase/ creatinine ratio, γ-glutamlytransferase, γ-glutamlytransferase/creatinine ratio, *N*-acetyl-β-D-glucosaminidase, *N*-acetyl-β-D-glucosaminidase/creatinine ratio, volume, and specific gravity	None

Table 1
Experimental Design and Materials and Methods in the Inhalation Studies of Decalin

2-Week Studies	3-Month Studies	2-Year Studies
Histopathology		
Histopathology was performed on 0 and 400 ppm rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined to the no-effect level: liver, lung, and nose. The kidney was examined in all groups of male F344/N rats.	Complete histopathology was performed on 0 and 400 ppm core study rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined to the no-effect level: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gall bladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, and mediastinal), mammary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. The kidneys from all male rats were also evaluated.	Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gall bladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, and mediastinal), mammary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Sperm Motility and Vaginal Cytology		
None	At the end of the studies, sperm samples were collected from core study male animals in the 0, 100, 200, and 400 ppm groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per testis, per gram testis, per cauda, and per gram cauda and epididymal spermatozoal motility. The left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from core study females exposed to 0, 100, 200, or 400 ppm for vaginal cytology evaluations. The percentage of time spent in the various estrous cycle stages and estrous cycle length were evaluated.	None

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Decalin

2-Week Studies	3-Month Studies	2-Year Studies
Renal Toxicity Studies in Rats		
Concentrations of *cis*- and *trans*-2-decalone and α2u-globulin in the right kidney were measured in groups of 5 F344/N males from each exposure concentration, and the fractional contribution of each isomer of 2-decalone was calculated. For assessment of cell proliferation, left kidney sections from male F344/N and NBR rats were stained with PCNA and examined for labeled cells.	Sixteen-hour urine volume and urinary decalol excretion were measured at each exposure concentration in groups of 5 male renal toxicity and 5 female clinical pathology rats at 2 weeks, 5 male and 5 female clinical pathology rats at 6 weeks, and 10 male and 10 female core study rats at week 12 (urine volume only). Urinary concentrations of decalol and creatinine were measured in all groups of rats at weeks 2 and 6; creatinine concentrations were also measured at week 12. Decalol concentrations were normalized to creatinine concentrations at weeks 2 and 6. Concentrations of *cis*- and *trans*-decalin, *cis*- and *trans*-2-decalone, and α2u-globulin were measured in right kidney samples from all groups of males at 2, 6, and 14 weeks; *cis*- and *trans*-decalin were measured in right kidney samples of females at week 14. The fractional contribution of each isomer of decalin and 2-decalone was calculated. For assessment of cell proliferation, left kidney sections from 5 male renal toxicity rats at 2 weeks, 5 male clinical pathology rats at 6 weeks, and 5 male core study rats at week 14 were stained with PCNA and examined for labeled cells.	None

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Missexed and pregnant animals and 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 are presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

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

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1– P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of

Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, urinalysis, renal toxicity, and spermatid and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber and fat than the NIH-07 diet previously used in toxicity and carcinogenicity studies (Rao, 1996, 1997). The NTP historical database for studies that use the NTP-2000 diet contains all 16 studies (15 for male rats) completed up to the present. Based on the extensive NTP historical database established for the NIH-07 diet, route of administration was not considered to be a significant variable for spontaneous neoplasms for the vast majority of sites. Thus, in general, the historical database will include studies with various routes of administration. For certain types of neoplasms where variations have been observed depending on route of administration, only studies with similar routes of administration will be used for comparison.

Quality Assurance Methods

The 3-month 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 covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of decalin was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* 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 have evolved from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity and mutagenicity (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). However, it should be noted that not all cancers arise through genotoxic mechanisms.

DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites (Ashby and Tennant, 1991). A positive response in the *Salmonella* test was shown to be the most predictive *in vitro* indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) (Tennant *et al.,* 1987; Zeiger *et al.,* 1990). Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. However, these other tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

2-WEEK STUDY

All male and female F344/N and male NBR rats survived to the end of the study (Tables 2 and 3). Final mean body weights and body weight gains of all exposed groups of rats were similar to those of the chamber control groups. There were no clinical findings related to decalin exposure.

Cell proliferation analyses were performed on the left kidney of male F344/N and NBR rats (Tables G1 and G2). The numbers of labeled cells and the labeling indices in 200 and 400 ppm F344/N males were significantly greater than those in the chamber controls. No significant differences in labeling indices were noted in NBR rats. Concentrations of α2u-globulin and *cis*- and *trans*-2-decalone in the right kidney were measured in male F344/N rats (Table G1); the α2u-globulin/soluble protein ratios were increased in exposed groups. Decalone concentrations in the exposed groups were similar; decalin was not measured in these 2-week studies.

Liver weights of 100 ppm or greater male F344/N and NBR rats and of all exposed groups of female rats were significantly greater than those of the chamber controls (Tables H1 and H2). Kidney weights of male F344/N rats exposed to 50 ppm or greater were significantly increased.

Microscopic lesions attributed to decalin exposure occurred in the kidney of male F344/N rats (Table 4). Minimal to marked hyaline droplet accumulation was present in all male F344/N rats and the severity increased with increasing exposure concentration. Minimal to mild degeneration and regeneration of renal cortical tubules occurred in all exposed male rats. There were significant increases in the incidences of granular casts of the renal medulla in F344/N males exposed to 50 ppm or greater. No exposure-related lesions occurred in male NBR or female F344/N rats.

Though apparent with the H&E stains, hyaline droplets were most visible in the sections stained with Mallory-Heidenhain stain. The droplets were bright pink to magenta and were within the proximal convoluted tubules. Degeneration was characterized by epithelial cells with abundant pale cytoplasm or pale vacuoles and pyknotic or missing nuclei. Regeneration was characterized by tubules lined by cells with basophilic cytoplasm and slightly enlarged nuclei. Granular casts were present within the outer strip of the outer medulla and were characterized by distended tubular lumina filled with cellular debris and proteinaceous material.

Exposure Concentration Selection Rationale: Because there were no effects of decalin on survival or body weights of male and female F344/N and male NBR rats in the 2-week study, decalin exposure concentrations selected for the 3-month inhalation study in F344/N rats were 0, 25, 50, 100, 200, and 400 ppm. The 400 ppm exposure concentration was chosen for the 2-week studies based on the LC_{50} of 710 ppm reported by Gaworski *et al.* (1985). The toxicokinetic data showed that the metabolism pathway was saturated at 400 ppm. The increased cell proliferation, α2u-globulin levels, and severity of kidney lesions in 400 ppm male rats in the 2-week studies were not considered severe enough to preclude the use of this exposure concentration in 3-month studies.

TABLE 2
Survival and Body Weights of F344/N Rats in the 2-Week Inhalation Study of Decalin

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	204 ± 4	233 ± 6	29 ± 3	
25	5/5	202 ± 4	230 ± 5	28 ± 2	99
50	5/5	205 ± 5	242 ± 5	37 ± 5	104
100	5/5	203 ± 4	234 ± 6	31 ± 2	100
200	5/5	206 ± 4	237 ± 6	30 ± 2	101
400	5/5	206 ± 4	234 ± 4	28 ± 2	100
Female					
0	5/5	144 ± 3	157 ± 5	13 ± 2	
25	5/5	144 ± 1	155 ± 2	12 ± 1	99
50	5/5	142 ± 3	157 ± 3	15 ± 1	100
100	5/5	144 ± 3	155 ± 5	11 ± 2	99
200	5/5	142 ± 2	152 ± 3	10 ± 1	97
400	5/5	142 ± 2	149 ± 3	7 ± 2	95

[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the chamber control group were not significant by Dunnett's test.

TABLE 3
Survival and Body Weights of Male NBR Rats in the 2-Week Inhalation Study of Decalin

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
0	5/5	232 ± 7	269 ± 6	37 ± 2	
25	5/5	229 ± 4	261 ± 5	32 ± 2	97
50	5/5	230 ± 5	266 ± 5	36 ± 2	99
100	5/5	234 ± 6	271 ± 6	37 ± 4	101
200	5/5	232 ± 7	267 ± 7	36 ± 3	99
400	5/5	233 ± 7	263 ± 8	30 ± 1	98

[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the chamber control group were not significant by Dunnett's test.

TABLE 4
Incidences of Nonneoplastic Lesions of the Kidney in Male F344/N Rats in the 2-Week Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
Number Examined Microscopically	5	5	5	5	5	5
Renal Tubule, Accumulation, Hyaline Droplet[a]	5 (1.2)[b]	5 (2.0)	5 (2.8)	5 (3.0)	5 (3.4)	5 (3.8)
Renal Tubule, Degeneration	0	5** (1.0)	5** (1.0)	5** (1.2)	5** (2.0)	5** (2.2)
Renal Tubule, Regeneration	0	5** (1.0)	5** (1.0)	5** (1.2)	5** (2.0)	5** (2.0)
Medulla, Casts Granular	0	2 (1.0)	4* (1.3)	5** (1.4)	5** (2.2)	5** (2.6)

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

3-Month Study

All rats survived to the end of the study (Table 5). Final mean body weights and body weight gains of all exposed groups were similar to those of the chamber control groups. There were no clinical findings related to decalin exposure.

Table 5
Survival and Body Weights of Rats in the 3-Month Inhalation Study of Decalin

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	99 ± 2	290 ± 5	191 ± 5	
25	10/10	98 ± 1	293 ± 8	195 ± 8	101
50	10/10	95 ± 2	279 ± 5	184 ± 5	96
100	10/10	96 ± 3	279 ± 4	183 ± 4	96
200	10/10	96 ± 2	300 ± 6	203 ± 6	103
400	10/10	98 ± 2	290 ± 5	192 ± 5	100
Female					
0	10/10	89 ± 2	171 ± 3	83 ± 3	
25	10/10	91 ± 2	169 ± 2	78 ± 2	99
50	10/10	91 ± 1	176 ± 3	85 ± 3	103
100	10/10	90 ± 2	176 ± 5	86 ± 4	103
200	10/10	89 ± 1	170 ± 3	80 ± 3	99
400	10/10	91 ± 3	166 ± 4	75 ± 2	97

[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the chamber control group were not significant by Dunnett's test.

At week 12, significant urine chemistry changes occurred in male rats (Tables 6 and F1) and were consistent with the renal toxicity data (Tables 7 and G3) and the renal lesions observed microscopically (Table 8). In the urine of exposed male rats, glucose/creatinine and protein/creatinine ratios were 20% to 90% greater than those in the chamber controls. In addition, aspartate aminotransferase/creatinine and lactate dehydrogenase/creatinine ratios were increased five- to sevenfold and three- to fourfold, respectively, in all exposed groups of males. The urine of females in exposed groups also demonstrated increases in aspartate aminotransferase/creatinine and lactate dehydrogenase/creatinine ratios. Although these increases were not as great as in the males, the enzyme activities indicated kidney toxicity in females.

No exposure-related changes occurred in the erythron or leukon. Transient increases in reticulocyte counts (day 3) and platelet counts (day 23) occurred in an exposure concentration-related fashion in males and females. These changes were minimal and were not considered toxicologically relevant. Mild transient decreases in serum alkaline phosphatase activities and increases in bile acid concentrations occurred on days 3 and 23, but returned to values similar to those of the chamber controls by the end of the study. At all time points, serum alanine aminotransferase activities demonstrated minimal exposure concentration-related decreases; sorbitol dehydrogenase, another marker of hepatocellular injury, was unchanged.

At 2 and 6 weeks and at study termination, five male rats per group were sacrificed for renal toxicity studies. Kidney tissue of male rats was examined for indices of cell proliferation. The numbers of PCNA-labeled cells and labeling indices were generally significantly greater than those of the chamber controls at both interim time

TABLE 6
Selected Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male						
Glucose/creatinine ratio	0.15 ± 0.04	0.18 ± 0.02*	0.21 ± 0.06*	0.20 ± 0.01**	0.29 ± 0.07**	0.21 ± 0.02**
Protein/creatinine ratio	1.24 ± 0.06	1.48 ± 0.09*	1.71 ± 0.05**	1.79 ± 0.10**	1.65 ± 0.08**	1.63 ± 0.07**
Aspartate aminotransferase/ creatinine ratio	0.15 ± 0.01	0.73 ± 0.04**	0.90 ± 0.04**	1.00 ± 0.08**	0.89 ± 0.06**	0.88 ± 0.06**
Lactate dehydrogenase/ creatinine ratio	0.41 ± 0.02	1.25 ± 0.07**	1.49 ± 0.08**	1.73 ± 0.12**	1.52 ± 0.10**	1.57 ± 0.08**
Female						
Glucose/creatinine ratio	0.11 ± 0.00	0.12 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.10 ± 0.01
Protein/creatinine ratio	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.09 ± 0.01
Aspartate aminotransferase/ creatinine ratio	0.03 ± 0.01	0.05 ± 0.00	0.06 ± 0.01**	0.05 ± 0.01*	0.07 ± 0.01**	0.07 ± 0.02**
Lactate dehydrogenase/ creatinine ratio	0.48 ± 0.07	0.70 ± 0.05*	0.75 ± 0.05**	0.82 ± 0.06**	0.95 ± 0.03**	1.02 ± 0.10**

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

TABLE 7
Selected Renal Toxicity Data for Male F344/N Rats in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	5	5	5	5	5	5
Cells labeled						
Week 2	74.8 ± 4.2	93.6 ± 3.7*	86.6 ± 5.8*	94.4 ± 5.3*	92.4 ± 5.5*	107.6 ± 9.4**
Week 6	69.8 ± 3.3	97.6 ± 3.4**	106.8 ± 1.9**	98.4 ± 5.3**	110.6 ± 5.9**	129.0 ± 7.2**
Week 14	64.6 ± 4.2	98.4 ± 1.2*	80.8 ± 6.4	89.2 ± 5.6	96.8 ± 5.0**	95.2 ± 4.1*
Cells counted						
Week 2	2,254 ± 87	2,243 ± 36	2,206 ± 67	2,206 ± 37	2,207 ± 56	2,188 ± 35
Week 6	2,201 ± 69	2,314 ± 34	2,217 ± 42	2,124 ± 39	2,197 ± 55	2,183 ± 39
Week 14	2,118 ± 31	2,184 ± 41	2,185 ± 63	2,184 ± 30	2,144 ± 36	2,127 ± 52
Labeling index (%)						
Week 2	3.33 ± 0.21	4.17 ± 0.13*	3.94 ± 0.29	4.27 ± 0.20**	4.20 ± 0.29*	4.90 ± 0.34**
Week 6	3.17 ± 0.11	4.22 ± 0.13**	4.82 ± 0.11**	4.64 ± 0.26**	5.03 ± 0.23**	5.91 ± 0.28**
Week 14	3.05 ± 0.19	4.51 ± 0.10**	3.70 ± 0.28*	4.08 ± 0.23*	4.51 ± 0.18**	4.48 ± 0.15**
α2u-Globulin (mg/g kidney)						
Week 2	0.15 ± 0.09	0.39 ± 0.15	0.44 ± 0.20	0.52 ± 0.26	0.84 ± 0.19**	2.72 ± 1.59**
Week 6	2.51 ± 1.31	6.17 ± 1.26	7.71 ± 3.96	5.31 ± 1.18	7.57 ± 0.90*	15.18 ± 5.69**
Week 14	2.86 ± 0.72	4.09 ± 1.10	10.94 ± 6.16	7.30 ± 1.56*	13.77 ± 3.68**	10.20 ± 5.06*
α2u-Globulin (ng/µg soluble protein)						
Week 2	3.65 ± 2.42	9.98 ± 3.99	12.3 ± 5.5	14.8 ± 7.3	23.9 ± 5.2**	64.5 ± 34.3**
Week 6	52.8 ± 28.8	126 ± 18	149 ± 68	102 ± 18	153 ± 16**	310 ± 94**
Week 14	60.4 ± 17.5	75.2 ± 17.8	184 ± 98	143 ± 38	251 ± 69**	192 ± 93*

* Significantly different (P≤0.05) from the chamber control group by Dunn's or Shirley's test
** P≤0.01
[a] Data are presented as mean ± standard error. Statistical tests were performed on unrounded data.

TABLE 8
Incidences of Nonneoplastic Lesions of the Kidney in Male F344/N Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
Number Examined Microscopically	10	10	10	10	10	10
Renal Tubule, Regeneration[a]	2 (1.0)[b]	10** (1.0)	10** (1.6)	10** (2.0)	10** (2.0)	10** (2.0)
Medulla, Casts Granular	0	2 (1.0)	7** (1.0)	8** (1.5)	10** (2.0)	10** (2.2)
Renal Tubule, Accumulation, Hyaline Droplet	10 (1.0)	10 (1.5)	10 (2.2)	10 (2.8)	10 (3.0)	10 (2.7)

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

points and at study termination in all exposed groups (Tables 7 and G3). Concentrations of α2u-globulin in the kidney as well as the α2u-globulin/soluble protein ratios were significantly increased in the 200 and 400 ppm groups at weeks 2 and 6 and at the end of the study. Kidney concentrations of α2u-globulin were also significantly increased in 100 ppm males at study termination.

The relative kidney and liver weights of male rats exposed to 50 ppm or greater and the absolute kidney and liver weights of 200 and 400 ppm males were significantly increased (Table H3). There were no significant differences between exposed and chamber control animals in sperm motility or vaginal cytology parameters (Tables I1 and I2).

Incidences and/or severities of hyaline droplet accumulation and renal tubule regeneration in the kidney generally increased with increasing exposure concentration at both time points and were less pronounced at 2 weeks than at 6 weeks (data not shown) or at the end of the study. Granular casts were seen in the kidney at 6 weeks (data not shown). The less severe changes at 2 weeks likely reflect male rats' relatively low production of α2u-globulin at this age. The renal changes that occurred at the 2-week interim sacrifice were also less severe than those in the 2-week study. Animals in the 2-week study were older at study start and were similar in age to those sacrificed at 6 weeks in the 3-month study.

At terminal sacrifice, incidences and severities of renal tubule regeneration and granular casts in the medulla were increased in the kidney of all groups of exposed male rats (Table 8). The severities of hyaline droplets, a change commonly seen in the proximal renal tubule of male rats in 3-month studies (Montgomery and Seely, 1990), generally increased with increasing exposure concentration. Epithelial cells within the proximal tubules contained variably sized spherical to sometimes angular eosinophilic hyaline droplets that expanded the cytoplasm. This change was observed and graded using the hematoxylin and eosin-stained sections; however, the findings were confirmed in the kidneys of five males from each group in which the Mallory-Heidenhain stain was used to stain the protein and visualize the droplets. Also, some of the epithelial cells within affected tubules appeared degenerative and necrotic, with some cells sloughed into the lumen. Granular casts were within the outer stripe of the outer medulla and were characterized by variably expanded tubular lumina filled with granular eosinophilic material (presumed to contain α2u protein and cellular debris from damaged proximal tubules). Chronic progressive nephropathy is a common spontaneous change in F344/N rats, particularly males, and regeneration of renal tubular epithelium is one of the earliest components identified by microscopy. It is identified by tubules with smaller basophilic cells that may appear more crowded with occasional mitotic figures present.

Exposure Concentration Selection Rationale: Because there were no significant differences in body weight or survival in males, exposure concentrations for males in the 2-year study were based primarily on the kidney lesions. Granular casts within renal tubules are thought to represent accumulations of α2u protein and cellular debris (necrotic epithelial cells) from damaged proximal renal tubules. Also, as is typical for α2u-globulin inducers, the severity of the spontaneous nephropathy was exacerbated in male F344/N rats. There was concern that with time, progression of the damage to renal tubules and nephropathy may result in compromised renal function and/or reduced survival. Because the incidences and severities of lesions in rats exposed to 200 ppm did not differ significantly from those exposed to 400 ppm, these concentrations were considered too high for a 2-year study; therefore, 100 ppm was selected as the highest exposure concentration. However, the rats in the 2-year study would receive NTP-2000 diet, which is designed to reduce the severity of spontaneous nephropathy in male F344/N rats. With no long-term experience with the NTP-2000 diet and α2u-globulin inducers, there was some uncertainty about potential progression of chemically induced renal lesions. Because of this uncertainty and the availability of limited cage space in the 400 ppm mouse chambers, an additional group of 20 male rats was exposed to 400 ppm. Because there were no significant adverse effects on body weights or survival of females, 400 ppm was selected as the highest exposure concentration for females in the 2-year study. Lower concentrations were selected based on blood decalin clearance data from the inhalation toxicokinetic studies. Based on elimination rates, 400 ppm was outside and 25 ppm was within the linear range.

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 9 and in the Kaplan-Meier survival curves (Figure 2). Survival of exposed groups was similar to that of the chamber control groups.

Body Weights and Clinical Findings

Mean body weights of 400 ppm males were slightly less than those of the chamber controls during the second year of the study (Tables 10 and 11; Figure 3). There were no exposure-related clinical findings.

Table 9
Survival of Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Male					
Animals initially in study	50	50	50	50	20
Missexed[a]	0	0	1	0	0
Moribund	17	21	23	23	6
Natural deaths	5	6	3	7	0
Animals surviving to study termination	28	23	23	20	14
Percent probability of survival at end of study[b]	56	46	47	40	70
Mean survival (days)[c]	684	675	697	673	711
Survival analysis[d]	P=0.169N	P=0.453	P=0.686	P=0.192	P=0.266N
Female					
Animals initially in study	50	50		50	50
Accidental death[a]	0	0		1	0
Moribund	16	10		10	17
Natural deaths	2	5		0	5
Animals surviving to study termination	32	35		39[e]	28
Percent probability of survival at end of study	64	70		80	56
Mean survival (days)	700	713		703	683
Survival analysis	P=0.076	P=0.554N		P=0.124N	P=0.391

[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 chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.
[e] Includes one animal that died during the last week of the study

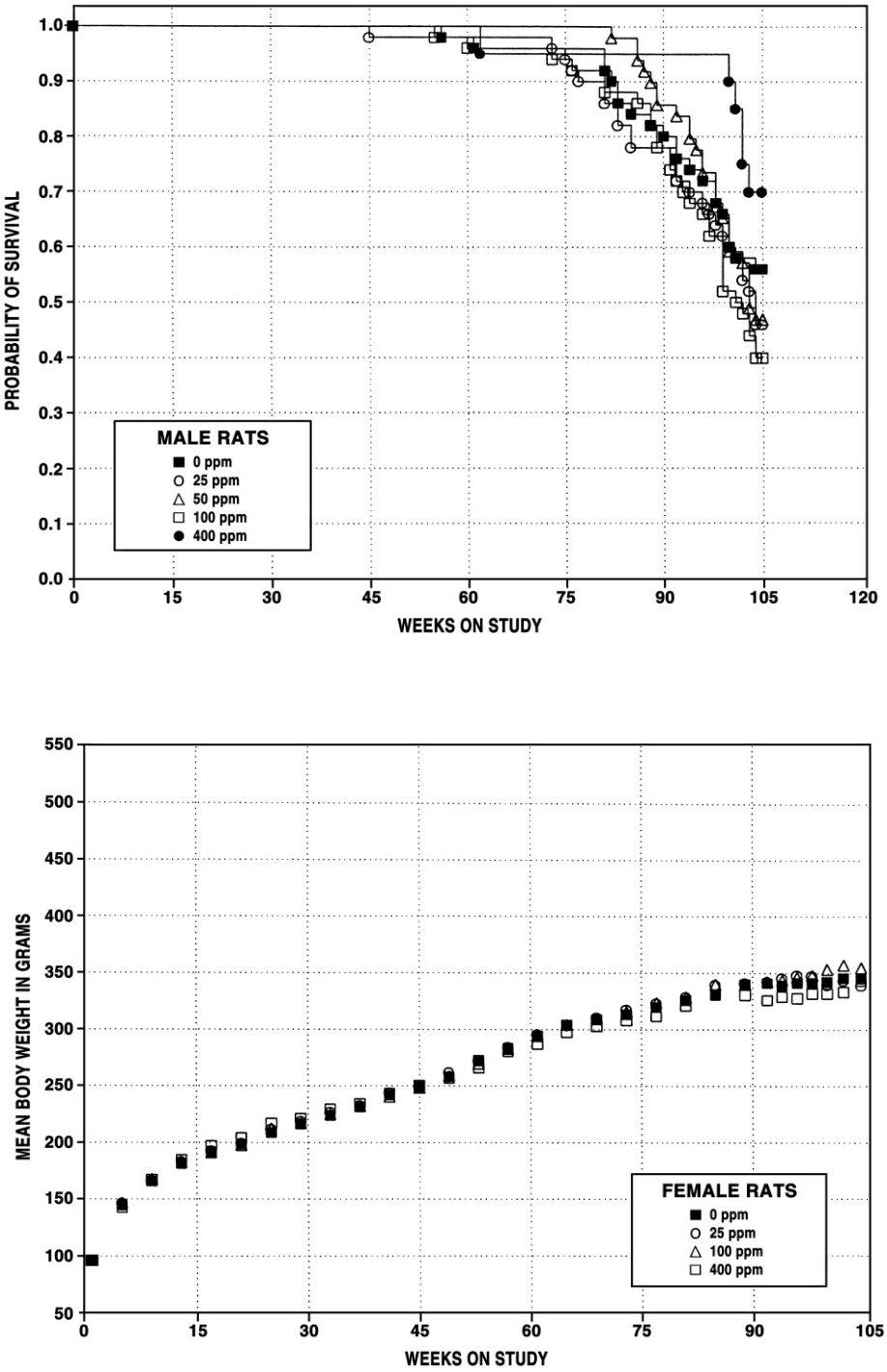


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Decalin by Inhalation for 2 Years

TABLE 10
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Decalin

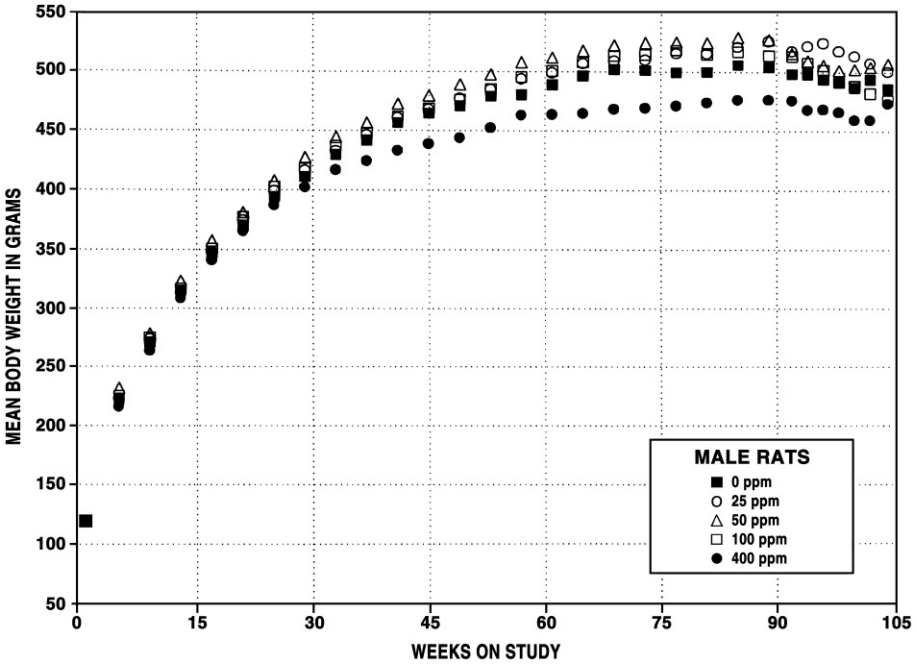
Weeks on Study	Chamber Control		25 ppm			50 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	118	50	118	100	50	121	103	50
5	222	50	223	101	50	232	105	49
9	271	50	274	101	50	278	103	49
13	315	50	313	99	50	323	103	49
17	347	50	349	100	50	358	103	49
21	370	50	375	101	50	381	103	49
25	394	50	399	101	50	408	104	49
29	411	50	417	101	50	428	104	49
33	430	50	433	101	50	445	104	49
37	442	50	447	101	50	457	103	49
41	457	50	461	101	50	473	104	49
45	465	50	468	101	50	480	103	49
49	471	50	478	101	49	489	104	49
53	479	50	485	101	49	498	104	49
57	481	49	494	103	49	508	106	49
61	489	49	499	102	49	512	105	49
65	496	48	507	102	49	518	104	49
69	502	48	510	102	49	523	104	49
73	501	48	511	102	49	525	105	49
77	500	48	516	103	46	526	105	49
81	500	48	516	103	45	525	105	49
85	506	43	522	103	41	530	105	48
89	505	41	527	105	39	528	105	43
92	499	39	519	104	39	517	104	42
94	498	38	523	105	36	510	102	41
96	494	37	525	106	35	506	102	38
98	492	35	519	105	33	502	102	35
100	487	33	515	106	31	503	103	32
102	494	29	508	103	29	505	102	29
104	486	29	501	103	26	508	104	24
Mean for weeks								
1-13	232		232	100		239	103	
14-52	421		425	101		435	103	
53-104	495		512	103		514	104	

TABLE 10
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Decalin

Weeks on Study	100 ppm Av. Wt. (g)	100 ppm Wt (% of controls)	100 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors
1	120	102	50	121	102	20
5	225	102	50	216	97	20
9	275	101	50	264	98	20
13	317	101	50	309	98	20
17	351	101	50	341	98	20
21	377	102	50	366	99	20
25	403	102	50	387	98	20
29	418	102	50	402	98	20
33	438	102	50	417	97	20
37	448	101	50	425	96	20
41	462	101	50	433	95	20
45	469	101	50	439	95	20
49	476	101	50	444	94	20
53	485	101	50	453	95	20
57	496	103	49	463	96	20
61	501	103	48	464	95	20
65	508	102	48	465	94	19
69	514	102	48	469	93	19
73	515	103	48	470	94	19
77	519	104	46	472	94	19
81	515	103	46	474	95	19
85	518	102	44	477	94	19
89	514	102	41	477	95	19
92	514	103	37	476	96	19
94	508	102	35	468	94	19
96	502	102	34	469	95	19
98	492	100	31	467	95	19
100	489	100	26	460	94	19
102	482	98	25	460	93	17
104	477	98	22	474	98	14
Mean for weeks						
1-13	234	101		228	98	
14-52	427	101		406	96	
53-104	503	102		468	95	

TABLE 11
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Decalin

Weeks on Study	Chamber Control		25 ppm			100 ppm			400 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	95	50	95	100	50	97	101	50	97	101	50
5	145	50	147	101	50	147	101	50	143	99	50
9	166	50	167	100	50	168	101	50	168	101	50
13	181	50	183	101	50	183	101	50	185	102	50
17	192	50	193	101	50	191	100	49	197	103	50
21	199	50	200	100	50	198	100	49	204	103	50
25	209	50	211	101	50	212	102	49	217	104	50
29	216	50	219	101	50	217	100	49	221	102	50
33	224	50	226	101	50	225	100	49	229	103	50
37	231	50	233	101	50	232	100	49	234	101	50
41	242	50	244	101	50	241	99	49	243	101	50
45	249	50	250	100	50	248	100	49	250	101	50
49	258	50	262	101	50	259	100	49	257	100	50
53	273	49	273	100	50	270	99	48	267	98	50
57	283	49	284	100	50	283	100	48	281	99	50
61	294	49	296	101	50	294	100	48	287	98	50
65	304	49	304	100	50	304	100	48	297	98	50
69	309	49	310	101	50	310	101	48	303	98	50
73	314	49	318	101	49	316	101	48	308	98	48
77	320	48	323	101	49	324	101	48	312	98	48
81	326	48	329	101	48	329	101	48	322	99	46
85	331	46	340	103	48	341	103	48	331	100	43
89	340	45	341	100	47	340	100	48	331	97	39
92	341	45	343	100	46	343	100	47	326	96	37
94	339	44	346	102	45	344	101	47	329	97	35
96	341	42	348	102	43	347	102	45	328	96	35
98	341	39	348	102	43	348	102	43	332	97	35
100	343	37	339	99	43	354	103	41	332	97	35
102	346	36	344	99	42	357	103	40	333	96	30
104	345	33	339	98	40	355	103	40	343	99	28
Mean for weeks											
1-13	147		148	101		149	101		148	101	
14-52	224		226	101		225	100		228	102	
53-104	323		325	101		327	101		315	98	



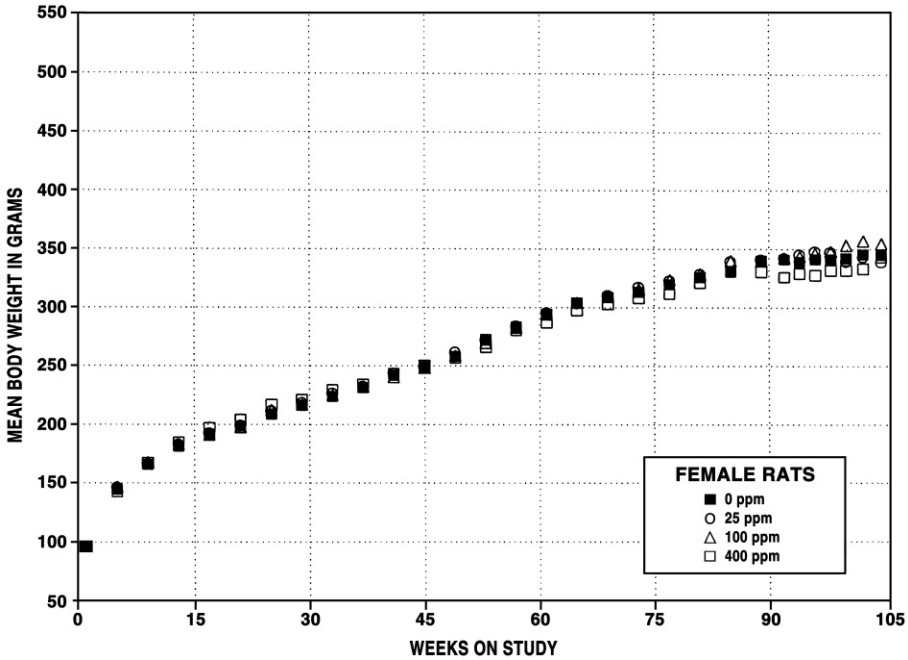


FIGURE 3
Growth Curves for Male and Female Rats Exposed to Decalin by Inhalation for 2 Years

Pathology and Statistical Analyses

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

Kidney: Incidences of renal tubule adenoma and adenoma or carcinoma (combined) were generally significantly increased in males exposed to 50 ppm or greater (Tables 12 and A3). Incidences of adenoma, carcinoma, and adenoma or carcinoma (combined) in all exposed groups of males exceeded the historical ranges in controls (all routes) given the NTP-2000 diet (Tables 12 and A4a). In the kidney, hyperplasia, adenoma, and carcinoma are thought to represent a continuum in the progression of proliferative lesions of the renal tubule epithelium; all exposed groups of males also had significantly increased incidences of hyperplasia (Tables 12 and A5). Hyperplasias were generally focal lesions characterized by increased numbers of tubule epithelial cells forming multiple layers that partially or totally filled the tubule lumen and usually caused dilation of the tubule. Adenomas were generally discrete expansile masses that were larger than hyperplasias (greater than the diameter of five tubules) and had a more complex structure. Carcinomas were less discrete and larger than adenomas with hemorrhage, necrosis, local invasion, and/or metastasis to distant sites.

The severity of nephropathy was greater in all exposed groups of males than in the chamber controls (Table 12). Changes related to nephropathy consisted of a spectrum of lesions. These lesions included varying degrees of tubular dilation, proteinaceous tubular casts, atrophy, regeneration and hypertrophy of tubular epithelium, thickening of tubular and glomerular basement membranes, interstitial fibrosis, and varying numbers and aggregates of mononuclear inflammatory cells within the interstitium. Incidences of hyaline droplet accumulation were generally increased in exposed males, and the increases were significant in the 25 and 100 ppm groups. The hyaline droplets were similar to those seen in the 3-month study. Because male rats' production of α2u-globulin declines later in life, an exposure-related increase in hyaline droplets was not expected at the end of a 2-year study. The vast majority of the affected animals died or were sacrificed early, which may explain the increased incidences. The incidences and severities of mineralization of the renal papilla were also increased in all exposed groups of males. The mineral appeared to be in tubules within the papilla and, in many instances, the profiles of mineral were elongate (linear mineralization), which is characteristic of α2u-globulin-induced nephropathy in 2-year studies. The incidences of transitional epithelium hyperplasia of the renal pelvis were significantly increased in all exposed groups of males. This change was generally mild and was characterized by increased thickness, often with papillary projections, of the transitional epithelium lining the renal pelvis.

Adrenal Gland: The incidences of benign or malignant pheochromocytoma (combined) were significantly increased in 100 and 400 ppm males (Tables 13 and A3). The incidence of benign pheochromocytoma in 400 ppm males, while not significantly increased, exceeded the historical range in controls (all routes) given the NTP-2000 diet (Tables 13 and A4b). The incidences of malignant and benign or malignant pheochromocytoma (combined) in 100 and 400 ppm males also exceeded the historical control ranges. One male in each of the 25, 50, and 100 ppm groups had a bilateral benign pheochromocytoma, as did two males in the 400 ppm group. Although pheochromocytoma is a common spontaneous neoplasm in male F344/N rats, this neoplasm has a lower spontaneous occurrence in females. No increased incidences of pheochromocytoma were seen in exposed groups of females (chamber control, 1/50; 25 ppm, 1/48; 100 ppm, 3/49; 400 ppm, 1/44; Table B3).

The incidence of hyperplasia of the adrenal medulla was significantly increased in 50 ppm males (Tables 13 and A5). However, the diagnosis of focal hyperplasia was made only in the absence of a neoplasm diagnosis at that site in an animal; therefore, groups with more neoplasms had fewer animals likely to be diagnosed with hyperplasia. Focal hyperplasia and pheochromocytoma are thought to constitute a morphologic continuum in the adrenal medulla. Focal hyperplasia consisted of irregular small foci of small- to normal-sized medullary cells arranged in packets or solid clusters slightly larger than normal; compression of surrounding parenchyma was minimal or absent. Benign pheochromocytomas were well-delineated masses, often with altered architecture and variable compression of surrounding parenchyma.

Neoplastic cells were arranged in variably sized aggregates, clusters, and/or variably thick trabecular cords. Larger neoplasms usually exhibited greater cellular pleomorphism and atypia than smaller neoplasms. Malignant pheochromocytomas were identified when there was invasion of or beyond the adrenal capsule.

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Number Examined Microscopically	50	50	49	50	20
Cortex, Renal Tubule, Hyperplasia[a]	0	11** (2.3)[b]	11** (2.1)	15** (3.1)	5** (1.8)
Nephropathy, Chronic	48 (1.4)	48 (2.3)	49 (2.6)	50 (2.3)	20 (3.0)
Cortex, Renal Tubule, Accumulation, Hyaline Droplet	2 (1.5)	9* (2.9)	7 (2.0)	11** (2.6)	2 (2.5)
Papilla, Mineralization	1 (1.0)	34** (2.4)	41** (2.9)	43** (3.1)	17** (3.3)
Pelvis, Transitional Epithelium, Hyperplasia	1 (1.0)	8* (1.5)	8* (2.1)	10** (2.4)	5** (1.6)
Renal Tubule, Adenoma, Multiple	0	0	0	0	1
Renal Tubule, Adenoma (includes multiple)[c]					
Overall rate[d]	1/50 (2%)	2/50 (4%)	6/49 (12%)	9/50 (18%)	5/20 (25%)
Adjusted rate[e]	2.4%	4.9%	14.0%	21.8%	26.7%
Terminal rate[f]	1/28 (4%)	0/23 (0%)	4/23 (17%)	5/20 (25%)	4/14 (29%)
First incidence (days)	733 (T)	644	680	617	716
Poly-3 test[g]	P=0.005	P=0.492	P=0.058	P=0.007	P=0.004
Renal Tubule, Carcinoma[h]	0	1	1	4	1
Renal Tubule, Adenoma or Carcinoma[c]					
Overall rate	1/50 (2%)	3/50 (6%)	7/49 (14%)	12/50 (24%)	6/20 (30%)
Adjusted rate	2.4%	7.3%	16.3%	28.9%	31.8%
Terminal rate	1/28 (4%)	1/23 (4%)	4/23 (17%)	7/20 (35%)	4/14 (29%)
First incidence (days)	733 (T)	644	680	617	708
Poly-3 test	P=0.002	P=0.296	P=0.031	P<0.001	P<0.001

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 3/906 (0.4% ± 0.9%), range 0%-2%
[d] Number of animals with neoplasm per number of animals with kidney examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[h] Historical incidence: 0/906

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Number Examined Microscopically	49	49	49	49	20
Hyperplasia[a]	10 (2.5)[b]	13 (2.9)	26** (2.5)	17 (2.4)	4 (2.3)
Pheochromocytoma, Benign, Bilateral	0	1	1	1	2
Pheochromocytoma, Benign (includes bilateral)[c]					
Overall rate[d]	7/49 (14%)	9/49 (18%)	11/49 (22%)	10/49 (20%)	6/20 (30%)
Adjusted rate[e]	16.7%	22.0%	25.0%	24.8%	31.8%
Terminal rate[f]	4/28 (14%)	8/23 (35%)	6/23 (26%)	6/20 (30%)	4/14 (29%)
First incidence (days)	561	589	602	600	708
Poly-3 test[g]	P=0.173	P=0.368	P=0.247	P=0.261	P=0.155
Pheochromocytoma, Malignant[h]					
Overall rate	2/49 (4%)	0/49 (0%)	2/49 (4%)	7/49 (14%)	3/20 (15%)
Adjusted rate	4.8%	0.0%	4.6%	17.3%	16.0%
Terminal rate	1/28 (4%)	0/23 (0%)	0/23 (0%)	3/20 (15%)	2/14 (14%)
First incidence (days)	706	—[i]	638	506	716
Poly-3 test	P=0.034	P=0.242N	P=0.679N	P=0.072	P=0.166
Pheochromocytoma, Benign or Malignant[j]					
Overall rate	8/49 (16%)	9/49 (18%)	13/49 (27%)	16/49 (33%)	8/20 (40%)
Adjusted rate	19.1%	22.0%	29.2%	38.6%	42.2%
Terminal rate	5/28 (18%)	8/23 (35%)	6/23 (26%)	8/20 (40%)	5/14 (36%)
First incidence (days)	561	589	602	506	708
Poly-3 test	P=0.038	P=0.476	P=0.196	P=0.038	P=0.049

** Significantly different ($P \leq 0.01$) from the chamber control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 100/903 (10.8% ± 5.8%), range 3%-24%
[d] Number of animals with neoplasm per number of animals with adrenal medulla examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by **N**.
[h] Historical incidence: 18/903 (2.3% ± 2.7%), range 0%-11%
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 116/903 (12.8% ± 5.9%), range 5%-27%

Lung and Pleura: Incidences of interstitial fibrosis, histiocytic infiltration, and alveolar proteinosis were increased in all exposed groups of females, and the increases were significant in 400 ppm females (Tables 14 and B5). The severities of interstitial fibrosis and alveolar proteinosis increased slightly with increasing exposure concentration. These individually diagnosed changes are all components of a focal lesion that appears to be a common incidental finding in aged F344/N rats, as evidenced by the incidences in the chamber control group. Although some lesions were determined to be more severe than others, none were considered marked and they were not considered clinically significant. These changes were most frequently subpleural and in some cases were associated with minimal to mild chronic inflammation of the visceral pleura, the incidence of which was significantly increased in the 400 ppm group. Alveolar septa were occasionally thickened by thin strands of eosinophilic fibrillar material (fibrosis). The histiocytic infiltrate was minimal to mild and consisted of scattered intraalveolar macrophages that contained large amounts of foamy intracytoplasmic material. The material was interpreted as pulmonary surfactant. In addition, scant amounts of eosinophilic material (surfactant) similar to that seen within the alveolar macrophages were also free within alveoli (alveolar proteinosis).

Thyroid Gland (C-cell): Incidences of hyperplasia were significantly increased in 400 ppm males and significantly decreased in 100 ppm males (chamber control, 6/50; 25 ppm, 6/50; 50 ppm, 6/49; 100 ppm, 0/49; 400 ppm, 7/20); incidences of this lesion were significantly decreased in all exposed female groups (chamber control, 15/50; 25 ppm, 7/49; 100 ppm, 6/49; 400 ppm, 6/50; Table B5). The incidences of neoplasms of the thyroid gland (C-cell) in exposed males and females were not significantly different from those in the chamber controls (Tables A3 and B3). The increased and decreased incidences of hyperplasia were considered normal variation and not related to decalin exposure.

Clitoral and Preputial Glands: The incidences of clitoral gland adenoma occurred with a negative trend and were significantly decreased in all exposed groups of females; the incidences of clitoral gland adenoma or carcinoma (combined) were significantly decreased in 100 and 400 ppm females (Tables 15 and B3). The incidence of adenoma in 400 ppm females was below the historical range in controls (all routes) given the NTP-2000 diet; however, the incidence in the chamber control group was at the upper end of the historical range (Tables 15 and B4). Proliferative lesions of the clitoral gland in females and preputial gland in males consist of a morphologic and biologic continuum. There were no significantly decreased incidences of clitoral gland carcinoma or hyperplasia in exposed females or of neoplasms in the preputial gland in exposed males (Tables 15, A3, B3, and B5). The incidences of preputial gland adenoma or carcinoma (combined) in exposed males were within the historical range [72/907 (7% ± 4%), range 0%-13%] (Tables 15 and A3). It was uncertain if the decreased incidences of clitoral gland neoplasms were related to decalin exposure.

TABLE 14
Incidences of Nonneoplastic Lesions of the Respiratory System in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control		25 ppm		100 ppm		400 ppm	
Lung[a]	50		50		49		50	
Interstitium, Fibrosis[b]	16	(1.4)[c]	24	(1.7)	23	(1.6)	28**	(2.1)
Alveolus, Infiltration Cellular, Histiocyte	21	(1.7)	26	(1.6)	29	(1.7)	29*	(2.0)
Alveolus, Proteinosis	11	(1.4)	16	(1.8)	15	(1.8)	23**	(1.9)
Pleura	20		25		25		28	
Inflammation, Chronic	15	(1.6)	17	(1.7)	23	(1.6)	27*	(2.3)

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

TABLE 15
Incidences of Neoplasms and Nonneoplastic Lesions of the Clitoral and Preputial Glands in Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Female					
Clitoral Gland[a]	48	49		49	50
Hyperplasia[b]	3 (3.7)[c]	3 (3.7)		1 (4.0)	3 (3.7)
Adenoma[d]					
Overall rate[e]	8/48 (17%)	2/49 (4%)		1/49 (2%)	0/50 (0%)
Adjusted rate[f]	18.3%	4.4%		2.2%	0.0%
Terminal rate[g]	7/31 (23%)	1/35 (3%)		1/39 (3%)	0/28 (0%)
First incidence (days)	666	722		734 (T)	—[i]
Poly-3 test[h]	P=0.014N	P=0.037N		P=0.012N	P=0.004N
Carcinoma	1	3		1	1
Adenoma or Carcinoma[j]					
Overall rate	9/48 (19%)	5/49 (10%)		2/49 (4%)	1/50 (2%)
Adjusted rate	20.4%	10.9%		4.3%	2.4%
Terminal rate	7/31 (23%)	4/35 (11%)		2/39 (5%)	0/28 (0%)
First incidence (days)	561	722		734 (T)	618
Poly-3 test	P=0.018N	P=0.171N		P=0.020N	P=0.010N
Male					
Preputial Gland	50	49	49	50	20
Adenoma	0	1	1	0	0
Carcinoma	0	1	1	3	2
Adenoma or Carcinoma[k]	0	2	2	3	2

(T) Terminal sacrifice
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 100/931 (10.7% ± 5.5%), range 2%-20%
[e] Number of animals with neoplasm per number of animals with clitoral gland examined microscopically
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 126/931 (13.4% ± 6.8%), range 2%-24%
[k] Historical incidence: 72/907 (7.4% ± 4.0%), range 0%-13%

MICE

2-WEEK STUDY

All mice survived to the end of the study (Table 16). Final mean body weights and body weight gains of all exposed groups were similar to those of the chamber control groups. There were no clinical findings related to decalin exposure.

Liver weights of 200 and 400 ppm males and females and 100 ppm females were significantly greater than those of the chamber controls (Table H4). No exposure-related lesions were observed in male or female mice.

Exposure Concentration Selection Rationale: Because there were no effects of decalin on survival or body weights of mice in the 2-week study and pharmacokinetic data indicated that decalin metabolism was saturated at 400 ppm, decalin exposure concentrations selected for the 3-month study in mice were 0, 25, 50, 100, 200, and 400 ppm.

TABLE 16
Survival and Body Weights of Mice in the 2-Week Inhalation Study of Decalin

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	20.5 ± 0.2	24.5 ± 0.2	4.0 ± 0.3	
25	5/5	21.1 ± 0.3	24.8 ± 0.6	3.7 ± 0.3	101
50	5/5	20.7 ± 0.3	24.8 ± 0.4	4.0 ± 0.2	101
100	5/5	20.6 ± 0.3	24.9 ± 0.7	4.3 ± 0.5	102
200	5/5	20.1 ± 0.6	24.3 ± 0.9	4.3 ± 0.3	100
400	5/5	20.2 ± 0.4	23.6 ± 0.5	3.5 ± 0.3	97
Female					
0	5/5	18.8 ± 0.5	21.1 ± 0.3	2.3 ± 0.3	
25	5/5	18.4 ± 0.4	20.6 ± 0.4	2.2 ± 0.3	98
50	5/5	18.5 ± 0.4	21.1 ± 0.7	2.6 ± 0.6	100
100	5/5	18.6 ± 0.4	21.4 ± 0.6	2.8 ± 0.3	101
200	5/5	18.3 ± 0.3	21.3 ± 0.5	3.0 ± 0.4	101
400	5/5	18.4 ± 0.5	21.6 ± 0.6	3.2 ± 0.4	102

[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the chamber control group were not significant by Dunnett's test.

3-Month Study

All mice survived to the end of the study (Table 17). Final mean body weights and body weight gains of all exposed groups were similar to those of the chambe control groups. There were no clinical findings related to decalin exposure.

Hematology data for mice are presented in Table F2. Minimal decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts occurred inconsistently in 200 and 400 ppm males and females. While these decreases suggest a possible biological effect, their minimal severities indicated they were not clinically or toxicologically relevant.

Liver weights of 200 and 400 ppm males and females were significantly greater than those of the chamber controls (Table H5). There was a significant exposure concentration-related decrease in the absolute spermatid head count and a significant decrease in absolute head count of the 400 ppm group compared to the chamber controls (Table I3). Estrous cycle lengths of exposed females were generally similar to that of the chamber controls (Table I4).

Table 17
Survival and Body Weights of Mice in the 3-Month Inhalation Study of Decalin

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	21.9 ± 0.5	36.1 ± 0.9	14.3 ± 0.7	
25	10/10	21.7 ± 0.5	35.4 ± 0.7	13.7 ± 0.7	98
50	10/10	21.9 ± 0.5	34.9 ± 1.1	13.0 ± 1.0	97
100	10/10	22.0 ± 0.6	35.2 ± 0.8	13.3 ± 0.9	98
200	10/10	21.9 ± 0.4	35.6 ± 0.9	13.7 ± 0.9	99
400	10/10	21.8 ± 0.5	34.5 ± 0.6	12.7 ± 0.4	96
Female					
0	10/10	19.6 ± 0.2	29.6 ± 0.5	10.0 ± 0.4	
25	10/10	20.0 ± 0.3	28.9 ± 0.5	8.9 ± 0.4	98
50	10/10	19.8 ± 0.2	31.6 ± 1.1	11.8 ± 1.0	107
100	10/10	19.5 ± 0.2	29.4 ± 0.7	9.9 ± 0.6	99
200	10/10	19.6 ± 0.3	31.0 ± 1.1	11.4 ± 0.9	105
400	10/10	19.1 ± 0.3	29.0 ± 0.6	9.9 ± 0.4	98

[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the chamber control group were not significant by Dunnett's test.

Incidences of centrilobular cytomegaly of the liver were increased in males exposed to 50 ppm or greater (Table 18), and the severity of this lesion was increased in the 400 ppm group. The enlargement (cytomegaly) was primarily due to an increased amount of slightly basophilic granular cytoplasm; however, nuclear enlargement (karyomegaly) was occasionally observed. The cells in affected animals appeared to have less glycogen, as evidenced by the loss of clear areas within the cytoplasm compared with the chamber controls. This change is synonymous with the diagnosis of centrilobular hypertrophy in the 2-year study. Minimal cytoplasmic alteration was noted in the kidney of all 400 ppm male mice. This change was characterized by loss of the vacuolization that is normally seen in the cortical renal tubule epithelium and is not likely to be of toxicologic significance.

Exposure Concentration Selection Rationale: Because there were no effects of decalin on survival or body weights of mice in the 3-month study, decalin exposure concentrations selected for the 2-year study in mice were 0, 25, 100, and 400 ppm. The concentrations were also selected based on blood decalin clearance data from the 2-week and 3-month toxicokinetic studies. Based on elimination rates, 25 ppm was within and 400 ppm was outside the linear range.

TABLE 18
Incidences of Nonneoplastic Lesions of the Liver and Kidney in Male Mice in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
Liver[a]	10	0	5	10	10	10
Centrilobular, Cytomegaly[b]	0		5* (1.0)[c]	3 (1.0)	9** (1.0)	10** (1.8)
Kidney	10	0	0	0	0	10
Cytoplasmic Alteration	0					10** (1.0)

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

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 19 and in the Kaplan-Meier survival curves (Figure 4). Survival of exposed groups of mice was similar to that of the chamber control groups.

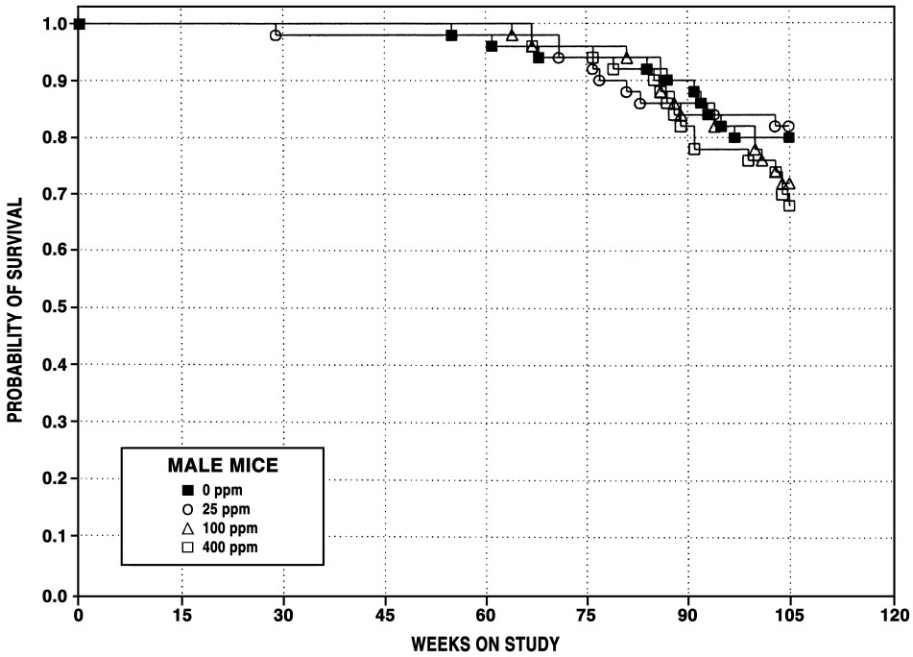
Body Weights and Clinical Findings

Mean body weights of exposed groups of mice were generally similar to those of the chamber control groups throughout the study (Tables 20 and 21; Figure 5). There were no clinical findings related to decalin exposure.

Table 19
Survival of Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	7	7	7	5
Natural deaths	3	2	7	11
Animals surviving to study termination	40[d]	41	36[d]	34[d]
Percent probability of survival at end of study[a]	80	82	72	68
Mean survival (days)[b]	701	697	702	697
Survival analysis[c]	P=0.161	P=1.000N	P=0.521	P=0.271
Female				
Animals initially in study	50	50	50	50
Accidental death[e]	0	0	1	0
Pregnant[e]	1	0	0	0
Moribund	10	15	11	8
Natural death	2	7	3	6
Animals surviving to study termination	37	28	35	36[d]
Percent probability of survival at end of study	76	56	72	72
Mean survival (days)	708	687	695	702
Survival analysis	P=0.570N	P=0.068	P=0.868	P=0.926

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



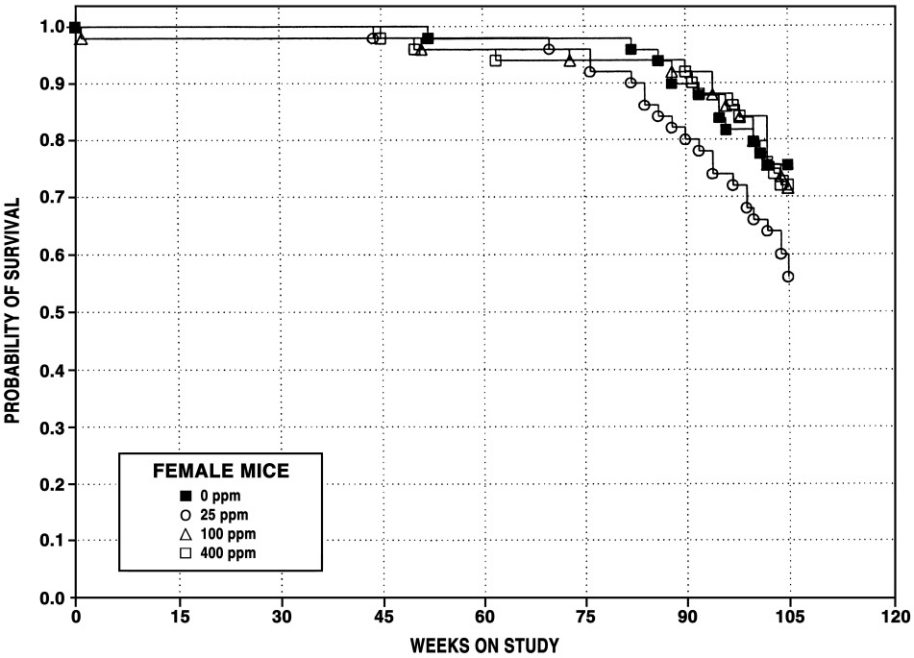


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Decalin by Inhalation for 2 Years

TABLE 20
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Decalin

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	25 ppm Av. Wt. (g)	25 ppm Wt. (% of controls)	25 ppm No. of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors
1	24.2	50	24.3	100	50	24.1	100	50	23.7	98	50
4	28.3	50	28.7	101	50	28.4	100	50	28.3	100	50
8	31.5	50	31.6	100	50	31.4	100	50	31.5	100	50
12	35.5	50	35.6	100	50	35.1	99	50	33.9	96	50
16	39.2	50	38.9	99	50	38.2	97	50	37.5	96	50
20	42.0	50	41.4	99	50	41.0	98	50	40.3	96	50
24	42.9	50	43.3	101	50	41.7	97	50	41.4	97	50
28	45.2	50	45.7	101	50	45.5	101	50	44.7	99	50
32	47.9	50	47.1	98	49	47.0	98	50	47.0	98	50
36	49.4	50	48.6	98	49	48.2	98	50	47.8	97	50
40	49.7	50	49.7	100	49	49.4	99	50	49.3	99	50
44	50.5	50	50.2	99	49	49.7	98	50	49.8	99	50
48	51.2	50	51.7	101	49	51.0	100	50	51.0	100	50
52	51.9	50	52.2	101	49	51.8	100	50	51.2	99	50
56	52.7	49	52.6	100	49	52.0	99	50	52.4	99	50
60	52.3	49	53.3	102	49	52.6	101	50	52.3	100	50
64	52.7	48	53.0	101	49	52.5	100	50	52.4	99	50
68	53.1	48	52.2	98	49	51.6	97	48	51.7	97	48
72	52.8	47	53.3	101	47	52.9	100	48	53.0	100	48
76	53.7	47	52.9	99	47	52.2	97	48	52.3	97	47
80	53.7	47	54.0	101	45	52.7	98	48	53.1	99	46
84	54.1	47	54.9	102	43	53.3	99	47	53.5	99	46
88	54.1	45	54.8	101	43	52.8	98	43	53.4	99	43
92	52.8	43	54.2	103	43	52.2	99	42	53.4	101	39
94	52.9	42	53.7	102	43	51.7	98	41	52.8	100	39
96	52.9	41	54.1	102	42	51.4	97	41	51.7	98	39
98	52.7	40	54.0	103	42	50.9	97	41	51.2	97	39
100	51.4	40	53.0	103	42	49.7	97	40	50.2	98	38
102	51.4	40	53.2	104	42	49.9	97	38	48.9	95	38
104	51.0	40	52.8	104	41	49.5	97	37	48.5	95	35
Mean for weeks											
1-12	29.9		30.1	101		29.8	100		29.4	98	
13-52	47.0		46.9	100		46.4	99		46.0	98	
53-104	52.8		53.5	101		51.7	98		51.9	98	

TABLE 21
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Decalin

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	25 ppm Av. Wt. (g)	25 ppm Wt. (% of controls)	25 ppm No. of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors
1	19.7	50	19.7	100	50	19.6	100	50	19.8	101	50
4	23.8	50	24.1	101	50	23.9	100	49	24.6	103	50
8	27.0	49	27.3	101	50	26.7	99	49	27.2	101	50
12	29.0	49	30.1	104	50	28.8	99	49	29.2	101	50
16	31.5	49	32.5	103	50	31.1	99	49	31.4	100	50
20	34.4	49	34.9	102	50	33.7	98	49	33.5	97	50
24	36.7	49	38.4	105	50	35.6	97	49	36.6	100	50
28	39.9	49	42.0	105	50	40.1	101	49	39.5	99	50
32	42.6	49	44.6	105	50	43.3	102	49	42.2	99	50
36	45.2	49	46.9	104	50	45.7	101	49	45.4	100	50
40	46.4	49	48.9	105	50	48.1	104	49	46.6	100	50
44	49.0	49	50.9	104	49	48.9	100	49	47.8	98	50
48	52.5	49	53.7	102	49	52.4	100	49	51.6	98	49
52	54.1	48	56.6	105	49	54.6	101	48	53.8	99	48
56	56.7	48	57.6	102	49	56.4	100	48	55.5	98	48
60	57.7	48	59.6	103	49	57.7	100	48	57.5	100	48
64	58.5	48	60.3	103	49	58.4	100	48	58.4	100	47
68	58.7	48	57.4	98	49	55.5	95	48	57.2	97	47
72	59.8	48	59.7	100	48	59.4	99	48	60.5	101	47
76	60.6	48	59.5	98	47	59.9	99	47	59.2	98	47
80	61.1	48	60.0	98	46	60.9	100	47	60.9	100	47
84	61.5	47	58.3	95	45	60.2	98	47	62.1	101	47
88	59.9	45	57.2	96	42	58.8	98	45	59.8	100	47
92	58.0	43	55.2	95	40	57.0	98	45	58.9	102	45
94	56.3	43	54.2	96	39	55.9	99	43	58.0	103	44
96	56.8	40	53.8	95	37	54.8	97	43	57.4	101	44
98	55.9	40	52.9	95	36	54.3	97	42	56.7	101	43
100	54.6	40	52.3	96	34	52.5	96	41	55.0	101	42
102	54.7	38	51.5	94	33	51.8	95	38	53.9	99	41
104	54.9	37	51.4	94	31	50.9	93	36	53.2	97	36
Mean for weeks											
1-12	24.9		25.3	102		24.8	100		25.2	101	
13-52	43.2		44.9	104		43.4	100		42.8	99	
53-104	57.9		56.3	97		56.5	98		57.8	100	

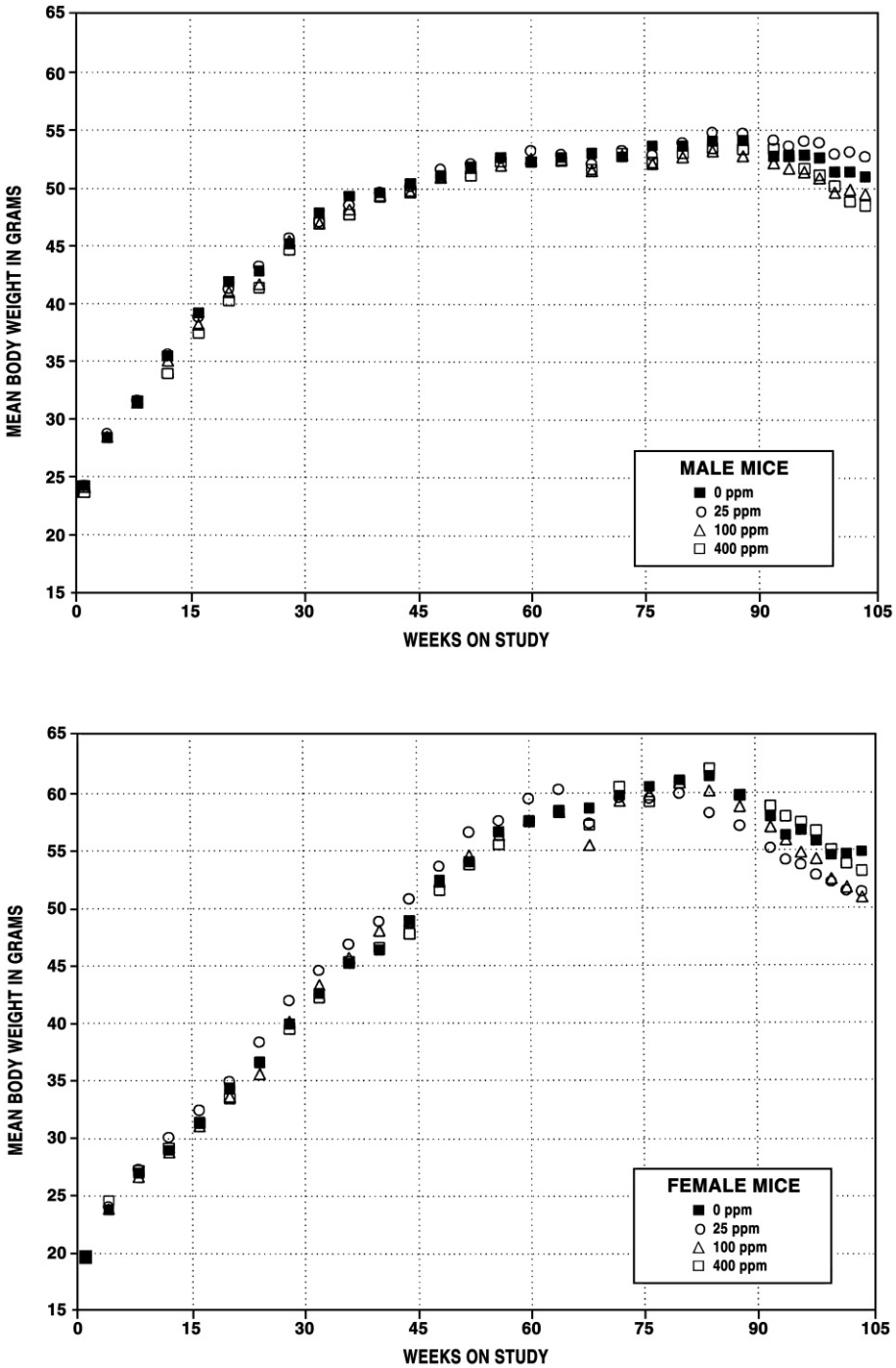


FIGURE 5
Growth Curves for Male and Female Mice Exposed to Decalin by Inhalation for 2 Years

Pathology and Statistical Analyses

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

Liver: The incidences of hepatocellular adenoma or carcinoma (combined) occurred with a positive trend in males; however, the incidences were within the historical control range (Tables 22, C3, and C4a). The incidences of hepatocellular adenoma in 400 ppm females and hepatocellular carcinoma in 25 ppm females were significantly greater than those in the chamber controls (Tables 22 and D3). The incidences of hepatocellular adenoma or carcinoma (combined) in 25 and 400 ppm females were significantly increased. The incidences of hepatocellular adenoma in 400 ppm females, hepatocellular carcinoma in 25 ppm females, and hepatocellular adenoma or carcinoma (combined) in 25 ppm females exceeded the historical ranges in controls (all routes) given NTP-2000 diet (Tables 22 and D4a). A hepatoblastoma was present in one 25 ppm male, one 400 ppm male, and one 400 ppm female (Tables 22, C1, and D1). The incidence of eosinophilic focus, a lesion which in some cases may be considered preneoplastic, was significantly increased in 400 ppm males but not in exposed groups of females (Tables 22, C5, and D5). Hepatocellular neoplasms tend to be common spontaneous lesions, and increased multiplicity of hepatocellular neoplasms typically accompanies increased incidences related to chemical exposure. Multiplicity was not increased in the exposed groups in the current study (Tables 22, C1, and D1). Because the most dramatic neoplasm incidence increase occurred in 25 ppm females, there was not a significant response in the 100 ppm group, and there were no supporting increases in neoplasm multiplicity, it was unclear if the increased neoplasm incidences in females were related to decalin exposure. The positive trend in male mice was not considered related to decalin exposure.

The incidences of centrilobular hypertrophy, necrosis, syncytial alteration, and erythrophagocytosis were significantly increased in 400 ppm males; the incidence of syncytial alteration was also significantly increased in 100 ppm males. Centrilobular hypertrophy was characterized by enlarged hepatocytes in the centrilobular area. These hepatocytes had granular or vacuolated cytoplasm and their nuclei were often enlarged. The necrosis was characterized by individual cell necrosis and/or foci of necrotic hepatocytes. The affected hepatocytes had brightly colored eosinophilic cytoplasm, and nuclear pyknosis and karyolysis were seen. Syncytial alteration was diagnosed when hepatocytes containing three or more (sometimes up to 20) nuclei were seen. Erythrophagocytosis was characterized by enlarged hepatocytes that had engulfed erythrocytes. There was often a thin rim of remaining hepatocellular cytoplasm visible around clusters of erythrocytes.

Uterus: The incidences of stromal polyp and stromal polyp or stromal sarcoma (combined) occurred with positive trends in female mice, and the combined incidence in the 400 ppm group exceeded the historical range in controls (Tables 23, D3, and D4b). This response may have been exposure related.

Testis: The incidences of interstitial cell adenoma occurred with a positive trend in male mice based on the occurrence of three of these neoplasms in the 400 ppm group (Tables 24 and C3). This neoplasm is rare in the testis of male $B6C3F_1$ mice, with a mean incidence of 1.1% in historical controls given the NTP-2000 diet. The incidence in 400 ppm males was at the upper end of the historical control range (Tables 24 and C4b). Hyperplasia, adenoma, and carcinoma are thought to represent a morphologic and biologic continuum relative to proliferative lesions of testicular interstitial cells. Carcinomas did not occur in this study, and hyperplasia occurred only in two chamber control animals. No clear morphologic features indicate the precise point at which hyperplasia has progressed to neoplasia, but the size of the lesion appears to be the best indicator to distinguish

TABLE 22
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Male				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus[a]	10	9	7	19*
Centrilobular, Hypertrophy	2 (1.5)[b]	0	4 (1.3)	36** (1.9)
Necrosis	0	1 (3.0)	3 (1.3)	19** (1.2)
Syncytial Alteration	26 (1.0)	28 (1.0)	36* (1.2)	44** (2.2)
Erythrophagocytosis	0	0	0	9** (1.6)
Hepatocellular Adenoma, Multiple	6	6	5	10
Hepatocellular Adenoma (includes multiple)	22	22	14	27
Hepatocellular Carcinoma, Multiple	0	0	2	0
Hepatocellular Carcinoma (includes multiple)	10	7	10	11
Hepatocellular Adenoma or Carcinoma[c]				
Overall rate[d]	28/50 (56%)	26/50 (52%)	22/50 (44%)	34/50 (68%)
Adjusted rate[e]	57.5%	53.7%	44.9%	72.2%
Terminal rate[f]	21/40 (53%)	20/41 (49%)	12/36 (33%)	24/34 (71%)
First incidence (days)	384	495	448	552
Poly-3 test[g]	P=0.026	P=0.431N	P=0.148N	P=0.094
Hepatoblastoma	0	1	0	1

TABLE 22
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Female				
Number Examined Microscopically	49	50	50	50
Eosinophilic Focus	8	6	11	11
Hepatocellular Adenoma, Multiple	3	2	1	3
Hepatocellular Adenoma (includes multiple)[h]				
Overall rate	7/49 (14%)	13/50 (26%)	8/50 (16%)	17/50 (34%)
Adjusted rate	15.6%	29.7%	17.6%	37.2%
Terminal rate	7/37 (19%)	9/28 (32%)	6/35 (17%)	14/36 (39%)
First incidence (days)	735 (T)	532	652	714
Poly-3 test	P=0.024	P=0.089	P=0.511	P=0.016
Hepatocellular Carcinoma, Multiple	0	1	0	0
Hepatocellular Carcinoma (includes multiple)[i]				
Overall rate	4/49 (8%)	16/50 (32%)	6/50 (12%)	5/50 (10%)
Adjusted rate	8.9%	35.5%	13.1%	10.9%
Terminal rate	3/37 (8%)	7/28 (25%)	3/35 (9%)	3/36 (8%)
First incidence (days)	703	488	594	636
Poly-3 test	P=0.115N	P=0.002	P=0.383	P=0.513
Hepatocellular Adenoma or Carcinoma[j]				
Overall rate	11/49 (22%)	27/50 (54%)	14/50 (28%)	20/50 (40%)
Adjusted rate	24.5%	58.4%	30.3%	43.5%
Terminal rate	10/37 (27%)	15/28 (54%)	9/35 (26%)	16/36 (44%)
First incidence (days)	703	488	594	636
Poly-3 test	P=0.339	P<0.001	P=0.351	P=0.043
Hepatoblastoma	0	0	0	1

* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** P≤0.01
(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 441/959 (48.4% ± 12.9%), range 26%-72%
[d] Number of animals with neoplasm per number of animals with liver examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[h] Historical incidence: 144/954 (15.9% ± 6.1%), range 7%-28%
[i] Historical incidence: 69/954 (7.8% ± 4.4%), range 3%-16%
[j] Historical incidence: 203/954 (22.6% ± 9.1%), range 9%-40%

TABLE 23
Incidences of Neoplasms of the Uterus in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Stromal Polyp[a]				
Overall rate[b]	0/49 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate[c]	0.0%	0.0%	4.4%	6.6%
Terminal rate[d]	0/37 (0%)	0/28 (0%)	1/35 (3%)	3/36 (8%)
First incidence (days)	—[f]	—	714	735 (T)
Poly-3 test[e]	P=0.049	—[g]	P=0.239	P=0.121
Stromal Polyp or Stromal Sarcoma[a]				
Overall rate	0/49 (0%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	4.4%	8.8%
Terminal rate	0/37 (0%)	0/28 (0%)	1/35 (3%)	4/36 (11%)
First incidence (days)	—	—	714	735 (T)
Poly-3 test	P=0.013	—	P=0.239	P=0.062

(T) Terminal sacrifice
[a] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 15/959 (1.6% ± 2.2%), range 0%-6%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[f] Not applicable; no neoplasms in animal group
[g] Value of statistic cannot be computed.

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Testis in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Number Examined Microscopically	50	50	50	50
Hyperplasia[a]	2 (1.0)[b]	0	0	0
Interstitial Cell Adenoma[c]				
Overall rate[d]	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate[e]	0.0%	0.0%	0.0%	6.7%
Terminal rate[f]	0/40 (0%)	0/41 (0%)	0/36 (0%)	2/34 (6%)
First incidence (days)	—[h]	—	—	602
Poly-3 test[g]	P=0.007	—[i]	—	P=0.116
Carcinoma	0	0	0	0

[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 10/958 (1.1% ± 1.7%), range 0%-6%
[d] Number of animals with neoplasm per number of animals with testis examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[h] Not applicable; no neoplasms in animal group
[i] Value of statistic cannot be computed

small adenomas from hyperplasia. Two of the interstitial cell adenomas in this study were small, but clearly fit the criteria for adenoma. The third adenoma also fit the criteria, but was marginally larger than the two hyperplasias in the chamber control group. The positive trend in the incidences of interstitial cell adenoma was not considered related to decalin exposure.

Pharmacokinetic Model

Physiologically based pharmacokinetic models representing the uptake, distribution, and metabolism of decalin in rats and mice were developed to describe the processes involved in decalin toxicokinetics (Appendix M). Data used to create the models were obtained from 3-month old male and female rats and mice exposed to decalin in a flow-through chamber at constant concentrations of 25, 100, or 400 ppm for 6 hours (single exposure). At each time point after exposure, blood was taken from four rats and mice, and the decalin concentrations in whole blood were measured. Kidneys were also collected from four male rats and female mice at these time points after exposure and decalin, decalone, and α2u-globulin concentrations were measured.

The models, which are flow-limited with the exception of the fat (diffusion-limited), contains compartments for total blood, liver, kidney, fat, and other organs. The latter compartments represent slowly and rapidly perfused tissues (e.g., skin, muscle, bone, heart, and brain). The model uses a steady-state lung and blood approximation that assumes rapid equilibration between alveolar space, arterial blood, and venous blood. The primary site for decalin metabolism was assumed to be the liver. In the liver, one metabolic pathway was taken into account (Michaelis-Menten). All the physiological parameters (ventilation rate, cardiac output, tissue volumes, capillary volumes, and blood flow rates to the tissues) used in this model were based on values obtained from the literature and scaled to the body weight. Partition coefficients for the different tissues were calculated from the logarithm of the octanol:water partition coefficient. Metabolic rates were estimated by optimizing the model to the available decalin blood time-course data. Goodness of fit was evaluated using a maximum likelihood ratio test.

According to the model, decalin was rapidly taken up into the blood as a result of a high blood:air partition coefficient. There are several conclusions that can be drawn from the physiologically based pharmacokinetic model. First, within each species, males and females metabolized decalin at the same rate. This is supported by the test using a sex/species specific model (12-parameter model). Second, the model predicts a higher rate of metabolism for mice, but this metabolic pathway saturates at a lower concentration in mice than in rats. Third, the model indicates a higher permeability in fat tissue of rats than in fat tissue of mice, which suggests that decalin resides longer in the fat of rats than in the fat of mice.

Genetic Toxicology

Decalin (1 to 10,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535 with or without Aroclor-induced rat or hamster liver S9 enzymes (Table E1). No induction of micronuclei in peripheral blood normochromatic erythrocytes (NCEs) was observed in female mice exposed to 25 to 400 ppm decalin for 3 months by inhalation (Table E2). In contrast to the negative results in females, a small but statistically significant increase in the frequency of micronucleated NCEs was noted in peripheral blood of male mice. A slight increase over the exposure range in the percentage of polychromatic erythrocytes was seen in males and females; all values, however, were within the normal range.

DISCUSSION AND CONCLUSIONS

Decalin was nominated for study because of widespread human exposure and lack of rodent carcinogenicity data. Decalin is among a diverse group of chemicals that is known to cause α2u-globulin accumulation in the kidney of male rats. The current studies of decalin were designed to investigate the potential carcinogenicity of decalin with special emphasis on the relationship between renal α2u-globulin accumulation, nephropathy, and renal carcinogenesis in male rats.

α2u-Globulin Nephropathy

A variety of chemicals, including branched or cyclic petroleum hydrocarbons (Murty *et al.*, 1988; Lehman-McKeeman, 1993; Swenberg and Lehman-McKeeman, 1999), cause α2u-globulin accumulation in the kidney of male rats, and this predisposes the rats to nephropathy and renal carcinogenesis. α2u-Globulin is produced in male rats by the liver parenchymal cells at puberty under the influence of testosterone and several additional interactive hormones (USEPA, 1991); the protein serves as a carrier for pheromone. It is secreted into the blood, filtered through the glomerulus, and partially reabsorbed by endocytosis into proximal tubule epithelial cells of the P2 segment. The fraction that is not absorbed is excreted in the urine, while the reabsorbed portion is catabolized by the lysosomes of the proximal tubule cells. However, binding of hydrocarbon or its metabolite to α2u-globulin changes the conformation of the protein so that it cannot be broken down by lysozymal enzymes. The accumulation of α2u-globulin in the proximal tubule epithelial cells of the P2 segment is thought to cause lysosomal dysfunction and the release of digestive enzymes into the cytoplasm, resulting in degeneration and necrosis of cells lining the proximal tubule (Swenberg *et al.*, 1989). However, this could not be confirmed by electron micrography (Eurell *et al.*, 1990). Subsequently, the necrotic epithelial cells are sloughed into the tubule lumen, and granular casts of necrotic cellular debris accumulate at the junction of the P3 segment of the proximal tubule and the thin loop of Henle. Regenerative proliferation of epithelial cells in the P2 segment occurs in response to the cell loss. The proliferative response may increase the likelihood of fixing DNA damage into heritable mutations or promoting clonal expansion of initiated cells, resulting in carcinogenesis (Melnick, 1992; Lehman-McKeeman, 1993).

Rat Studies

A top exposure concentration of 400 ppm was selected for the 2-week studies based on the 4-hour inhalation LC_{50} of 710 ppm for male Sprague-Dawley rats reported by Gaworski *et al.* (1985). Nine- to ten-week-old rats were used in the current 2-week studies because the kidney effects of short-term decalin exposure would be better demonstrated in male rats of sufficient maturity to synthesize α2u-globulin (Murty *et al.*, 1988). In the current 2-week and 3-month studies, survival and body weight gains were not affected in the 400 ppm groups, but the presence of kidney lesions, the elevation of PCNA labeling indices, the increase in liver weights, and the elimination kinetics data indicating that 400 ppm was above the linear range, suggested that 400 ppm would be an appropriate exposure limit for the current 2-year study in male and female F344/N rats, as outlined in the dose selection principles for NTP studies by Bucher *et al.* (1996).

In the current 2-week rat studies, the major lesion was the α2u-globulin hyaline droplet syndrome that occurred in male F344/N rats, but not in female F344/N or male NBR rats, which do not synthesize appreciable amounts of α2u-globulin. The lesion was characterized by exposure concentration-related increases in α2u-globulin/soluble protein ratios, labeling indices in the kidney, hyaline droplet accumulation, degeneration and regeneration in renal cortical tubules, and granular casts in the renal medulla. The concentrations of the decalin metabolites, *cis*- and *trans*-2-decalone, were similar in the kidneys of all exposed groups of male F344/N rats, indicating that decalone accumulation in the kidney was not exposure concentration-related and may easily be saturated. Kidney decalin levels were not determined in the 2-week study, but they were shown to be exposure concentration-related at 2 weeks in the 3-month study. It is likely that accumulation of decalin, decalone, and α2u-globulin in male F344/N rats led to the histopathologic changes in the kidney.

Similar renal histopathologic changes have been reported in male Fischer 344 rats exposed to 125 ppm decalin by inhalation continuously for 5 days (Kanerva *et al.*, 1987) or to 200 ppm decalin 6 hours per day, 5 days per week for 22 days (MacEwen and Vernot, 1978). Kidney lesions also occurred in male Fischer 344 and Sprague-Dawley rats after 12 to 14 days of gavage administration of decalin (Olson *et al.*, 1986; Stone *et al.*, 1987b; Saito *et al.*, 1992). Eurell *et al.* (1990) reported that exfoliated renal tubule epithelial cells could be seen in the tubular lumen of male Sprague-Dawley rats 24 hours after three daily 60 mg/kg decalin gavage administrations.

An exposure concentration-related increase in absolute and relative kidney weights occurred in male F344/N rats in the current 2-week study. Increases in kidney weights did not occur in male NBR or female F344/N rats. The increase in kidney weights in male F344/N rats was probably related to the increased α2u-globulin (hyaline droplet) accumulation and the histopathologic changes in the kidney.

The absolute and relative liver weights of male and female F344/N and male NBR rats increased in an exposure concentration-related manner in the 2-week studies. There were no accompanying histopathologic changes. The increased liver weights may have been related to increased metabolic enzyme activity (Kanerva *et al.*, 1987). In male F344/N rats, increases in liver weights may also reflect increased synthesis of α2u-globulin (Kohn and Melnick, 1999).

In the current 3-month rat study, hyaline droplets, granular casts, and renal cortex regeneration were present in all exposed groups of male F344/N rats examined, and the incidences and/or severities increased with increasing exposure concentration. The incidences and severities of these lesions were increased at 3 months compared to those in males sacrificed at 2 or 6 weeks, indicating time-related development of these lesions. Other investigators also reported that accumulation of hyaline droplets and formation of granular casts were dose and time dependent (Stone *et al.*, 1987a,b; Read *et al.*, 1988). These renal lesions did not occur in female F344/N rats.

Urinary decalol levels demonstrated that inhaled decalin was metabolized into decalol and excreted. In exposed male rat groups, no further increases in kidney decalin and decalone levels were observed from weeks 6 to 14, whereas kidney α2u-globulin levels continued to increase in all but the 400 ppm group. Binding to α2u-globulin and reabsorption of decalin and decalone were not determined; however, the data clearly showed that not all α2u-globulin bound to decalin and decalone. In exposed female F344/N rats, kidney decalin levels were low compared to those in males. Urinary decalol levels in females were significantly higher than those in males, indicating that decalin was metabolized into decalol and excreted more efficiently in females than in males.

Urinalysis indicated that decalin exposure caused small increases in urine glucose and protein concentrations in males but not in females. Urinary aspartate aminotransferase and lactate dehydrogenase levels were increased in males and females. The increases in males were greater than those in females and were probably related to the renal lesions. In females, the increases were mild and were not accompanied by renal lesions.

In the exposed male F344/N rats, labeling indices in the kidney were increased, but the increases were not exposure concentration or time related. In the current 3-month study, there was an increase in the amount of hyaline droplets within the epithelial cells of the P2 segment of the renal tubule. Based on immunohistochemical assessment and ELISA, the increased protein was α2u-globulin. Histologically, there were a few necrotic cells and mitoses in the affected P2 segment as well as aggregates of these sloughed dead cells in the form of granular casts in the outer strip of the outer medulla. While it is plausible that direct chemical effects could cause a similar scenario of cell death and granular casts, this histological presentation is characteristic of chemicals that induce accumulation of α2u-globulin in the kidney. Less specific, but generally considered a component of the spectrum of these renal changes, is an exacerbation of the spontaneous chronic progressive nephropathy (CPN). In the F344/N male rat, however, it is difficult to assess whether chemical-associated exacerbated nephropathy is an independent event or secondary to the hyaline droplet nephropathy. There clearly are a significant number of chemicals (e.g., trichloroethylene) that caused an exacerbation of the CPN, many with an increase in renal tubule neoplasms, with no evidence of an increase in hyaline droplets (NTP, 1988; Swenberg and Lehman-McKeeman, 1999). Evaluations using PCNA and/or BrdU labeling generally demonstrate increased rates of cell replication with α2u-globulin inducers; however, once again this is a fairly nonspecific response.

In the 2-year rat study, incidences of renal tubule adenoma or carcinoma (combined) were significantly increased in the 50, 100, and 400 ppm groups of males. The incidences of renal tubule hyperplasia, papilla mineralization, and pelvis transitional epithelial hyperplasia were also significantly increased in exposed groups of males. α2u-Globulin production in male F344/N rats declines later in life, and evidence of α2u-globulin nephropathy would be expected to diminish even in rats continuously exposed to decalin. Increased incidences and severities of hyaline droplet accumulation of the kidney occurred in rats that died early in the 25 to 100 ppm groups. The development of neoplasms, renal tubule hyperplasia, papilla mineralization, and pelvis transitional epithelial hyperplasia of the kidney in males was likely related to hyaline droplet accumulation that occurred earlier in life; neither α2u-globulin or chemical-related kidney lesions occurred in female rats.

In the 2-year rat study, the incidences of benign or malignant pheochromocytoma (combined) of the adrenal gland in 100 and 400 ppm males were significantly increased. Previous NTP studies revealed a significant association between severe nephropathy and pheochromocytoma in male F344/N rats (Nyska *et al.*, 1999), and a similar correlation occurred in the present study. Logistic regression procedures revealed a significant ($P<0.05$) association between nephropathy severity and the occurrence of pheochromocytoma after adjusting for differences in survival. However, since nephropathy severity was highly correlated ($P<0.001$) with increasing exposure concentrations of decalin, it was not possible to determine with certainty if the increases in the incidences of pheochromocytoma were indirect effects of decalin exposure resulting from an increased nephropathy severity, or if it was a direct effect of decalin exposure unrelated to the nephropathy severity. Either of these conclusions is consistent with the data. However, the correlation between pheochromocytoma occurrence and nephropathy severity was stronger than the correlation between pheochromocytoma occurrence and either survival or exposure concentration. Irritation of the respiratory tract tissues was not observed.

Mouse Studies

In the 2-week and 3-month mouse studies, liver weights of 200 and 400 ppm males and females were greater than those of the chamber controls. In the 3-month study, the incidences of centrilobular cytomegaly of the liver were increased in males exposed to 50 ppm or greater. The decrease in spermatid heads/testis was not supported by other spermatid and sperm measurements and is considered of no biological significance.

In the 2-year mouse study, the incidences of hepatocellular adenoma or carcinoma (combined) occurred with a positive trend in males, and increased incidences of eosinophilic focus, centrilobular hypertrophy, necrosis, and syncytial alteration occurred in 400 ppm males. Decalin was considered hepatotoxic in male mice. The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in 25 and 400 ppm females. In the absence of an exposure concentration-related response in either sex, the hepatocarcinogenic effect of decalin in female mice was considered an equivocal finding, and in males, the response was so weak it was considered no evidence of carcinogenic activity. Interestingly, Gaworski *et al.* (1985) reported that female C57BL/6 mice exposed to 283 mg/m^3 decalin for 90 days by inhalation developed a slight increase in hepatocellular neoplasm incidence during lifetime postexposure observation; the tumor rate was not given.

Gaworski *et al.* (1985) reported that female C57BL/6 mice exposed to 5 or 50 ppm decalin 24 hours per day for 90 days developed hepatocellular cytoplasmic vacuolization, an indication of fatty change. The lesion disappeared 19 months after exposure. In the current 3-month mouse study, hepatocellular cytoplasmic vacuolization did not occur.

In the current 2-year study, the incidences of stromal polyp and stromal polyp or stromal sarcoma (combined) of the uterus were increased in 100 and 400 ppm female mice. Although the increased incidences were not significant, positive trends did occur, and the combined incidence in the 400 ppm group exceeded the historical control range. Therefore, this response was also considered an equivocal finding in female mice.

Gaworski *et al.* (1985) also reported that male Fischer 344 rats and female C57BL/6 mice exposed to 0, 5, or 50 ppm decalin vapor for 13 weeks developed pituitary gland tumors after a 19-month postexposure observation period. No pituitary gland neoplasms occurred in mice in the current 2-year study.

CONCLUSIONS

Under the conditions of these studies, there was *clear evidence of carcinogenic activity** of decalin in male F344/N rats based on increased incidences of renal tubule neoplasms. The increased incidences of benign or malignant pheochromocytoma (combined) of the adrenal medulla in male rats were also considered to be exposure related. There was *no evidence of carcinogenic activity* of decalin in female F344/N rats exposed to 25, 100, or 400 ppm. There was *no evidence of carcinogenic activity* of decalin in male $B6C3F_1$ mice exposed to 25, 100, or 400 ppm. There was *equivocal evidence of carcinogenic activity* of decalin in female $B6C3F_1$ mice based on marginally increased incidences of hepatocellular and uterine neoplasms.

Exposure of male rats to decalin resulted in nonneoplastic lesions of the kidney characteristic of α2u-globulin accumulation. Nonneoplastic lesions of the liver were observed in male mice exposed to decalin.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF DECALIN

TABLE A1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin 78
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Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	20
Early deaths					
Moribund	17	21	23	23	6
Natural deaths	5	6	3	7	
Survivors					
Terminal sacrifice	28	23	23	20	14
Missexed			1		
Animals examined microscopically	50	50	49	50	20
Alimentary System					
Intestine large, colon	(48)	(47)	(48)	(49)	(20)
Polyp adenomatous		1 (2%)			
Intestine small, jejunum	(47)	(45)	(46)	(47)	(20)
Intestine small, ileum	(46)	(45)	(46)	(48)	(20)
Leiomyoma				1 (2%)	
Liver	(50)	(50)	(49)	(50)	(20)
Histiocytic sarcoma		1 (2%)			
Histiocytic sarcoma, metastatic, skeletal muscle		1 (2%)			
Mesentery	(16)	(19)	(20)	(13)	(10)
Carcinoma, metastatic, urinary bladder		1 (5%)			
Schwannoma malignant				1 (8%)	
Oral mucosa		(2)	(2)	(1)	
Pharyngeal, squamous cell carcinoma				1 (100%)	
Pharyngeal, squamous cell papilloma		1 (50%)	2 (100%)		
Pancreas	(50)	(50)	(49)	(50)	(20)
Carcinoma			1 (2%)		
Carcinoma, metastatic, kidney		1 (2%)			
Salivary glands	(50)	(50)	(49)	(50)	(20)
Sarcoma			1 (2%)		
Schwannoma malignant				1 (2%)	
Stomach, glandular	(50)	(50)	(49)	(50)	(20)
Tongue		(1)	(2)	(1)	
Squamous cell papilloma		1 (100%)	1 (50%)		
Endocrine System					
Adrenal medulla	(49)	(49)	(49)	(49)	(20)
Pheochromocytoma malignant	2 (4%)		2 (4%)	7 (14%)	3 (15%)
Pheochromocytoma benign	7 (14%)	8 (16%)	10 (20%)	9 (18%)	4 (20%)
Bilateral, pheochromocytoma benign		1 (2%)	1 (2%)	1 (2%)	2 (10%)
Islets, pancreatic	(50)	(50)	(49)	(50)	(20)
Adenoma	3 (6%)	3 (6%)	3 (6%)	2 (4%)	1 (5%)
Carcinoma	4 (8%)	1 (2%)		4 (8%)	
Pituitary gland	(50)	(50)	(49)	(49)	(20)
Craniopharyngeal duct, craniopharyngioma		1 (2%)			
Pars distalis, adenoma	27 (54%)	33 (66%)	25 (51%)	25 (51%)	9 (45%)
Pars distalis, carcinoma			1 (2%)	1 (2%)	
Thyroid gland	(50)	(50)	(49)	(49)	(20)
C-cell, adenoma	7 (14%)	4 (8%)	4 (8%)	3 (6%)	2 (10%)
C-cell, carcinoma		2 (4%)	1 (2%)		
Follicular cell, carcinoma			1 (2%)	1 (2%)	

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
General Body System					
Peritoneum		(2)	(2)	(2)	
Genital System					
Epididymis	(50)	(50)	(49)	(50)	(20)
Preputial gland	(50)	(49)	(49)	(50)	(20)
Adenoma		1 (2%)	1 (2%)		
Carcinoma		1 (2%)	1 (2%)	3 (6%)	2 (10%)
Prostate, NOS	(50)	(50)	(49)	(50)	(20)
Carcinoma, metastatic, urinary bladder		1 (2%)			
Ventral, adenoma		1 (2%)			
Seminal vesicle	(50)	(50)	(49)	(50)	(20)
Carcinoma, metastatic, kidney		1 (2%)			
Testes	(50)	(50)	(49)	(50)	(20)
Bilateral, interstitial cell, adenoma	34 (68%)	31 (62%)	39 (80%)	29 (58%)	16 (80%)
Interstitial cell, adenoma	6 (12%)	10 (20%)	8 (16%)	15 (30%)	4 (20%)
Hematopoietic System					
Bone marrow	(50)	(50)	(49)	(50)	(20)
Histiocytic sarcoma		1 (2%)			
Lymph node	(8)	(10)	(14)	(11)	(1)
Deep cervical, carcinoma, metastatic, kidney		1 (10%)			
Pancreatic, histiocytic sarcoma		1 (10%)			
Lymph node, bronchial	(7)	(8)	(18)	(17)	(7)
Lymph node, mandibular	(3)	(2)		(3)	(1)
Lymph node, mesenteric	(50)	(50)	(49)	(49)	(20)
Carcinoma, metastatic, urinary bladder		1 (2%)			
Histiocytic sarcoma, metastatic, skeletal muscle		1 (2%)			
Lymph node, mediastinal	(48)	(45)	(44)	(48)	(16)
Carcinoma, metastatic, kidney		1 (2%)			
Spleen	(50)	(50)	(49)	(50)	(20)
Capsule, carcinoma, metastatic, kidney		1 (2%)			
Thymus	(50)	(48)	(47)	(50)	(20)
Integumentary System					
Mammary gland	(50)	(50)	(49)	(50)	(20)
Adenoma	1 (2%)				
Carcinoma	1 (2%)	1 (2%)		1 (2%)	
Fibroadenoma	2 (4%)	1 (2%)	3 (6%)	1 (2%)	
Skin	(50)	(50)	(49)	(50)	(20)
Basal cell adenoma	1 (2%)	2 (4%)			1 (5%)
Keratoacanthoma	1 (2%)	2 (4%)		1 (2%)	
Squamous cell papilloma	1 (2%)		1 (2%)		
Trichoepithelioma				1 (2%)	
Pinna, neural crest tumor	1 (2%)		1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)	5 (10%)	3 (6%)	2 (4%)	1 (5%)
Subcutaneous tissue, fibrosarcoma	2 (4%)			1 (2%)	
Subcutaneous tissue, lipoma		1 (2%)	1 (2%)		
Subcutaneous tissue, schwannoma benign			1 (2%)		
Subcutaneous tissue, schwannoma malignant	1 (2%)				

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Musculoskeletal System					
Bone	(50)	(50)	(49)	(50)	(20)
Osteosarcoma				1 (2%)	
Cranium, osteoma				1 (2%)	
Cranium, squamous cell carcinoma, metastatic, oral mucosa				1 (2%)	
Skeletal muscle		(1)		(5)	
Histiocytic sarcoma		1 (100%)			
Nervous System					
Brain	(50)	(50)	(49)	(50)	(20)
Carcinoma, metastatic, pituitary gland		1 (2%)	1 (2%)	1 (2%)	
Respiratory System					
Lung	(50)	(50)	(49)	(50)	(20)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)	
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)		1 (5%)
Carcinoma, metastatic, kidney		1 (2%)		1 (2%)	
Carcinoma, metastatic, urinary bladder		1 (2%)			
Histiocytic sarcoma, metastatic, liver		1 (2%)			
Histiocytic sarcoma, metastatic, skeletal muscle		1 (2%)			
Neural crest tumor, metastatic, skin			1 (2%)		
Pleura	(9)	(8)	(8)	(5)	(6)
Special Senses System					
Eye		(2)	(2)	(2)	(1)
Carcinoma, metastatic, pituitary gland		1 (50%)			
Harderian gland	(1)			(2)	
Squamous cell carcinoma, metastatic, oral mucosa				1 (50%)	
Zymbal's gland			(2)	(2)	
Carcinoma			2 (100%)	2 (100%)	
Urinary System					
Kidney	(50)	(50)	(49)	(50)	(20)
Histiocytic sarcoma, metastatic, liver		1 (2%)			
Histiocytic sarcoma, metastatic, skeletal muscle		1 (2%)			
Bilateral, renal tubule, carcinoma		1 (2%)			
Cortex, renal tubule, adenoma	1 (2%)	2 (4%)	6 (12%)	9 (18%)	3 (15%)
Cortex, renal tubule, adenoma, multiple					1 (5%)
Cortex, renal tubule, carcinoma			1 (2%)	4 (8%)	1 (5%)
Pelvis, transitional epithelium, carcinoma	1 (2%)				
Pelvis, transitional epithelium, papilloma		1 (2%)			
Renal tubule, adenoma					1 (5%)
Urinary bladder	(50)	(49)	(49)	(49)	(20)
Transitional epithelium, carcinoma		1 (2%)			
Transitional epithelium, papilloma				1 (2%)	

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(49)	(50)	(20)
Histiocytic sarcoma		2 (4%)			
Leukemia mononuclear	19 (38%)	23 (46%)	27 (55%)	25 (50%)	10 (50%)
Lymphoma malignant			1 (2%)	1 (2%)	
Mesothelioma malignant	1 (2%)	2 (4%)	2 (4%)	5 (10%)	
Neoplasm Summary					
Total animals with primary neoplasms[c]	49	50	49	50	20
Total primary neoplasms	127	145	154	161	62
Total animals with benign neoplasms	47	49	49	48	20
Total benign neoplasms	94	111	111	102	45
Total animals with malignant neoplasms	27	28	32	42	13
Total malignant neoplasms	32	34	42	59	17
Total animals with metastatic neoplasms		5	2	4	
Total metastatic neoplasms		18	2	16	
Total animals with uncertain neoplasms–benign or malignant	1		1		
Total uncertain neoplasms	1		1		

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	387	421	561	561	572	577	581	589	614	628	638	638	658	666	680	680	688	694	694	700	706	728	733	733	733
Carcass ID Number	031	042	039	043	050	016	038	003	011	037	023	046	044	017	001	008	021	033	047	029	048	020	005	007	012
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+		+		+	+							+			+	+	+	+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pheochromocytoma malignant																					X				
Pheochromocytoma benign			X																		X	X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X						X						
Carcinoma		X							X																
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X	X			X	X	X		X				X	X	X		X	X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X														X				
General Body System																									
None																									
Genital System																									
Coagulating gland																		+							
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma											X		X	X	X	X	X		X	X	X	X	X	X	X
Interstitial cell, adenoma							X		X									X							

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	013	015	019	022	024	026	027	028	034	045	002	004	006	009	010	014	018	025	030	032	035	036	040	041	049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+	+				+	+				+					+						+				16
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth													+													1
Cardiovascular System																										
Blood vessel		+			+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	44
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant								X																		2
Pheochromocytoma benign		X										X									X			X		7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									3
Carcinoma											X												X			4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X			X				X	X		X	X	X	X	X	X		X		X		X		27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X	X	X			X		X																	7
General Body System																										
None																										
Genital System																										
Coagulating gland												+										+				3
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	34
Interstitial cell, adenoma									X	X			X													6

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	387	421	561	561	572	577	581	589	614	628	638	638	658	666	680	680	688	694	694	700	706	728	733	733	733
Carcass ID Number	031	042	039	043	050	016	038	003	011	037	023	046	044	017	001	008	021	033	047	029	048	020	005	007	012
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+	+	+		+		+				
Lymph node, bronchial	M	M	M	M	A	M	M	M	M	M	+	M	+	M	+	+	M	M	M	+	M	+	M	M	M
Lymph node, mandibular	M	M	M	M	A	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Fibroadenoma																						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma									X																
Keratoacanthoma																X									
Squamous cell papilloma																									
Pinna, neural crest tumor																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma	X																								
Subcutaneous tissue, schwannoma, malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura													+												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	013	015	019	022	024	026	027	028	034	045	002	004	006	009	010	014	018	025	030	032	035	036	040	041	049	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+				+																		8
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	7
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	+	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Carcinoma													X													1
Fibroadenoma				X																						2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Keratoacanthoma																										1
Squamous cell papilloma								X																		1
Pinna, neural crest tumor																								X		1
Subcutaneous tissue, fibroma									X		X															2
Subcutaneous tissue, fibrosarcoma																									X	2
Subcutaneous tissue, schwannoma, malignant			X																							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma								X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura	+	+		+	+				+			+										+	+			9
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland			+																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	387	421	561	561	572	577	581	589	614	628	638	638	658	666	680	680	688	694	694	700	706	728	733	733	733
Carcass ID Number	031	042	039	043	050	016	038	003	011	037	023	046	044	017	001	008	021	033	047	029	048	020	005	007	012
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, renal tubule, adenoma																									
Pelvis, transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X		X		X	X	X	X	X		X	X	X	X			
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	013	015	019	022	024	026	027	028	034	045	002	004	006	009	010	014	018	025	030	032	035	036	040	041	049	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, renal tubule, adenoma																									X	1
Pelvis, transitional epithelium, carcinoma																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X	X		X							X			X	X	X						19
Mesothelioma malignant							X																			1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	315	509	525	532	538	561	567	581	581	589	592	638	638	644	652	670	673	681	688	694	701	708	708	721	722
Carcass ID Number	208	244	234	204	222	228	246	215	248	247	227	206	223	214	226	201	203	235	216	210	218	213	229	233	217
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Polyp adenomatous																									
Intestine large, rectum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, cecum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+
Intestine small, duodenum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, jejunum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	A	+
Intestine small, ileum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Histiocytic sarcoma, metastatic, skeletal muscle														X											
Mesentery			+					+			+		+				+	+	+		+				
Carcinoma, metastatic, urinary bladder								X																	
Oral mucosa																			+						
Pharyngeal, squamous cell papilloma																			X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X															
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			X
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Craniopharyngeal duct, craniopharyngioma					X																				
Pars distalis, adenoma		X	X		X	X					X	X	X			X	X	X	X	X	X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X				X	
C-cell, carcinoma																									
General Body System																									
Peritoneum																			+				+		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	722	725	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	
Carcass ID Number	225	211	202	205	207	212	221	224	230	231	239	242	243	245	249	250	209	219	220	232	236	237	238	240	241	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous										X																1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Histiocytic sarcoma, metastatic, skeletal muscle																										1
Mesentery	+	+			+		+				+			+			+	+				+	+		+	19
Carcinoma, metastatic, urinary bladder																										1
Oral mucosa							+																			2
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney							X																			1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign				X	X		X			X								X		X		X				8
Bilateral, pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									3
Carcinoma							X																			1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Craniopharyngeal duct, craniopharyngioma																										1
Pars distalis, adenoma	X	X	X	X	X	X	X			X	X			X	X	X	X		X			X	X			33
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X							X																	4
C-cell, carcinoma				X																					X	2
General Body System																										
Peritoneum																										2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	315	509	525	532	538	561	567	581	581	589	592	638	638	644	652	670	673	681	688	694	701	708	708	721	722
Carcass ID Number	208	244	234	204	222	228	246	215	248	247	227	206	223	214	226	201	203	235	216	210	218	213	229	233	217
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis					+																				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma													X												
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder								X																	
Ventral, adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X	X	X			X	X	X	X		X	X			X	X		
Interstitial cell, adenoma				X	X		X					X					X				X			X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Lymph node		+		+		+			+	+					+					+		+			
Deep cervical, carcinoma, metastatic, kidney																									
Pancreatic, histiocytic sarcoma		X																							
Lymph node, bronchial	M	M	M	M	M	+	M	+	M	M	M	M	+	M	+	M	M	M	M	+	M	+	M	M	+
Lymph node, mandibular	M	M	M	M	M	M	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder								X																	
Histiocytic sarcoma, metastatic, skeletal muscle														X											
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, carcinoma, metastatic, kidney																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																X									
Keratoacanthoma			X													X									
Subcutaneous tissue, fibroma				X													X						X		
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+											
Histiocytic sarcoma														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	722	725	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	
Carcass ID Number	225	211	202	205	207	212	221	224	230	231	239	242	243	245	249	250	209	219	220	232	236	237	238	240	241	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																X										1
Carcinoma																										1
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, urinary bladder																									1	
Ventral, adenoma															X											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney							X																			1
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	31
Interstitial cell, adenoma				X	X																					10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node							+									+										10
Deep cervical, carcinoma, metastatic, kidney							X																			1
Pancreatic, histiocytic sarcoma																										1
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	8
Lymph node, mandibular	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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, urinary bladder																										1
Histiocytic sarcoma, metastatic, skeletal muscle																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	45
Carcinoma, metastatic, kidney							X																			1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, carcinoma, metastatic, kidney							X																			1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma							X																			1
Fibroadenoma									X																	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma											X															2
Keratoacanthoma																										2
Subcutaneous tissue, fibroma																					X	X				5
Subcutaneous tissue, lipoma																						X				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Histiocytic sarcoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	315	509	525	532	538	561	567	581	581	589	592	638	638	644	652	670	673	681	688	694	701	708	708	721	722
Carcass ID Number	208	244	234	204	222	228	246	215	248	247	227	206	223	214	226	201	203	235	216	210	218	213	229	233	217
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland					X																				
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, kidney																									
Carcinoma, metastatic, urinary bladder								X																	
Histiocytic sarcoma, metastatic, liver		X																							
Histiocytic sarcoma, metastatic, skeletal muscle														X											
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura					+																+		+		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+				+																
Carcinoma, metastatic, pituitary gland					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, liver		X																							
Histiocytic sarcoma, metastatic, skeletal muscle														X											
Bilateral, renal tubule, carcinoma																									
Cortex, renal tubule, adenoma														X											
Pelvis, transitional epithelium, papilloma																									
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma								X																	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X												X											
Leukemia mononuclear	X					X	X	X	X	X		X	X		X	X		X		X		X		X	X
Mesothelioma malignant																			X				X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	722	725	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	
Carcass ID Number	225	211	202	205	207	212	221	224	230	231	239	242	243	245	249	250	209	219	220	232	236	237	238	240	241	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X															1
Carcinoma, metastatic, kidney							X																			1
Carcinoma, metastatic, urinary bladder																										1
Histiocytic sarcoma, metastatic, liver																										1
Histiocytic sarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura								+										+		+	+				+	8
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Carcinoma, metastatic, pituitary gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, liver																										1
Histiocytic sarcoma, metastatic, skeletal muscle																										1
Bilateral, renal tubule, carcinoma							X																			1
Cortex, renal tubule, adenoma		X																								2
Pelvis, transitional epithelium, papilloma											X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, carcinoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Leukemia mononuclear				X		X	X				X					X	X			X	X					23
Mesothelioma malignant																										2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 50 ppm

Number of Days on Study	574	596	602	605	610	617	617	638	652	658	665	666	671	680	680	680	688	694	699	699	708	715	715	716
Carcass ID Number	433	431	424	404	429	401	432	447	439	446	405	406	412	435	436	442	418	425	438	443	420	410	426	403
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, ileum	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+		+	+					+	+			+	+		+	+		+		+	
Oral mucosa																								
Pharyngeal, squamous cell papilloma																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								X
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																								
Squamous cell papilloma																								
Tooth																		+						
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant								X												X				
Pheochromocytoma benign			X			X					X					X								
Bilateral, pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X							X	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X						X	X		X				X	X				X		X		X	X
Pars distalis, carcinoma						X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma			X													X								
C-cell, carcinoma																								
Follicular cell, carcinoma										X														
General Body System																								
Peritoneum																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 50 ppm

Number of Days on Study	718	722	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	430	417	413	414	419	421	422	427	428	437	440	448	450	402	407	408	409	411	415	416	423	441	444	445	449	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery	+				+		+	+								+				+	+		+		+	20
Oral mucosa													+										+			2
Pharyngeal, squamous cell papilloma													X										X			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma										X																1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue						+																			+	2
Squamous cell papilloma						X																				1
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										2
Pheochromocytoma benign							X					X				X			X				X	X		10
Bilateral, pheochromocytoma benign	X																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																	3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X					X	X		X	X	X	X	X		X	X		X	X		X	X		X		25
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma						X											X									4
C-cell, carcinoma																X										1
Follicular cell, carcinoma																										1
General Body System																										
Peritoneum												+						+								2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 50 ppm

Number of Days on Study	574	596	602	605	610	617	617	638	652	658	665	666	671	680	680	680	688	694	694	699	708	715	715	716
Carcass ID Number	433	431	424	404	429	401	432	447	439	446	405	406	412	435	436	442	418	425	438	443	420	410	426	403
Genital System																								
Coagulating gland																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma								X																
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X			X		X	X		X	X	X		X	X	X	X			X	X	X	X
Interstitial cell, adenoma				X	X		X							X					X	X				
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+	+			+		+						+				+	+	+	
Lymph node, bronchial	M	+	M	+	+	+	M	+	+	M	+	M	M	M	+	M	+	M	M	+	+	M	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma												X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Pinna, neural crest tumor													X											
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, lipoma																					X			
Subcutaneous tissue, schwannoma benign																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland						X																		
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X					
Alveolar/bronchiolar carcinoma																		X						
Neural crest tumor, metastatic, skin													X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																			+		+			+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 50 ppm

Number of Days on Study	718	722	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	430	417	413	414	419	421	422	427	428	437	440	448	450	402	407	408	409	411	415	416	423	441	444	445	449	Total Tissues/ Tumors
Genital System																										
Coagulating gland							+																			1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X														1
Carcinoma																										1
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	39
Interstitial cell, adenoma	X																X									8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+					+	+											+			+					14
Lymph node, bronchial	M	M	M	M	M	M	M	+	+	M	+	M	M	M	M	M	M	+	M	M	+	M	M	+	+	18
Lymph node, mandibular	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	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma													X						X							3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																		X								1
Pinna, neural crest tumor																										1
Subcutaneous tissue, fibroma												X					X	X								3
Subcutaneous tissue, lipoma																										1
Subcutaneous tissue, schwannoma benign																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma								X																		2
Alveolar/bronchiolar carcinoma																										1
Neural crest tumor, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura		+					+								+		+	+								8
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 50 ppm

Number of Days on Study	574	596	602	605	610	617	617	638	652	658	665	666	671	680	680	680	688	694	694	699	708	715	715	716
Carcass ID Number	433	431	424	404	429	401	432	447	439	446	405	406	412	435	436	442	418	425	438	443	420	410	426	403
Special Senses System																								
Eye					+																			
Lacrimal gland																								+
Zymbal's gland																				+				
Carcinoma																				X				
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, renal tubule, adenoma														X										X
Cortex, 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		X	X	X	X	
Lymphoma malignant																								
Mesothelioma malignant																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 50 ppm

Number of Days on Study	718	722	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	430	417	413	414	419	421	422	427	428	437	440	448	450	402	407	408	409	411	415	416	423	441	444	445	449	Total Tissues/ Tumors
Special Senses System																										
Eye																						+				2
Lacrimal gland																		+								2
Zymbal's gland												+														2
Carcinoma												X														2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortex, renal tubule, adenoma					X	X														X					X	6
Cortex, renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear		X	X	X				X	X		X					X			X		X					27
Lymphoma malignant																X										1
Mesothelioma malignant												X						X								2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	379	419	506	529	561	567	600	613	615	617	617	634	634	638	649	652	669	673	679	687	687	687	688	688	705
Carcass ID Number	649	630	605	636	601	640	624	650	607	631	647	611	615	617	635	644	626	638	645	618	625	633	632	646	612
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant, metastatic, testes		X																							
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes		X																							
Mesentery		+								+				+			+			+					
Mesothelioma malignant, metastatic, testes		X																							
Schwannoma malignant																									
Oral mucosa																			+						
Pharyngeal, squamous cell carcinoma																			X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes		X																							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant, metastatic, testes		X																							
Tongue																			+						
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+		+		+		+	+	+		+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes		X																							
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pheochromocytoma malignant			X												X										X
Pheochromocytoma benign							X												X	X					
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X					X					
Carcinoma																							X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X			X	X	X		X	X		X			X	X	X		X	X	X	X	X	
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X										X					
Follicular cell, carcinoma																		X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	708	715	716	722	722	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	
Carcass ID Number	627	639	643	634	648	602	604	606	610	613	614	619	621	622	623	629	637	641	642	603	608	609	616	620	628	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Serosa, mesothelioma malignant, metastatic, testes																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma																	X									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Mesentery	+						+	+								+	+			+	+			+		13
Mesothelioma malignant, metastatic, testes																										1
Schwannoma malignant																					X					1
Oral mucosa																										1
Pharyngeal, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant															X											1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, mesothelioma malignant, metastatic, testes																										1
Tongue																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	45
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant				X			X			X		X														7
Pheochromocytoma benign			X			X	X							X	X		X									9
Bilateral, pheochromocytoma benign											X															1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Carcinoma																X						X		X		4
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X			X			X			X		X	X		X	X			X					X	25
Pars distalis, carcinoma																						X				1
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma														X												3
Follicular cell, carcinoma																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	379	419	506	529	561	567	600	613	615	617	617	634	634	638	649	652	669	673	679	687	687	687	688	688	705
Carcass ID Number	649	630	605	636	601	640	624	650	607	631	647	611	615	617	635	644	626	638	645	618	625	633	632	646	612
General Body System																									
Peritoneum																									
Tissue NOS									+																
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X					X			X	X		X		X		X	X	X				X
Interstitial cell, adenoma		X	X		X	X	X			X				X		X		X				X		X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+								+		+		+			+	+			+		
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	+	M	M	M	+	M	+	M	M	+
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Mesothelioma malignant, metastatic, testes		X																							
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes		X																							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma			X																						
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																								X	
Cranium, osteoma																									
Cranium, squamous cell carcinoma, metastatic, oral mucosa																			X						
Skeletal muscle		+												+										+	
Mesothelioma malignant, metastatic, testes		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	708	715	716	722	722	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	
Carcass ID Number	627	639	643	634	648	602	604	606	610	613	614	619	621	622	623	629	637	641	642	603	608	609	616	620	628	Total Tissues/ Tumors
General Body System																										
Peritoneum			+													+										2
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma							X																	X		3
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	29
Interstitial cell, adenoma					X											X				X		X				15
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+									+												+		11
Lymph node, bronchial	+	M	+	+	+	+	M	M	M	M	M	M	+	+	M	M	M	+	M	+	+	M	+	M	M	17
Lymph node, mandibular	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma		X																								1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma													X													1
Trichoepithelioma									X																	1
Subcutaneous tissue, fibroma											X															2
Subcutaneous tissue, fibrosarcoma																				X						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Cranium, osteoma																						X				1
Cranium, squamous cell carcinoma, metastatic, oral mucosa																										1
Skeletal muscle		+	+																							5
Mesothelioma malignant, metastatic, testes																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																						X				1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	379	419	506	529	561	567	600	613	615	617	617	634	634	638	649	652	669	673	679	687	687	687	688	688	688	705
Carcass ID Number	649	630	605	636	601	640	624	650	607	631	647	611	615	617	635	644	626	638	645	618	625	633	632	646	646	612
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Carcinoma, metastatic, kidney																					X					
Mesothelioma malignant, metastatic, testes		X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura		+																								
Mesothelioma malignant, metastatic, testes		X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye								+																		
Harderian gland					+														+							
Squamous cell carcinoma, metastatic, oral mucosa																			X							
Lacrimal gland												+														
Zymbal's gland																									+	
Carcinoma																									X	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, mesothelioma malignant, metastatic, testes		X																								
Cortex, renal tubule, adenoma											X					X	X						X			
Cortex, renal tubule, carcinoma											X										X					
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																										X
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X		X			X	X	X	X	X				X		X	X			X
Lymphoma malignant																										
Mesothelioma malignant		X																		X						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	708	715	716	722	722	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734		
Carcass ID Number	627	639	643	634	648	602	604	606	610	613	614	619	621	622	623	629	637	641	642	603	608	609	616	620	628		Total Tissues/ Tumors
Respiratory System																											
Larynx	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma																							X				1
Carcinoma, metastatic, kidney																											1
Mesothelioma malignant, metastatic, testes																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pleura					+													+					+		+		5
Mesothelioma malignant, metastatic, testes																											1
Trachea	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Special Senses System																											
Eye																								+			2
Harderian gland																											2
Squamous cell carcinoma, metastatic, oral mucosa																											1
Lacrimal gland																											1
Zymbal's gland							+																				2
Carcinoma							X																				2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Capsule, mesothelioma malignant, metastatic, testes																											1
Cortex, renal tubule, adenoma						X								X	X		X							X			9
Cortex, renal tubule, carcinoma													X									X					4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Transitional epithelium, papilloma																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear	X		X		X	X	X	X	X	X	X	X	X					X									25
Lymphoma malignant		X																									1
Mesothelioma malignant			X													X									X		5

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	433	694	706	708	708	716	733	733	733	733	733	733	734	734	734	734	734	734	734	734	
Carcass ID Number	819	806	810	807	813	802	803	805	808	809	818	820	801	804	811	812	814	815	816	817	Total Tissues/ Tumors
Alimentary System																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Mesentery				+				+		+	+	+	+	+		+		+		+	10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Tooth														+							1
Cardiovascular System																					
Blood vessel		+			+	+	+		+		+	+					+	+	+	+	11
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Endocrine System																					
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pheochromocytoma malignant						X			X	X											3
Pheochromocytoma benign					X				X			X				X					4
Bilateral, pheochromocytoma benign				X													X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adenoma										X											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pars distalis, adenoma		X	X	X		X		X		X			X		X					X	9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
C-cell, adenoma				X			X														2
General Body System																					
None																					
Genital System																					
Coagulating gland									+												1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Carcinoma								X	X												2
Prostate, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Bilateral, interstitial cell, adenoma		X	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	16
Interstitial cell, adenoma	X			X		X		X													4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	433	694	706	708	708	716	733	733	733	733	733	733	734	734	734	734	734	734	734	734	
Carcass ID Number	819	806	810	807	813	802	803	805	808	809	818	820	801	804	811	812	814	815	816	817	Total Tissues/ Tumors
Hematopoietic System																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node	+																				1
Lymph node, bronchial	M	M	+	+	M	M	M	+	+	M	+	M	M	M	+	M	M	M	M	+	7
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node, mediastinal	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	16
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Integumentary System																					
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Basal cell adenoma												X									1
Subcutaneous tissue, fibroma							X														1
Musculoskeletal System																					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Nervous System																					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Respiratory System																					
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Alveolar/bronchiolar carcinoma										X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pleura			+			+						+				+	+	+			6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Special Senses System																					
Eye			+																		1
Lacrimal gland							+														1
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Cortex, renal tubule, adenoma								X		X										X	3
Cortex, renal tubule, adenoma, multiple						X															1
Cortex, renal tubule, carcinoma					X																1
Renal tubule, adenoma													X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Leukemia mononuclear	X	X	X	X	X					X	X		X			X	X				10

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma					
Overall rate[a]	7/49 (14%)	9/49 (18%)	11/49 (22%)	10/49 (20%)	6/20 (30%)
Adjusted rate[b]	16.7%	22.0%	25.0%	24.8%	31.8%
Terminal rate[c]	4/28 (14%)	8/23 (35%)	6/23 (26%)	6/20 (30%)	4/14 (29%)
First incidence (days)	561	589	602	600	708
Poly-3 test[d]	P=0.173	P=0.368	P=0.247	P=0.261	P=0.155
Adrenal Medulla: Malignant Pheochromocytoma					
Overall rate	2/49 (4%)	0/49 (0%)	2/49 (4%)	7/49 (14%)	3/20 (15%)
Adjusted rate	4.8%	0.0%	4.6%	17.3%	16.0%
Terminal rate	1/28 (4%)	0/23 (0%)	0/23 (0%)	3/20 (15%)	2/14 (14%)
First incidence (days)	706	—[e]	638	506	716
Poly-3 test	P=0.034	P=0.242N	P=0.679N	P=0.072	P=0.166
Adrenal Medulla: Benign or Malignant Pheochromocytoma					
Overall rate	8/49 (16%)	9/49 (18%)	13/49 (27%)	16/49 (33%)	8/20 (40%)
Adjusted rate	19.1%	22.0%	29.2%	38.6%	42.2%
Terminal rate	5/28 (18%)	8/23 (35%)	6/23 (26%)	8/20 (40%)	5/14 (36%)
First incidence (days)	561	589	602	506	708
Poly-3 test	P=0.038	P=0.476	P=0.196	P=0.038	P=0.049
Kidney (Renal Tubule): Adenoma					
Overall rate	1/50 (2%)	2/50 (4%)	6/49 (12%)	9/50 (18%)	5/20 (25%)
Adjusted rate	2.4%	4.9%	14.0%	21.8%	26.7%
Terminal rate	1/28 (4%)	0/23 (0%)	4/23 (17%)	5/20 (25%)	4/14 (29%)
First incidence (days)	733 (T)	644	680	617	716
Poly-3 test	P=0.005	P=0.492	P=0.058	P=0.007	P=0.004
Kidney (Renal Tubule): Carcinoma					
Overall rate	0/50 (0%)	1/50 (2%)	1/49 (2%)	4/50 (8%)	1/20 (5%)
Adjusted rate	0.0%	2.5%	2.3%	9.8%	5.3%
Terminal rate	0/28 (0%)	1/23 (4%)	0/23 (0%)	2/20 (10%)	0/14 (0%)
First incidence (days)	—	733 (T)	694	617	708
Poly-3 test	P=0.303	P=0.493	P=0.503	P=0.056	P=0.334
Kidney (Renal Tubule): Adenoma or Carcinoma					
Overall rate	1/50 (2%)	3/50 (6%)	7/49 (14%)	12/50 (24%)	6/20 (30%)
Adjusted rate	2.4%	7.3%	16.3%	28.9%	31.8%
Terminal rate	1/28 (4%)	1/23 (4%)	4/23 (17%)	7/20 (35%)	4/14 (29%)
First incidence (days)	733 (T)	644	680	617	708
Poly-3 test	P=0.002	P=0.296	P=0.031	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	2/50 (4%)	1/50 (2%)	3/49 (6%)	1/50 (2%)	1/20 (5%)
Adjusted rate	4.7%	2.5%	7.0%	2.5%	5.4%
Terminal rate	1/28 (4%)	1/23 (4%)	1/23 (4%)	1/20 (5%)	1/14 (7%)
First incidence (days)	680	733 (T)	694	733 (T)	733 (T)
Poly-3 test	P=0.646	P=0.513N	P=0.507	P=0.517N	P=0.706
Mammary Gland: Fibroadenoma					
Overall rate	2/50 (4%)	1/50 (2%)	3/49 (6%)	1/50 (2%)	0/20 (0%)
Adjusted rate	4.8%	2.5%	7.0%	2.5%	0.0%
Terminal rate	1/28 (4%)	1/23 (4%)	2/23 (9%)	0/20 (0%)	0/14 (0%)
First incidence (days)	728	733 (T)	666	715	—
Poly-3 test	P=0.324N	P=0.512N	P=0.508	P=0.515N	P=0.428N

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Mammary Gland: Fibroadenoma or Adenoma					
Overall rate	3/50 (6%)	1/50 (2%)	3/49 (6%)	1/50 (2%)	0/20 (0%)
Adjusted rate	7.1%	2.5%	7.0%	2.5%	0.0%
Terminal rate	2/28 (7%)	1/23 (4%)	2/23 (9%)	0/20 (0%)	0/14 (0%)
First incidence (days)	728	733 (T)	666	715	—
Poly-3 test	P=0.248N	P=0.317N	P=0.655N	P=0.321N	P=0.291N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma					
Overall rate	4/50 (8%)	2/50 (4%)	3/49 (6%)	2/50 (4%)	0/20 (0%)
Adjusted rate	9.5%	4.9%	7.0%	4.9%	0.0%
Terminal rate	3/28 (11%)	2/23 (9%)	2/23 (9%)	0/20 (0%)	0/14 (0%)
First incidence (days)	728	733 (T)	666	687	—
Poly-3 test	P=0.182N	P=0.352N	P=0.490N	P=0.355N	P=0.201N
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma					
Overall rate	0/50 (0%)	2/50 (4%)	3/49 (6%)	0/50 (0%)	0/20 (0%)
Adjusted rate	0.0%	4.9%	7.0%	0.0%	0.0%
Terminal rate	0/28 (0%)	1/23 (4%)	3/23 (13%)	0/20 (0%)	0/14 (0%)
First incidence (days)	—	688	733 (T)	—[f]	—
Poly-3 test	P=0.429N	P=0.230	P=0.120	—	—
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma					
Overall rate	0/50 (0%)	2/50 (4%)	3/49 (6%)	1/50 (2%)	0/20 (0%)
Adjusted rate	0.0%	4.9%	7.0%	2.5%	0.0%
Terminal rate	0/28 (0%)	1/23 (4%)	3/23 (13%)	0/20 (0%)	0/14 (0%)
First incidence (days)	—	688	733 (T)	679	—
Poly-3 test	P=0.457N	P=0.230	P=0.120	P=0.492	—
Pancreatic Islets: Adenoma					
Overall rate	3/50 (6%)	3/50 (6%)	3/49 (6%)	2/50 (4%)	1/20 (5%)
Adjusted rate	7.1%	7.3%	7.0%	4.9%	5.4%
Terminal rate	1/28 (4%)	1/23 (4%)	1/23 (4%)	0/20 (0%)	1/14 (7%)
First incidence (days)	658	708	680	649	733 (T)
Poly-3 test	P=0.535N	P=0.645	P=0.659N	P=0.520N	P=0.624N
Pancreatic Islets: Carcinoma					
Overall rate	4/50 (8%)	1/50 (2%)	0/49 (0%)	4/50 (8%)	0/20 (0%)
Adjusted rate	9.2%	2.5%	0.0%	9.9%	0.0%
Terminal rate	2/28 (7%)	1/23 (4%)	0/23 (0%)	3/20 (15%)	0/14 (0%)
First incidence (days)	421	733 (T)	—	688	—
Poly-3 test	P=0.326N	P=0.197N	P=0.062N	P=0.605	P=0.209N
Pancreatic Islets: Adenoma or Carcinoma					
Overall rate	7/50 (14%)	4/50 (8%)	3/49 (6%)	6/50 (12%)	1/20 (5%)
Adjusted rate	16.0%	9.8%	7.0%	14.7%	5.4%
Terminal rate	3/28 (11%)	2/23 (9%)	1/23 (4%)	3/20 (15%)	1/14 (7%)
First incidence (days)	421	708	680	649	733 (T)
Poly-3 test	P=0.292N	P=0.299N	P=0.163N	P=0.553N	P=0.227N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	27/50 (54%)	33/50 (66%)	25/49 (51%)	25/49 (51%)	9/20 (45%)
Adjusted rate	58.6%	72.0%	55.5%	56.5%	47.1%
Terminal rate	14/28 (50%)	14/23 (61%)	14/23 (61%)	8/19 (42%)	5/14 (36%)
First incidence (days)	561	509	574	506	694
Poly-3 test	P=0.121N	P=0.120	P=0.467N	P=0.508N	P=0.280N

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma					
Overall rate	27/50 (54%)	33/50 (66%)	26/49 (53%)	26/49 (53%)	9/20 (45%)
Adjusted rate	58.6%	72.0%	57.2%	58.8%	47.1%
Terminal rate	14/28 (50%)	14/23 (61%)	14/23 (61%)	9/19 (47%)	5/14 (36%)
First incidence (days)	561	509	574	506	694
Poly-3 test	P=0.121N	P=0.120	P=0.534N	P=0.577	P=0.280N
Preputial Gland: Carcinoma					
Overall rate	0/50 (0%)	1/49 (2%)	1/49 (2%)	3/50 (6%)	2/20 (10%)
Adjusted rate	0.0%	2.5%	2.3%	7.3%	10.7%
Terminal rate	0/28 (0%)	0/23 (0%)	0/23 (0%)	2/20 (10%)	2/14 (14%)
First incidence (days)	—	638	638	379	733 (T)
Poly-3 test	P=0.053	P=0.490	P=0.504	P=0.114	P=0.075
Preputial Gland: Adenoma or Carcinoma					
Overall rate	0/50 (0%)	2/49 (4%)	2/49 (4%)	3/50 (6%)	2/20 (10%)
Adjusted rate	0.0%	5.0%	4.7%	7.3%	10.7%
Terminal rate	0/28 (0%)	1/23 (4%)	1/23 (4%)	2/20 (10%)	2/14 (14%)
First incidence (days)	—	638	638	379	733 (T)
Poly-3 test	P=0.122	P=0.226	P=0.241	P=0.114	P=0.075
Skin: Basal Cell Adenoma					
Overall rate	1/50 (2%)	2/50 (4%)	0/49 (0%)	0/50 (0%)	1/20 (5%)
Adjusted rate	2.4%	4.9%	0.0%	0.0%	5.4%
Terminal rate	0/28 (0%)	1/23 (4%)	0/23 (0%)	0/20 (0%)	1/14 (7%)
First incidence (days)	614	670	—	—	733 (T)
Poly-3 test	P=0.518	P=0.487	P=0.499N	P=0.511N	P=0.569
Skin: Trichoepithelioma or Basal Cell Adenoma					
Overall rate	1/50 (2%)	2/50 (4%)	0/49 (0%)	1/50 (2%)	1/20 (5%)
Adjusted rate	2.4%	4.9%	0.0%	2.5%	5.4%
Terminal rate	0/28 (0%)	1/23 (4%)	0/23 (0%)	1/20 (5%)	1/14 (7%)
First incidence (days)	614	670	—	733 (T)	733 (T)
Poly-3 test	P=0.490	P=0.487	P=0.499N	P=0.749	P=0.569
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma					
Overall rate	3/50 (6%)	3/50 (6%)	1/49 (2%)	2/50 (4%)	1/20 (5%)
Adjusted rate	7.0%	7.2%	2.4%	5.0%	5.4%
Terminal rate	1/28 (4%)	1/23 (4%)	1/23 (4%)	2/20 (10%)	1/14 (7%)
First incidence (days)	614	525	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.613N	P=0.651	P=0.305N	P=0.527N	P=0.625N
Skin (Subcutaneous Tissue): Fibroma					
Overall rate	2/50 (4%)	5/50 (10%)	3/49 (6%)	2/50 (4%)	1/20 (5%)
Adjusted rate	4.8%	12.0%	7.0%	4.9%	5.4%
Terminal rate	2/28 (7%)	2/23 (9%)	3/23 (13%)	1/20 (5%)	1/14 (7%)
First incidence (days)	733 (T)	532	733 (T)	506	733 (T)
Poly-3 test	P=0.503N	P=0.211	P=0.506	P=0.684	P=0.707
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma					
Overall rate	4/50 (8%)	5/50 (10%)	3/49 (6%)	3/50 (6%)	1/20 (5%)
Adjusted rate	9.3%	12.0%	7.0%	7.3%	5.4%
Terminal rate	3/28 (11%)	2/23 (9%)	3/23 (13%)	2/20 (10%)	1/14 (7%)
First incidence (days)	387	532	733 (T)	506	733 (T)
Poly-3 test	P=0.380N	P=0.481	P=0.504N	P=0.527N	P=0.494N

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Testes: Adenoma					
Overall rate	40/50 (80%)	41/50 (82%)	47/49 (96%)	44/50 (88%)	20/20 (100%)
Adjusted rate	88.9%	88.0%	97.5%	91.5%	100.0%
Terminal rate	27/28 (96%)	21/23 (91%)	23/23 (100%)	19/20 (95%)	14/14 (100%)
First incidence (days)	581	532	596	419	433
Poly-3 test	P=0.089	P=0.591N	P=0.056	P=0.467	P=0.087
Thyroid Gland (C-Cell): Adenoma					
Overall rate	7/50 (14%)	4/50 (8%)	4/49 (8%)	3/49 (6%)	2/20 (10%)
Adjusted rate	16.4%	9.8%	9.2%	7.5%	10.7%
Terminal rate	5/28 (18%)	1/23 (4%)	2/23 (9%)	1/20 (5%)	1/14 (7%)
First incidence (days)	581	694	602	617	708
Poly-3 test	P=0.487N	P=0.283N	P=0.251N	P=0.184N	P=0.422N
Thyroid Gland (C-Cell): Adenoma or Carcinoma					
Overall rate	7/50 (14%)	6/50 (12%)	5/49 (10%)	3/49 (6%)	2/20 (10%)
Adjusted rate	16.4%	14.7%	11.6%	7.5%	10.7%
Terminal rate	5/28 (18%)	3/23 (13%)	3/23 (13%)	1/20 (5%)	1/14 (7%)
First incidence (days)	581	694	602	617	708
Poly-3 test	P=0.381N	P=0.532N	P=0.368N	P=0.184N	P=0.422N
All Organs: Mononuclear Cell Leukemia					
Overall rate	19/50 (38%)	23/50 (46%)	27/49 (55%)	25/50 (50%)	10/20 (50%)
Adjusted rate	42.8%	50.0%	57.0%	55.9%	50.2%
Terminal rate	8/28 (29%)	8/23 (35%)	8/23 (35%)	9/20 (45%)	5/14 (36%)
First incidence (days)	614	315	596	529	433
Poly-3 test	P=0.483	P=0.316	P=0.122	P=0.149	P=0.389
All Organs: Malignant Mesothelioma					
Overall rate	1/50 (2%)	2/50 (4%)	2/49 (4%)	5/50 (10%)	0/20 (0%)
Adjusted rate	2.4%	4.9%	4.7%	12.1%	0.0%
Terminal rate	1/28 (4%)	0/23 (0%)	2/23 (9%)	2/20 (10%)	0/14 (0%)
First incidence (days)	733 (T)	688	733 (T)	419	—
Poly-3 test	P=0.486N	P=0.491	P=0.504	P=0.095	P=0.665N
All Organs: Benign Neoplasms					
Overall rate	47/50 (94%)	49/50 (98%)	49/49 (100%)	48/50 (96%)	20/20 (100%)
Adjusted rate	98.3%	99.8%	100.0%	97.8%	100.0%
Terminal rate	28/28 (100%)	23/23 (100%)	23/23 (100%)	20/20 (100%)	14/14 (100%)
First incidence (days)	561	509	574	419	433
Poly-3 test	P=0.816	P=0.670	P=0.619	P=0.751N	P=0.849
All Organs: Malignant Neoplasms					
Overall rate	27/50 (54%)	**29/50** (58%)	32/49 (65%)	42/50 (84%)	13/20 (65%)
Adjusted rate	58.7%	60.6%	67.2%	86.8%	65.0%
Terminal rate	14/28 (50%)	9/23 (39%)	11/23 (48%)	16/20 (80%)	7/14 (50%)
First incidence (days)	387	315	596	379	433
Poly-3 test	P=0.309	P=0.508	P=0.257	P<0.001	P=0.415

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
All Organs: Benign or Malignant Neoplasms					
Overall rate	49/50 (98%)	50/50 (100%)	49/49 (100%)	50/50 (100%)	20/20 (100%)
Adjusted rate	99.0%	100.0%	100.0%	100.0%	100.0%
Terminal rate	28/28 (100%)	23/23 (100%)	23/23 (100%)	20/20 (100%)	14/14 (100%)
First incidence (days)	387	315	574	379	433
Poly-3 test	P=0.983	P=0.851	P=0.853	P=0.851	P=0.947

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed 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 Renal Tubule Neoplasms in Control Male F344/N Rats

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
trans-Cinnamaldehyde (feed)	0/100	0/100	0/100
Citral (feed)	0/100	0/100	0/100
Decalin (inhalation)	1/50	0/50	1/50
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	0/50	0/50
Dipropylene glycol (drinking water)	1/47	0/47	1/47
Elmiron® (gavage)	0/50	0/50	0/50
2,4-Hexadienal (gavage)	0/50	0/50	0/50
Indium phosphide (inhalation)	0/50	0/50	0/50
60-Hz Magnetic fields (whole body exposure)	0/100	0/100	0/100
Methacrylonitrile (gavage)	0/50	0/50	0/50
Naphthalene (inhalation)	0/49	0/49	0/49
o-Nitrotoluene (feed)	0/60	0/60	0/60
p-Nitrotoluene (feed)	0/50	0/50	0/50
Sodium nitrite (drinking water)	0/50	0/50	0/50
Vanadium pentoxide (inhalation)	1/50	0/50	1/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	3/906 (0.3%)	0/906	3/906 (0.3%)
Mean ± standard deviation	0.4% ± 0.9%		0.4% ± 0.9%
Range	0%-2%		0%-2%

[a] Data as of January 31, 2002

TABLE A4b
Historical Incidence of Adrenal Medulla Pheochromocytoma in Control Male F344/N Rats

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence in Controls Given NTP-2000 Diet[a]			
trans-Cinnamaldehyde (feed)	5/100	0/100	5/100
Citral (feed)	10/100	0/100	10/100
Decalin (inhalation)	7/49	2/49	8/49
p,p′-Dichlorodiphenyl sulfone (feed)	4/50	2/50	6/50
Dipropylene glycol (drinking water)	4/47	5/47	9/47
Elmiron® (gavage)	7/50	1/50	7/50
2,4-Hexadienal (gavage)	7/50	0/50	7/50
Indium phosphide (inhalation)	10/50	0/50	10/50
60-Hz Magnetic fields (whole body exposure)	24/98	2/98	26/98
Methacrylonitrile (gavage)	3/50	1/50	4/50
Naphthalene (inhalation)	4/49	1/49	5/49
o-Nitrotoluene (feed)	2/60	2/60	4/60
p-Nitrotoluene (feed)	3/50	0/50	3/50
Sodium nitrite (drinking water)	6/50	1/50	7/50
Vanadium pentoxide (inhalation)	4/50	1/50	5/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	100/903 (11.1%)	18/903 (2.0%)	116/903 (12.8%)
Mean ± standard deviation	10.8% ± 5.8%	2.3% ± 2.7%	12.8% ± 5.9%
Range	3%-24%	0%-11%	5%-27%

[a] Data as of January 31, 2002

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	20
Early deaths					
Moribund	17	21	23	23	6
Natural deaths	5	6	3	7	
Survivors					
Terminal sacrifice	28	23	23	20	14
Missexed			1		
Animals examined microscopically	50	50	49	50	20
Alimentary System					
Intestine large, colon	(48)	(47)	(48)	(49)	(20)
Ulcer			1 (2%)		
Liver	(50)	(50)	(49)	(50)	(20)
Angiectasis				1 (2%)	1 (5%)
Clear cell focus	2 (4%)	1 (2%)	3 (6%)	3 (6%)	
Congestion			1 (2%)		
Cyst	1 (2%)		1 (2%)		
Degeneration, cystic	1 (2%)				
Hepatodiaphragmatic nodule	7 (14%)	5 (10%)	7 (14%)	4 (8%)	4 (20%)
Infiltration cellular, lymphohistiocytic					2 (10%)
Mixed cell focus	3 (6%)		1 (2%)		
Necrosis	1 (2%)	1 (2%)	2 (4%)		
Thrombosis		1 (2%)	1 (2%)		
Vacuolization cytoplasmic		2 (4%)	1 (2%)	1 (2%)	
Bile duct, hyperplasia			2 (4%)	1 (2%)	3 (15%)
Hepatocyte, regeneration	2 (4%)	1 (2%)	4 (8%)	2 (4%)	1 (5%)
Mesentery	(16)	(19)	(20)	(13)	(10)
Necrosis	7 (44%)	9 (47%)	12 (60%)	4 (31%)	2 (20%)
Artery, inflammation					1 (10%)
Fat, hemorrhage			2 (10%)		2 (20%)
Fat, necrosis	9 (56%)	6 (32%)	6 (30%)	6 (46%)	5 (50%)
Oral mucosa		(2)	(2)	(1)	
Inflammation, chronic				1 (100%)	
Pharyngeal, hyperplasia, squamous		1 (50%)			
Pancreas	(50)	(50)	(49)	(50)	(20)
Acinus, atrophy	1 (2%)	2 (4%)	3 (6%)	2 (4%)	2 (10%)
Acinus, hyperplasia				1 (2%)	
Salivary glands	(50)	(50)	(49)	(50)	(20)
Inflammation, suppurative			1 (2%)		
Stomach, forestomach	(50)	(50)	(49)	(50)	(20)
Erosion	1 (2%)				
Hyperplasia, squamous				1 (2%)	
Inflammation, suppurative				1 (2%)	1 (5%)
Ulcer		5 (10%)	4 (8%)	3 (6%)	1 (5%)
Stomach, glandular	(50)	(50)	(49)	(50)	(20)
Erosion		1 (2%)	1 (2%)		
Necrosis				1 (2%)	
Ulcer		1 (2%)	2 (4%)		

[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 Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Alimentary System (continued)					
Tongue		(1)	(2)	(1)	
Inflammation			1 (50%)		
Tooth	(1)		(1)		(1)
Inflammation			1 (100%)		
Peridontal tissue, inflammation	1 (100%)				1 (100%)
Cardiovascular System					
Blood vessel	(44)	(50)	(49)	(45)	(11)
Thrombosis					1 (9%)
Pulmonary artery, inflammation					1 (9%)
Heart	(50)	(50)	(49)	(50)	(20)
Cardiomyopathy	5 (10%)	5 (10%)	4 (8%)	9 (18%)	3 (15%)
Atrium, thrombosis	2 (4%)	2 (4%)	5 (10%)	2 (4%)	1 (5%)
Valve, thrombosis	1 (2%)				
Endocrine System					
Adrenal cortex	(50)	(50)	(49)	(50)	(20)
Hyperplasia	1 (2%)	1 (2%)	3 (6%)		
Necrosis			1 (2%)	2 (4%)	
Vacuolization cytoplasmic	2 (4%)	6 (12%)	5 (10%)	2 (4%)	1 (5%)
Adrenal medulla	(49)	(49)	(49)	(49)	(20)
Hyperplasia	10 (20%)	13 (27%)	26 (53%)	17 (35%)	4 (20%)
Necrosis		1 (2%)		1 (2%)	
Islets, pancreatic	(50)	(50)	(49)	(50)	(20)
Hyperplasia	1 (2%)		1 (2%)		
Parathyroid gland	(49)	(48)	(49)	(49)	(20)
Hyperplasia				1 (2%)	
Pituitary gland	(50)	(50)	(49)	(49)	(20)
Cyst	1 (2%)	1 (2%)	1 (2%)		1 (5%)
Hemorrhage	1 (2%)			2 (4%)	
Pars distalis, hyperplasia	7 (14%)	4 (8%)	5 (10%)	6 (12%)	1 (5%)
Pars intermedia, hyperplasia				1 (2%)	
Thyroid gland	(50)	(50)	(49)	(49)	(20)
C-cell, hyperplasia	6 (12%)	6 (12%)	6 (12%)		7 (35%)
Follicular cell, hyperplasia		1 (2%)	2 (4%)		
General Body System					
None					

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Genital System					
Epididymis	(50)	(50)	(49)	(50)	(20)
Spermatocele				1 (2%)	
Preputial gland	(50)	(49)	(49)	(50)	(20)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)	1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)		1 (2%)	
Prostate, NOS	(50)	(50)	(49)	(50)	(20)
Hyperplasia	1 (2%)	3 (6%)			
Hypertrophy				1 (2%)	
Inflammation					2 (10%)
Inflammation, suppurative	18 (36%)	21 (42%)	14 (29%)	24 (48%)	9 (45%)
Epithelium, dorsal, hyperplasia					1 (5%)
Epithelium, ventral, hyperplasia			1 (2%)	1 (2%)	
Seminal vesicle	(50)	(50)	(49)	(50)	(20)
Dilatation				1 (2%)	
Testes	(50)	(50)	(49)	(50)	(20)
Artery, inflammation				1 (2%)	
Germinal epithelium, atrophy	6 (12%)	4 (8%)	8 (16%)	7 (14%)	4 (20%)
Interstitial cell, hyperplasia	9 (18%)	17 (34%)	7 (14%)	16 (32%)	1 (5%)
Hematopoietic System					
Bone marrow	(50)	(50)	(49)	(50)	(20)
Hyperplasia, reticulum cell				1 (2%)	
Myelofibrosis			1 (2%)		1 (5%)
Lymph node	(8)	(10)	(14)	(11)	(1)
Ectasia			1 (7%)		
Deep cervical, infiltration cellular, histiocyte			1 (7%)		
Deep cervical, inflammation, suppurative				1 (9%)	
Pancreatic, ectasia	1 (13%)			1 (9%)	
Pancreatic, pigmentation			1 (7%)		
Lymph node, bronchial	(7)	(8)	(18)	(17)	(7)
Ectasia			1 (6%)		1 (14%)
Inflammation, chronic					1 (14%)
Pigmentation				1 (6%)	
Lymph node, mesenteric	(50)	(50)	(49)	(49)	(20)
Ectasia			1 (2%)	1 (2%)	
Hyperplasia, lymphohistiocytic			1 (2%)		
Lymph node, mediastinal	(48)	(45)	(44)	(48)	(16)
Angiectasis		3 (7%)	1 (2%)	2 (4%)	1 (6%)
Inflammation	1 (2%)				
Inflammation, chronic				1 (2%)	
Pigmentation				1 (2%)	
Spleen	(50)	(50)	(49)	(50)	(20)
Accessory spleen	1 (2%)			2 (4%)	2 (10%)
Congestion			4 (8%)		
Fibrosis	3 (6%)	3 (6%)	4 (8%)	5 (10%)	2 (10%)
Hematopoietic cell proliferation		1 (2%)		3 (6%)	
Hemorrhage		5 (10%)	2 (4%)	2 (4%)	1 (5%)
Hyperplasia, lymphoid					1 (5%)
Hyperplasia, lymphohistiocytic			1 (2%)		1 (5%)
Necrosis	1 (2%)	1 (2%)	2 (4%)	2 (4%)	1 (5%)
Thymus	(50)	(48)	(47)	(50)	(20)
Cyst		1 (2%)		1 (2%)	
Metaplasia, squamous				1 (2%)	

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Integumentary System					
Mammary gland	(50)	(50)	(49)	(50)	(20)
Galactocele		2 (4%)			1 (5%)
Epithelium, hyperplasia		1 (2%)			
Skin	(50)	(50)	(49)	(50)	(20)
Cyst	3 (6%)	1 (2%)			
Cyst epithelial inclusion	2 (4%)	2 (4%)	5 (10%)		
Hyperkeratosis	2 (4%)	1 (2%)		1 (2%)	1 (5%)
Hyperplasia		1 (2%)			
Inflammation, acute			1 (2%)		
Inflammation, chronic					1 (5%)
Ulcer		1 (2%)		2 (4%)	
Subcutaneous tissue, fibrosis		1 (2%)			
Subcutaneous tissue, hemorrhage				1 (2%)	
Subcutaneous tissue, inflammation, suppurative	1 (2%)				
Musculoskeletal System					
Bone	(50)	(50)	(49)	(50)	(20)
Femur, degeneration			1 (2%)		
Joint, femur, tibia, fracture			1 (2%)		
Vertebra, fracture	1 (2%)				
Skeletal muscle		(1)		(5)	
Inflammation, chronic				1 (20%)	
Nervous System					
Brain	(50)	(50)	(49)	(50)	(20)
Compression	2 (4%)	2 (4%)	5 (10%)	5 (10%)	1 (5%)
Hemorrhage	2 (4%)	1 (2%)	2 (4%)	3 (6%)	
Inflammation, suppurative			1 (2%)		
Respiratory System					
Larynx	(50)	(50)	(49)	(49)	(20)
Foreign body	2 (4%)	1 (2%)	3 (6%)	2 (4%)	
Inflammation, chronic	2 (4%)		3 (6%)	2 (4%)	1 (5%)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (5%)
Metaplasia, squamous	1 (2%)				
Epiglottis, hyperplasia			1 (2%)		1 (5%)
Epiglottis, metaplasia, squamous					1 (5%)
Glands, degeneration		1 (2%)			
Squamous epithelium, hyperplasia			1 (2%)		
Lung	(50)	(50)	(49)	(50)	(20)
Hemorrhage	1 (2%)		4 (8%)	3 (6%)	
Inflammation, suppurative		1 (2%)	1 (2%)	2 (4%)	
Mineralization			1 (2%)		
Alveolar epithelium, hyperplasia	10 (20%)	8 (16%)	6 (12%)	9 (18%)	4 (20%)
Alveolar epithelium, metaplasia, squamous	1 (2%)	1 (2%)	1 (2%)		1 (5%)
Alveolus, infiltration cellular, histiocyte	14 (28%)	15 (30%)	6 (12%)	11 (22%)	10 (50%)
Alveolus, pigmentation	1 (2%)				
Alveolus, proteinosis	6 (12%)	7 (14%)	2 (4%)	4 (8%)	2 (10%)
Bronchiole, hyperplasia	1 (2%)				
Bronchiole, metaplasia, squamous		1 (2%)			
Goblet cell, hyperplasia				1 (2%)	
Interstitium, fibrosis	9 (18%)	10 (20%)	7 (14%)	6 (12%)	4 (20%)
Interstitium, inflammation, chronic	5 (10%)	2 (4%)	2 (4%)	1 (2%)	1 (5%)

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	400 ppm
Respiratory System (continued)					
Nose	(49)	(49)	(49)	(50)	(20)
Foreign body	1 (2%)	4 (8%)	2 (4%)		1 (5%)
Inflammation, suppurative	2 (4%)	4 (8%)	8 (16%)	4 (8%)	
Goblet cell, hyperplasia		1 (2%)	2 (4%)	2 (4%)	1 (5%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)				
Respiratory epithelium, hyperplasia	1 (2%)			1 (2%)	
Respiratory epithelium, metaplasia, squamous			1 (2%)		
Respiratory epithelium, necrosis	1 (2%)				
Pleura	(9)	(8)	(8)	(5)	(6)
Inflammation, chronic	9 (100%)	7 (88%)	6 (75%)	4 (80%)	5 (83%)
Mesothelium, hyperplasia		1 (13%)	3 (38%)		1 (17%)
Trachea	(50)	(50)	(49)	(49)	(20)
Inflammation, suppurative				1 (2%)	
Metaplasia, squamous			1 (2%)		
Special Senses System					
Eye		(2)	(2)	(2)	(1)
Atrophy				1 (50%)	
Inflammation, suppurative		1 (50%)			
Anterior chamber, hemorrhage		1 (50%)			
Lens, cataract		1 (50%)	1 (50%)	2 (100%)	1 (100%)
Harderian gland	(1)			(2)	
Inflammation, chronic	1 (100%)				
Urinary System					
Kidney	(50)	(50)	(49)	(50)	(20)
Cyst			2 (4%)	1 (2%)	
Glomerulosclerosis			1 (2%)		
Hydronephrosis		1 (2%)			
Infarct	1 (2%)	1 (2%)	1 (2%)		1 (5%)
Inflammation, suppurative				1 (2%)	
Nephropathy, chronic	48 (96%)	48 (96%)	49 (100%)	50 (100%)	20 (100%)
Cortex, renal tubule, accumulation, hyaline droplet	2 (4%)	9 (18%)	7 (14%)	11 (22%)	2 (10%)
Cortex, renal tubule, atypia cellular	1 (2%)				
Cortex, renal tubule, hyperplasia		11 (22%)	11 (22%)	15 (30%)	5 (25%)
Cortex, renal tubule, mineralization				1 (2%)	
Medulla, casts granular					1 (5%)
Papilla, mineralization	1 (2%)	34 (68%)	41 (84%)	43 (86%)	17 (85%)
Pelvis, inflammation, suppurative	1 (2%)				
Pelvis, transitional epithelium, hyperplasia	1 (2%)	8 (16%)	8 (16%)	10 (20%)	5 (25%)
Urinary bladder	(50)	(49)	(49)	(49)	(20)
Calculus microscopic observation only				1 (2%)	
Inflammation, suppurative				1 (2%)	
Muscularis, hyperplasia					1 (5%)
Transitional epithelium, hyperplasia				1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF DECALIN

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

	Chamber Control	25 ppm	100 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	16	10	10	17
Natural deaths	2	5		5
Survivors				
Died last week of study			1	
Terminal sacrifice	32	35	38	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Liver	(50)	(48)	(49)	(50)
Histiocytic sarcoma		1 (2%)		
Mesentery	(26)	(20)	(20)	(17)
Oral mucosa	(1)			(2)
Gingival, squamous cell carcinoma	1 (100%)			
Stomach, glandular	(50)	(47)	(49)	(49)
Adenoma		1 (2%)		
Tongue	(2)			(1)
Squamous cell carcinoma	1 (50%)			
Squamous cell papilloma	1 (50%)			
Cardiovascular System				
None				
Endocrine System				
Adrenal medulla	(50)	(48)	(49)	(49)
Pheochromocytoma malignant		2 (4%)	1 (2%)	
Pheochromocytoma benign	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Islets, pancreatic	(50)	(47)	(49)	(49)
Adenoma	1 (2%)			
Carcinoma	1 (2%)	1 (2%)	1 (2%)	
Pituitary gland	(50)	(49)	(49)	(50)
Pars distalis, adenoma	34 (68%)	27 (55%)	29 (59%)	30 (60%)
Pars distalis, carcinoma		1 (2%)	1 (2%)	1 (2%)
Thyroid gland	(50)	(49)	(49)	(50)
C-cell, adenoma	5 (10%)	3 (6%)	2 (4%)	3 (6%)
C-cell, carcinoma	3 (6%)		1 (2%)	
Follicular cell, adenoma			1 (2%)	
General Body System				
None				

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Genital System				
Clitoral gland	(48)	(49)	(49)	(50)
Adenoma	8 (17%)	2 (4%)	1 (2%)	
Carcinoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Ovary	(50)	(50)	(49)	(50)
Granulosa cell tumor malignant		1 (2%)		
Granulosa cell tumor benign		2 (4%)		
Thecoma malignant	1 (2%)			
Uterus	(50)	(49)	(49)	(50)
Polyp stromal	6 (12%)	8 (16%)	14 (29%)	12 (24%)
Sarcoma stromal				1 (2%)
Bilateral, polyp stromal	1 (2%)			
Endometrium, carcinoma			2 (4%)	1 (2%)
Vagina	(1)			(2)
Sarcoma	1 (100%)			
Hematopoietic System				
Bone marrow	(50)	(49)	(49)	(50)
Lymph node	(6)		(4)	(2)
Lymph node, bronchial	(2)	(10)	(7)	(5)
Carcinoma, metastatic, uterus			1 (14%)	
Lymph node, mesenteric	(50)	(50)	(49)	(49)
Lymph node, mediastinal	(45)	(46)	(49)	(44)
Spleen	(50)	(49)	(49)	(50)
Sarcoma		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Carcinoma	5 (10%)	3 (6%)	6 (12%)	3 (6%)
Fibroadenoma	17 (34%)	14 (28%)	17 (35%)	18 (36%)
Fibroadenoma, multiple	8 (16%)	8 (16%)	3 (6%)	5 (10%)
Skin	(50)	(50)	(49)	(50)
Basal cell adenoma				1 (2%)
Basal cell carcinoma	1 (2%)		1 (2%)	
Sarcoma	1 (2%)			
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma			1 (2%)	
Subcutaneous tissue, fibroma			1 (2%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)	
Subcutaneous tissue, neural crest tumor	1 (2%)			1 (2%)
Subcutaneous tissue, sarcoma			1 (2%)	
Subcutaneous tissue, schwannoma malignant			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Humerus, osteosarcoma		1 (2%)	1 (2%)	
Skeletal muscle	(1)	(2)	(1)	
Carcinoma, metastatic, uterus			1 (100%)	
Carcinoma, metastatic, Zymbal's gland		1 (50%)		
Osteosarcoma, metastatic, bone		1 (50%)		
Rhabdomyosarcoma	1 (100%)			

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Nervous System				
Brain	(50)	(49)	(49)	(50)
Carcinoma, metastatic, pituitary gland			1 (2%)	1 (2%)
Respiratory System				
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Alveolar/bronchiolar carcinoma	1 (2%)			
Carcinoma, metastatic, uterus			1 (2%)	1 (2%)
Granulosa cell tumor malignant, metastatic, ovary		1 (2%)		
Osteosarcoma, metastatic, bone		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)		
Pleura	(20)	(25)	(25)	(28)
Carcinoma, metastatic, uterus			1 (4%)	
Special Senses System				
Zymbal's gland		(1)		
Carcinoma		1 (100%)		
Urinary System				
Kidney	(50)	(46)	(49)	(50)
Granulosa cell tumor malignant, metastatic, ovary		1 (2%)		
Pelvis, transitional epithelium, carcinoma				1 (2%)
Urinary bladder	(50)	(47)	(49)	(50)
Sarcoma, metastatic, vagina	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Leukemia mononuclear	11 (22%)	15 (30%)	12 (24%)	14 (28%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	44	46	48
Total primary neoplasms	114	96	103	95
Total animals with benign neoplasms	46	41	44	44
Total benign neoplasms	83	66	72	72
Total animals with malignant neoplasms	25	22	25	18
Total malignant neoplasms	30	30	31	22
Total animals with metastatic neoplasms	1	4	2	2
Total metastatic neoplasms	1	6	5	2
Total animals with uncertain neoplasms–benign or malignant	1			1
Total uncertain neoplasms	1			1

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	359	525	561	573	609	639	652	652	666	666	666	680	688	705	716	716	717	722	734	734	735	735	735	735	735	735
Carcass ID Number	105	127	120	104	135	144	145	150	101	116	142	112	110	148	124	140	113	146	114	122	108	117	119	125	126
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+	+	+		+		+		+			+					+			+	+	+	+	+
Oral mucosa																	+									
Gingival, squamous cell carcinoma																	X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue										+					+											
Squamous cell carcinoma															X											
Squamous cell papilloma										X																
Tooth												+														
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X											
Carcinoma																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X	X		X			X	X	X		X	X			X	X	X		X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X		X									X
C-cell, carcinoma																			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 B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	129	130	133	134	136	138	139	141	143	147	149	102	103	106	107	109	111	115	118	121	123	128	131	132	137	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+	+	+		+		+	+		+		+			+				+		+	+	+		26
Oral mucosa																										1
Gingival, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										2
Squamous cell carcinoma																										1
Squamous cell papilloma																										1
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X		X	X	X	X	X					X	X		X	X	X	34
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																			X					X		5
C-cell, carcinoma		X																			X					3
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	359	525	561	573	609	639	652	652	666	666	666	680	688	705	716	716	717	722	734	734	735	735	735	735	735
Carcass ID Number	105	127	120	104	135	144	145	150	101	116	142	112	110	148	124	140	113	146	114	122	108	117	119	125	126
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X											X			
Carcinoma			X																						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thecoma malignant																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X				X																
Bilateral, polyp stromal																									
Vagina	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M				M			M	
Sarcoma														X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node													+		+	+		+						+	
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	M	M
Lymph node, mandibular	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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X			X					X									
Fibroadenoma	X	X				X			X		X						X	X		X			X		
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma										X															
Sarcoma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, neural crest tumor																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Rhabdomyosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	129	130	133	134	136	138	139	141	143	147	149	102	103	106	107	109	111	115	118	121	123	128	131	132	137	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Adenoma					X		X							X	X				X		X					8
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thecoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X															X				X			X			6
Bilateral, polyp stromal																			X							1
Vagina		M										M	M	M	M	M										1
Sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																	+					M				6
Lymph node, bronchial	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
Lymph node, mandibular	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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X													X		5
Fibroadenoma			X				X	X				X		X	X	X		X								17
Fibroadenoma, multiple	X				X	X				X										X	X	X			X	8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Sarcoma																						X				1
Subcutaneous tissue, fibrosarcoma		X																								1
Subcutaneous tissue, neural crest tumor																				X						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																			+							1
Rhabdomyosarcoma																			X							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	359	525	561	573	609	639	652	652	666	666	666	680	688	705	716	716	717	722	734	734	735	735	735	735	735	735
Carcass ID Number	105	127	120	104	135	144	145	150	101	116	142	112	110	148	124	140	113	146	114	122	108	117	119	125	126
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+		+				+			+						+	+	+				+		+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																										
Harderian gland																	+									
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter														+												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, vagina														X												
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X					X	X					X						X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	129	130	133	134	136	138	139	141	143	147	149	102	103	106	107	109	111	115	118	121	123	128	131	132	137	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	1
Alveolar/bronchiolar carcinoma																				X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+		+	+		+					+			+					+	+	+				+	20
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																								+		1
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, vagina																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X								X			X				X	X					11

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	499	533	613	635	638	656	663	706	708	708	722	722	722	728	728	734	734	735	735	735	735	735	735	735	735
Carcass ID Number	308	324	318	345	331	306	330	313	302	342	304	311	335	338	348	332	337	301	303	305	307	310	314	315	317
Alimentary System																									
Esophagus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Mesentery								+		+		+	+	+	+			+	+		+				
Pancreas	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant							X	X																	
Pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Parathyroid gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X	X	X				X	X	X			X		X					X	X	X	X	X
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma																							X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant				X																					
Granulosa cell tumor benign																									
Oviduct																									
Uterus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X	X																			X	
Vagina	M	M	M	M	M	M	M			M			M	M	M	M									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	320	322	326	327	334	344	346	347	349	309	312	316	319	321	323	325	328	329	333	336	339	340	341	343	350	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Mesentery	+	+	+		+		+			+						+		+	+		+				+	20
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma											X															1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																										2
Pheochromocytoma benign			X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma							X		X			X				X	X	X	X	X	X	X		X	X	27
Pars distalis, carcinoma			X																							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X												X								X				3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																								X		2
Carcinoma				X										X												3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																										1
Granulosa cell tumor benign															X										X	2
Oviduct							+																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal				X						X	X								X	X						8
Vagina														M				M								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	499	533	613	635	638	656	663	706	708	708	722	722	722	728	728	734	734	735	735	735	735	735	735	735	735
Carcass ID Number	308	324	318	345	331	306	303	313	302	342	304	311	335	338	348	332	337	301	303	305	307	310	314	315	317
Hematopoietic System																									
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, bronchial	M	+	M	M	M	+	M	M	+	M	M	M	+	+	M	M	M	M	+	M	M	M	M	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Thymus	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X													X	
Fibroadenoma						X		X		X				X	X				X					X	X
Fibroadenoma, multiple									X			X	X									X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, osteosarcoma					X																				
Skeletal muscle		+			+																				
Carcinoma, metastatic, Zymbal's gland		X																							
Osteosarcoma, metastatic, bone					X																				
Nervous System																									
Brain	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary				X																					
Osteosarcoma, metastatic, bone					X																				
Pheochromocytoma malignant, metastatic, adrenal medulla								X																	
Nose	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura					+				+	+		+		+		+	+	+	+			+			
Trachea	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear													+	+											
Eye					+		+																		
Zymbal's gland		+		M																					
Carcinoma		X																							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	320	322	326	327	334	344	346	347	349	309	312	316	319	321	323	325	328	329	333	336	339	340	341	343	350	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node													M													
Lymph node, bronchial	M	M	+	M	M	M	M	M	M	+	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	10
Lymph node, mandibular	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma														X												1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																								X		3
Fibroadenoma									X					X				X		X	X		X			14
Fibroadenoma, multiple			X								X								X			X				8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Humerus, osteosarcoma																										1
Skeletal muscle																										2
Carcinoma, metastatic, Zymbal's gland																										1
Osteosarcoma, metastatic, bone																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant, metastatic, ovary																										1
Osteosarcoma, metastatic, bone																										1
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pleura	+	+	+	+		+	+	+	+		+		+					+		+	+	+	+			25
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Ear																										2
Eye																										2
Zymbal's gland																										1
Carcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	499	533	613	635	638	656	663	706	708	708	722	722	722	728	728	734	734	735	735	735	735	735	735	735	735
Carcass ID Number	308	324	318	345	331	306	330	313	302	342	304	311	335	338	348	332	337	301	303	305	307	310	314	315	317
Urinary System																									
Kidney	A	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary				X																					
Urinary bladder	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Leukemia mononuclear						X		X		X	X		X										X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	320	322	326	327	334	344	346	347	349	309	312	316	319	321	323	325	328	329	333	336	339	340	341	343	350	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Granulosa cell tumor malignant, metastatic, ovary																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear				X	X				X	X			X	X	X								X			15

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	113	349	617	665	665	666	679	680	688	694	722	734	734	734	734	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	711	742	744	705	728	702	722	736	749	703	734	710	716	729	740	708	709	713	714	723	725	726	731	735	737
Alimentary System																									
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+			+	+							+		+	+	+			+			+		
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																				X					
Pheochromocytoma benign									X															X	
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X	X		X						X	X		X	X		X		X	
Pars distalis, carcinoma									X																
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma					X																				
Follicular cell, adenoma					X																				
General Body System																									
None																									
Genital System																									
Clitoral gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma												X													
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X	X		X		X				X			X	X		X					
Endometrium, carcinoma																								X	
Vagina	M	M	M	M	M	M	M	M	M	M		M						M			M			M	

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	738	739	741	743	746	748	701	704	706	707	712	715	717	718	719	720	721	724	727	730	732	733	745	747	750	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery				+	+		+			+	+				+	+	+					+	+	+		20
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Pheochromocytoma benign																							X			3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma															X											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X	X		X		X		X		X	X	X		X	X	X	X	X	X		X	X	X	29
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																	X		X							2
C-cell, carcinoma																										1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X											1
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal	X		X				X						X		X	X										14
Endometrium, carcinoma																						X				2
Vagina																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	1	3	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	1	4	1	6	6	6	7	8	8	9	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	9	7	5	5	6	9	0	8	4	2	4	4	4	4	5	5	5	5	5	5	5	5	5	5
Carcass ID Number	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	1	4	4	0	2	0	2	3	4	0	3	1	1	2	4	0	0	1	1	2	2	2	3	3	3
	1	2	4	5	8	2	2	6	9	3	4	0	6	9	0	8	9	3	4	3	5	6	1	5	7
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node											+	+												+	
Lymph node, bronchial	A	M	M	+	M	M	+	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	+	M
Carcinoma, metastatic, uterus																								X	
Lymph node, mandibular	A	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X			X				X											
Fibroadenoma				X	X	X						X	X					X		X					X
Fibroadenoma, multiple											X														
Skin	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									X
Squamous cell carcinoma											X														
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, sarcoma										X															
Subcutaneous tissue, schwannoma malignant						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, osteosarcoma																									
Skeletal muscle																								+	
Carcinoma, metastatic, uterus																								X	
Nervous System																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland									X																
Respiratory System																									
Larynx	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																								X	
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura			+			+					+	+	+		+	+	+		+		+	+		+	
Carcinoma, metastatic, uterus																								X	
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	738	739	741	743	746	748	701	704	706	707	712	715	717	718	719	720	721	724	727	730	732	733	745	747	750	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																					+					4
Lymph node, bronchial	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	7
Carcinoma, metastatic, uterus																										1
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma											X							X		X						6
Fibroadenoma		X		X	X	X	X				X	X	X		X											17
Fibroadenoma, multiple	X																				X					3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell carcinoma																										1
Squamous cell carcinoma																										1
Squamous cell papilloma																						X				1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma									X																	1
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Humerus, osteosarcoma							X																			1
Skeletal muscle																										1
Carcinoma, metastatic, uterus																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura				+			+	+	+	+	+	+		+	+	+	+		+						+	25
Carcinoma, metastatic, uterus																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	1	3	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	1	4	1	6	6	6	7	8	8	9	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	9	7	5	5	6	9	0	8	4	2	4	4	4	4	5	5	5	5	5	5	5	5	5	5
Carcass ID Number	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	1	4	4	0	2	0	2	3	4	0	3	1	1	2	4	0	0	1	1	2	2	2	3	3	3
	1	2	4	5	8	2	2	6	9	3	4	0	6	9	0	8	9	3	4	3	5	6	1	5	7
Special Senses System																									
Ear										+															+
Eye						+												+						+	
Urinary System																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X					X							X						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	738	739	741	743	746	748	701	704	706	707	712	715	717	718	719	720	721	724	727	730	732	733	745	747	750	Total Tissues/ Tumors
Special Senses System																										
Ear																										2
Eye																						+	+			5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X					X	X								X	X	X	X			X	12

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	478	492	538	538	561	566	580	589	590	599	602	618	634	644	644	694	699	700	702	706	708	708	734	734	734
Carcass ID Number	901	930	911	949	941	924	947	906	905	909	934	902	933	916	917	918	939	943	915	928	923	937	927	929	942
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+							+			+		+			+				+					
Oral mucosa		+																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Tongue															+										
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X		X	X				X		X		X	X		X	X		X	X	X	X	
Pars distalis, carcinoma														X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X															
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal								X		X							X						X	X	
Sarcoma stromal	X																								
Endometrium, carcinoma	X																								
Vagina	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M						M

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	904	908	910	919	920	926	932	935	936	938	946	950	903	907	912	913	914	921	922	925	931	940	944	945	948	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+	+	+		+	+			+	+					+		+	+		+			17
Oral mucosa												+														2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X		X	X	X		X	X	X	X	X				X			X		X	X	X	30
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X														X				3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X											X			X	X		X	X				X	12
Sarcoma stromal																										1
Endometrium, carcinoma																										1
Vagina	M	M	+				M	M	M			M	M	M			M				M	M			M	2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	478	492	538	538	561	566	580	589	590	590	602	618	634	644	644	694	699	700	702	706	708	708	734	734	734
Carcass ID Number	901	930	911	949	941	924	947	906	905	909	934	902	933	916	917	918	939	943	915	928	923	937	927	929	942
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+																	
Lymph node, bronchial	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M
Lymph node, mandibular	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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	A	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Fibroadenoma								X	X	X		X	X	X								X		X	X
Fibroadenoma, multiple																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, neural crest tumor																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland														X											
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Pleura		+						+	+				+		+	+				+	+	+	+		+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+																			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, transitional epithelium, carcinoma																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X			X					X	X		X	X			X		X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	904	908	910	919	920	926	932	935	936	938	946	950	903	907	912	913	914	921	922	925	931	940	944	945	948	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, bronchial	M	M	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	5
Lymph node, mandibular	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	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																			X						X	3
Fibroadenoma			X	X	X			X			X			X					X				X	X		18
Fibroadenoma, multiple							X					X			X		X									5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																							X			1
Subcutaneous tissue, fibroma				X											X											2
Subcutaneous tissue, neural crest tumor		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura		+	+	+		+		+	+	+		+	+		+	+	+	+	+	+		+			+	28
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye						+								+											+	4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, transitional epithelium, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X															X		X			X	14

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	1/50 (2%)	1/48 (2%)	3/49 (6%)	1/49 (2%)
Adjusted rate[b]	2.3%	2.2%	6.5%	2.5%
Terminal rate[c]	1/32 (3%)	1/35 (3%)	2/39 (5%)	1/28 (4%)
First incidence (days)	734 (T)	734 (T)	688	734 (T)
Poly-3 test[d]	P=0.635N	P=0.756N	P=0.320	P=0.741
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	1/50 (2%)	3/48 (6%)	4/49 (8%)	1/49 (2%)
Adjusted rate	2.3%	6.5%	8.6%	2.5%
Terminal rate	1/32 (3%)	1/35 (3%)	3/39 (8%)	1/28 (4%)
First incidence (days)	734 (T)	663	688	734 (T)
Poly-3 test	P=0.421N	P=0.316	P=0.191	P=0.741
Clitoral Gland: Adenoma				
Overall rate	8/48 (17%)	2/49 (4%)	1/49 (2%)	0/50 (0%)
Adjusted rate	18.3%	4.4%	2.2%	0.0%
Terminal rate	7/31 (23%)	1/35 (3%)	1/39 (3%)	0/28 (0%)
First incidence (days)	666	722	734 (T)	—[e]
Poly-3 test	P=0.014N	P=0.037N	P=0.012N	P=0.004N
Clitoral Gland: Carcinoma				
Overall rate	1/48 (2%)	3/49 (6%)	1/49 (2%)	1/50 (2%)
Adjusted rate	2.3%	6.6%	2.2%	2.4%
Terminal rate	0/31 (0%)	3/35 (9%)	1/39 (3%)	0/28 (0%)
First incidence (days)	561	734 (T)	734 (T)	618
Poly-3 test	P=0.456N	P=0.320	P=0.750N	P=0.750
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	9/48 (19%)	5/49 (10%)	2/49 (4%)	1/50 (2%)
Adjusted rate	20.4%	10.9%	4.3%	2.4%
Terminal rate	7/31 (23%)	4/35 (11%)	2/39 (5%)	0/28 (0%)
First incidence (days)	561	722	734 (T)	618
Poly-3 test	P=0.018N	P=0.171N	P=0.020N	P=0.010N
Mammary Gland: Fibroadenoma				
Overall rate	25/50 (50%)	22/50 (44%)	20/50 (40%)	23/50 (46%)
Adjusted rate	53.2%	46.5%	42.6%	51.8%
Terminal rate	18/32 (56%)	14/35 (40%)	16/39 (41%)	15/28 (54%)
First incidence (days)	359	656	665	589
Poly-3 test	P=0.450	P=0.329N	P=0.203N	P=0.533N
Mammary Gland: Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted rate	11.1%	6.4%	12.9%	7.2%
Terminal rate	2/32 (6%)	2/35 (6%)	4/39 (10%)	2/28 (7%)
First incidence (days)	652	722	679	702
Poly-3 test	P=0.441N	P=0.339N	P=0.521	P=0.400N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	29/50 (58%)	24/50 (48%)	25/50 (50%)	25/50 (50%)
Adjusted rate	61.2%	50.7%	52.8%	56.2%
Terminal rate	20/32 (63%)	15/35 (43%)	19/39 (49%)	16/28 (57%)
First incidence (days)	359	656	665	589
Poly-3 test	P=0.554N	P=0.202N	P=0.267N	P=0.388N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.7%	0.0%	0.0%	0.0%
Terminal rate	0/32 (0%)	0/35 (0%)	0/39 (0%)	0/28 (0%)
First incidence (days)	666	—	—	—
Poly-3 test	P=0.198N	P=0.112N	P=0.114N	P=0.133N
Ovary: Benign or Malignant Granulosa Cell Tumor				
Overall rate	0/50 (0%)	3/50 (6%)	0/49 (0%)	0/50 (0%)
Adjusted rate	0.0%	6.4%	0.0%	0.0%
Terminal rate	0/32 (0%)	2/35 (6%)	0/39 (0%)	0/28 (0%)
First incidence (days)	—	635	—	—
Poly-3 test	P=0.273N	P=0.128	—[f]	—
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	34/50 (68%)	27/49 (55%)	29/49 (59%)	30/50 (60%)
Adjusted rate	70.7%	55.7%	61.7%	65.7%
Terminal rate	23/32 (72%)	18/35 (51%)	25/39 (64%)	18/28 (64%)
First incidence (days)	525	499	665	492
Poly-3 test	P=0.464	P=0.090N	P=0.237N	P=0.377N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	34/50 (68%)	28/49 (57%)	30/49 (61%)	31/50 (62%)
Adjusted rate	70.7%	57.7%	63.6%	67.4%
Terminal rate	23/32 (72%)	19/35 (54%)	25/39 (64%)	18/28 (64%)
First incidence (days)	525	499	665	492
Poly-3 test	P=0.430	P=0.129N	P=0.301N	P=0.447N
Skin: Squamous Cell Papilloma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.2%	0.0%	6.5%	2.4%
Terminal rate	0/32 (0%)	0/35 (0%)	2/39 (5%)	1/28 (4%)
First incidence (days)	666	—	722	734 (T)
Poly-3 test	P=0.570	P=0.492N	P=0.317	P=0.744
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.5%	0.0%	6.5%	4.8%
Terminal rate	2/32 (6%)	0/35 (0%)	2/39 (5%)	2/28 (7%)
First incidence (days)	734 (T)	—	694	734 (T)
Poly-3 test	P=0.419	P=0.227N	P=0.518	P=0.670
Thyroid Gland (C-Cell): Adenoma				
Overall rate	5/50 (10%)	3/49 (6%)	2/49 (4%)	3/50 (6%)
Adjusted rate	11.2%	6.6%	4.3%	7.1%
Terminal rate	3/32 (9%)	3/35 (9%)	2/39 (5%)	2/28 (7%)
First incidence (days)	716	734 (T)	734 (T)	590
Poly-3 test	P=0.484N	P=0.342N	P=0.203N	P=0.389N
Thyroid Gland (C-Cell): Carcinoma				
Overall rate	3/50 (6%)	0/49 (0%)	1/49 (2%)	0/50 (0%)
Adjusted rate	6.7%	0.0%	2.2%	0.0%
Terminal rate	3/32 (9%)	0/35 (0%)	0/39 (0%)	0/28 (0%)
First incidence (days)	734 (T)	—	665	—
Poly-3 test	P=0.213N	P=0.114N	P=0.291N	P=0.131N

Table B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	3/49 (6%)	3/49 (6%)	3/50 (6%)
Adjusted rate	17.9%	6.6%	6.5%	7.1%
Terminal rate	6/32 (19%)	3/35 (9%)	2/39 (5%)	2/28 (7%)
First incidence (days)	716	734 (T)	665	590
Poly-3 test	P=0.249N	P=0.090N	P=0.086N	P=0.116N
Uterus: Stromal Polyp				
Overall rate	7/50 (14%)	8/50 (16%)	14/50 (28%)	12/50 (24%)
Adjusted rate	15.5%	16.9%	29.8%	28.1%
Terminal rate	5/32 (16%)	6/35 (17%)	10/39 (26%)	9/28 (32%)
First incidence (days)	609	635	665	589
Poly-3 test	P=0.109	P=0.537	P=0.081	P=0.117
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	7/50 (14%)	8/50 (16%)	14/50 (28%)	13/50 (26%)
Adjusted rate	15.5%	16.9%	29.8%	29.9%
Terminal rate	5/32 (16%)	6/35 (17%)	10/39 (26%)	9/28 (32%)
First incidence (days)	609	635	665	478
Poly-3 test	P=0.071	P=0.537	P=0.081	P=0.082
All Organs: Mononuclear Cell Leukemia				
Overall rate	11/50 (22%)	15/50 (30%)	12/50 (24%)	14/50 (28%)
Adjusted rate	24.1%	31.8%	25.7%	31.5%
Terminal rate	6/32 (19%)	10/35 (29%)	10/39 (26%)	5/28 (18%)
First incidence (days)	639	656	617	538
Poly-3 test	P=0.364	P=0.276	P=0.528	P=0.292
All Organs: Benign Neoplasms				
Overall rate	46/50 (92%)	41/50 (82%)	44/50 (88%)	44/50 (88%)
Adjusted rate	92.8%	82.4%	92.2%	91.7%
Terminal rate	30/32 (94%)	27/35 (77%)	36/39 (92%)	26/28 (93%)
First incidence (days)	359	499	665	492
Poly-3 test	P=0.348	P=0.100N	P=0.616N	P=0.573N
All Organs: Malignant Neoplasms				
Overall rate	25/50 (50%)	22/50 (44%)	25/50 (50%)	18/50 (36%)
Adjusted rate	52.9%	44.8%	52.5%	39.4%
Terminal rate	12/32 (38%)	12/35 (34%)	18/39 (46%)	6/28 (21%)
First incidence (days)	561	533	617	478
Poly-3 test	P=0.157N	P=0.278N	P=0.566N	P=0.134N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	44/50 (88%)	46/50 (92%)	48/50 (96%)
Adjusted rate	98.0%	88.0%	95.6%	96.0%
Terminal rate	31/32 (97%)	29/35 (83%)	37/39 (95%)	26/28 (93%)
First incidence (days)	359	499	617	478
Poly-3 test	P=0.383	P=0.057N	P=0.460N	P=0.500N

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

TABLE B4
Historical Incidence of Clitoral Gland Neoplasms in Control Female F344/N Rats

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
trans-Cinnamaldehyde (feed)	4/99	9/99	13/99
Citral (feed)	15/98	1/98	16/98
Decalin (inhalation)	8/48	1/48	9/48
p,p′-Dichlorodiphenyl sulfone (feed)	1/47	0/47	1/47
Dipropylene glycol (drinking water)	6/48	5/48	10/48
Elmiron® (gavage)	3/50	0/50	3/50
2,4-Hexadienal (gavage)	5/50	2/50	7/50
Indium phosphide (inhalation)	5/49	0/49	5/49
60-Hz Magnetic fields (whole body exposure)	11/90	0/90	11/90
Methacrylonitrile (gavage)	2/49	1/49	3/49
Naphthalene (inhalation)	4/49	0/49	4/49
o-Nitrotoluene (feed)	12/59	2/59	14/59
p-Nitrotoluene (feed)	7/50	2/50	8/50
Riddelliine	7/49	3/49	10/49
Sodium nitrite (drinking water)	8/46	2/46	10/46
Vanadium pentoxide (inhalation)	2/50	0/50	2/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	100/931 (10.7%)	28/931 (3.0%)	126/931 (13.5%)
Mean ± standard deviation	10.7% ± 5.5%	2.9% ± 3.3%	13.4% ± 6.8%
Range	2%-20%	0%-10%	2%-24%

[a] Data as of January 31, 2002

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	16	10	10	17
Natural deaths	2	5		5
Survivors				
Died last week of study			1	
Terminal sacrifice	32	35	38	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(48)	(46)	(49)	(45)
Muscularis, inflammation, chronic	1 (2%)			
Liver	(50)	(48)	(49)	(50)
Angiectasis	1 (2%)	2 (4%)		1 (2%)
Basophilic focus		2 (4%)	1 (2%)	
Clear cell focus	7 (14%)	5 (10%)	4 (8%)	2 (4%)
Congestion	1 (2%)		1 (2%)	
Hepatodiaphragmatic nodule	9 (18%)	6 (13%)	6 (12%)	7 (14%)
Inflammation, granulomatous			1 (2%)	
Necrosis	2 (4%)	2 (4%)		
Vacuolization cytoplasmic	3 (6%)		2 (4%)	
Bile duct, hyperplasia	1 (2%)			
Hepatocyte, regeneration		1 (2%)		
Periportal, pigmentation			1 (2%)	
Serosa, hemorrhage		1 (2%)		
Mesentery	(26)	(20)	(20)	(17)
Necrosis	26 (100%)	20 (100%)	20 (100%)	16 (94%)
Oral mucosa	(1)			(2)
Inflammation, chronic	1 (100%)			
Pharyngeal, hyperplasia, squamous				2 (100%)
Pancreas	(50)	(47)	(49)	(49)
Acinus, atrophy	1 (2%)			1 (2%)
Stomach, forestomach	(50)	(47)	(49)	(49)
Erosion				1 (2%)
Hyperplasia, squamous	1 (2%)		1 (2%)	1 (2%)
Mineralization	1 (2%)			
Ulcer	2 (4%)	2 (4%)	1 (2%)	
Stomach, glandular	(50)	(47)	(49)	(49)
Mineralization	1 (2%)			
Tongue	(2)			(1)
Epithelium, hyperplasia				1 (100%)
Tooth	(1)			
Pulp, inflammation, suppurative	1 (100%)			

[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 Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Cardiovascular System				
Heart	(50)	(50)	(49)	(50)
Cardiomyopathy	1 (2%)		1 (2%)	
Artery, mineralization	1 (2%)			
Atrium, thrombosis	2 (4%)	2 (4%)	1 (2%)	
Ventricle, angiectasis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(48)	(49)	(49)
Hyperplasia	3 (6%)		2 (4%)	2 (4%)
Hypertrophy	1 (2%)			
Necrosis				1 (2%)
Vacuolization cytoplasmic	7 (14%)	7 (15%)	11 (22%)	8 (16%)
Adrenal medulla	(50)	(48)	(49)	(49)
Hyperplasia	3 (6%)	2 (4%)		
Islets, pancreatic	(50)	(47)	(49)	(49)
Hyperplasia			1 (2%)	
Parathyroid gland	(49)	(48)	(48)	(47)
Hyperplasia	1 (2%)			
Pituitary gland	(50)	(49)	(49)	(50)
Angiectasis	1 (2%)			
Cyst	1 (2%)	4 (8%)	3 (6%)	
Hemorrhage		1 (2%)		1 (2%)
Pars distalis, angiectasis	2 (4%)			
Pars distalis, hyperplasia	7 (14%)	9 (18%)	8 (16%)	5 (10%)
Thyroid gland	(50)	(49)	(49)	(50)
C-cell, hyperplasia	15 (30%)	7 (14%)	6 (12%)	6 (12%)
General Body System				
None				
Genital System				
Clitoral gland	(48)	(49)	(49)	(50)
Cyst	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Hyperplasia	3 (6%)	3 (6%)	1 (2%)	3 (6%)
Inflammation, chronic	1 (2%)			1 (2%)
Ovary	(50)	(50)	(49)	(50)
Cyst	3 (6%)	4 (8%)	6 (12%)	3 (6%)
Uterus	(50)	(49)	(49)	(50)
Atrophy			1 (2%)	
Hemorrhage				1 (2%)
Endometrium, hyperplasia		3 (6%)		1 (2%)
Endometrium, inflammation, suppurative			1 (2%)	
Endometrium, metaplasia, squamous		1 (2%)		
Vagina	(1)			(2)
Epithelium, hyperplasia				1 (50%)

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Hematopoietic System				
Lymph node	(6)		(4)	(2)
Hyperplasia, lymphoid	1 (17%)			
Deep cervical, ectasia	1 (17%)			1 (50%)
Deep cervical, hyperplasia, lymphoid			1 (25%)	
Deep cervical, infiltration cellular, histiocyte	1 (17%)			
Deep cervical, pigmentation	1 (17%)			
Pancreatic, pigmentation			1 (25%)	
Thoracic, hyperplasia, plasma cell				1 (50%)
Lymph node, bronchial	(2)	(10)	(7)	(5)
Ectasia	1 (50%)	1 (10%)		
Infiltration cellular, histiocyte			1 (14%)	
Inflammation, suppurative	1 (50%)			
Pigmentation		2 (20%)		1 (20%)
Lymph node, mediastinal	(45)	(46)	(49)	(44)
Angiectasis	1 (2%)	2 (4%)		1 (2%)
Hyperplasia, plasma cell				1 (2%)
Inflammation, suppurative	1 (2%)			
Pigmentation		1 (2%)		
Spleen	(50)	(49)	(49)	(50)
Accessory spleen	1 (2%)	1 (2%)		1 (2%)
Fibrosis	1 (2%)			3 (6%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	2 (4%)
Hemorrhage	3 (6%)			
Necrosis		1 (2%)	1 (2%)	1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Galactocele	3 (6%)	1 (2%)	5 (10%)	1 (2%)
Skin	(50)	(50)	(49)	(50)
Cyst epithelial inclusion		1 (2%)		
Erosion				1 (2%)
Ulcer				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fracture			1 (2%)	
Cranium, hemorrhage		1 (2%)		
Nervous System				
Brain	(50)	(49)	(49)	(50)
Compression	6 (12%)	5 (10%)	6 (12%)	3 (6%)
Hemorrhage	1 (2%)	1 (2%)	3 (6%)	6 (12%)
Thrombosis			1 (2%)	
Cerebrum, gliosis			1 (2%)	

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Respiratory System				
Larynx	(50)	(49)	(49)	(48)
Foreign body		1 (2%)		3 (6%)
Inflammation, chronic	2 (4%)	4 (8%)	2 (4%)	2 (4%)
Inflammation, suppurative		2 (4%)		4 (8%)
Epiglottis, metaplasia, squamous		1 (2%)	1 (2%)	
Respiratory epithelium, hyperplasia		1 (2%)		
Respiratory epithelium, metaplasia, squamous				1 (2%)
Respiratory epithelium, epiglottis, degeneration		1 (2%)	1 (2%)	
Squamous epithelium, hyperplasia				1 (2%)
Lung	(50)	(50)	(49)	(50)
Congestion				1 (2%)
Foreign body				1 (2%)
Alveolar epithelium, hyperplasia	9 (18%)	14 (28%)	8 (16%)	14 (28%)
Alveolar epithelium, metaplasia, squamous			1 (2%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	21 (42%)	26 (52%)	29 (59%)	29 (58%)
Alveolus, pigmentation				1 (2%)
Alveolus, proteinosis	11 (22%)	16 (32%)	15 (31%)	23 (46%)
Bronchiole, mineralization	1 (2%)			
Interstitium, fibrosis	16 (32%)	24 (48%)	23 (47%)	28 (56%)
Interstitium, inflammation, chronic	1 (2%)	6 (12%)	6 (12%)	4 (8%)
Mediastinum, hyperplasia, histiocytic				1 (2%)
Mediastinum, pigmentation				1 (2%)
Perivascular, pigmentation	1 (2%)			
Nose	(50)	(48)	(49)	(49)
Foreign body	1 (2%)	4 (8%)	3 (6%)	1 (2%)
Inflammation, suppurative	3 (6%)	5 (10%)	7 (14%)	3 (6%)
Goblet cell, hyperplasia	1 (2%)	1 (2%)	5 (10%)	2 (4%)
Nasolacrimal duct, inflammation, suppurative	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Olfactory epithelium, degeneration, hyaline				1 (2%)
Respiratory epithelium, hyperplasia		1 (2%)	1 (2%)	2 (4%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Pleura	(20)	(25)	(25)	(28)
Inflammation, chronic	15 (75%)	17 (68%)	23 (92%)	27 (96%)
Mesothelium, hyperplasia	2 (10%)	7 (28%)	8 (32%)	2 (7%)
Special Senses System				
Eye	(1)	(2)	(5)	(4)
Atrophy		2 (100%)		
Anterior chamber, hemorrhage				1 (25%)
Choroid, sclera, mineralization			1 (20%)	
Cornea, hyperplasia				1 (25%)
Cornea, inflammation, suppurative		1 (50%)		
Lens, cataract	1 (100%)		3 (60%)	2 (50%)
Harderian gland	(1)			
Inflammation, suppurative	1 (100%)			

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Urinary System				
Kidney	(50)	(46)	(49)	(50)
Cyst	1 (2%)	2 (4%)	1 (2%)	
Cytoplasmic alteration	1 (2%)			1 (2%)
Nephropathy, chronic	44 (88%)	45 (98%)	48 (98%)	48 (96%)
Cortex, renal tubule, hyperplasia	1 (2%)	4 (9%)	4 (8%)	2 (4%)
Papilla, mineralization	3 (6%)	2 (4%)	4 (8%)	4 (8%)
Pelvis, dilatation	1 (2%)		1 (2%)	1 (2%)
Pelvis, mineralization	11 (22%)	16 (35%)	19 (39%)	18 (36%)
Pelvis, transitional epithelium, hyperplasia		2 (4%)	2 (4%)	2 (4%)
Renal tubule, mineralization	1 (2%)			
Renal tubule, pigmentation				1 (2%)
Ureter	(1)			
Mineralization	1 (100%)			
Necrosis	1 (100%)			
Urinary bladder	(50)	(47)	(49)	(50)
Degeneration		1 (2%)		
Necrosis	1 (2%)			
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF DECALIN

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TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	100 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	7	7	5
Natural deaths	3	2	7	11
Survivors				
Died last week of study	1		1	1
Terminal sacrifice	39	41	35	33
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(40)	(41)	(40)
Intestine large, cecum	(48)	(48)	(49)	(46)
Polyp adenomatous	1 (2%)			
Intestine small, duodenum	(47)	(48)	(47)	(43)
Carcinoma			1 (2%)	
Intestine small, jejunum	(46)	(48)	(47)	(43)
Carcinoma		1 (2%)	1 (2%)	
Liver	(50)	(50)	(50)	(50)
Cholangioma		1 (2%)		
Hemangiosarcoma	1 (2%)	3 (6%)		2 (4%)
Hepatoblastoma		1 (2%)		1 (2%)
Hepatocellular carcinoma	10 (20%)	7 (14%)	8 (16%)	11 (22%)
Hepatocellular carcinoma, multiple			2 (4%)	
Hepatocellular adenoma	16 (32%)	16 (32%)	9 (18%)	17 (34%)
Hepatocellular adenoma, multiple	6 (12%)	6 (12%)	5 (10%)	10 (20%)
Histiocytic sarcoma			1 (2%)	
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Mesentery	(14)	(11)	(10)	(15)
Liposarcoma				1 (7%)
Sarcoma, metastatic, uncertain primary site				1 (7%)
Pancreas	(49)	(50)	(50)	(49)
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, uncertain primary site				2 (4%)
Salivary glands	(50)	(50)	(50)	(49)
Stomach, forestomach	(49)	(50)	(49)	(50)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Stomach, glandular	(49)	(49)	(48)	(48)
Liposarcoma, metastatic, mesentery				1 (2%)
Tooth	(23)	(26)	(22)	(21)
Sarcoma, metastatic, uncertain primary site				1 (5%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Carcinoma, metastatic, uncertain primary site				1 (2%)
Hemangiosarcoma	1 (2%)	1 (2%)		
Hemangiosarcoma, metastatic, liver				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Subcapsular, adenoma	2 (4%)	1 (2%)		4 (8%)
Adrenal medulla	(49)	(50)	(50)	(50)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Islets, pancreatic	(49)	(50)	(50)	(49)
Adenoma	1 (2%)		2 (4%)	2 (4%)
Pituitary gland	(48)	(50)	(50)	(49)
Pars distalis, adenoma	1 (2%)	1 (2%)		
Thyroid gland	(48)	(48)	(49)	(49)
Follicular cell, carcinoma			1 (2%)	
General Body System				
Peritoneum				(1)
Hemangiosarcoma, metastatic, liver				1 (100%)
Genital System				
Coagulating gland	(1)			
Adenoma	1 (100%)			
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Preputial gland	(49)	(49)	(50)	(50)
Hemangiosarcoma			2 (4%)	
Prostate	(48)	(50)	(50)	(50)
Seminal vesicle	(49)	(50)	(50)	(50)
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma				3 (6%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(48)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Lymph node	(1)		(3)	(1)
Lymph node, bronchial	(42)	(36)	(40)	(41)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)	2 (5%)
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, uncertain primary site				2 (5%)
Lymph node, mandibular	(31)	(36)	(32)	(22)
Carcinoma, metastatic, harderian gland	1 (3%)			
Liposarcoma, metastatic, mesentery				1 (5%)
Lymph node, mesenteric	(49)	(48)	(50)	(47)
Histiocytic sarcoma			1 (2%)	
Liposarcoma, metastatic, mesentery				1 (2%)
Plasma cell tumor malignant		1 (2%)		
Sarcoma, metastatic, uncertain primary site				2 (4%)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Hematopoietic System (continued)				
Lymph node, mediastinal	(41)	(36)	(42)	(35)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Sarcoma, metastatic, uncertain primary site				2 (6%)
Spleen	(49)	(50)	(50)	(49)
Hemangiosarcoma		3 (6%)		2 (4%)
Thymus	(44)	(44)	(42)	(40)
Carcinoma, metastatic, uncertain primary site				1 (3%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)		
Subcutaneous tissue, hemangioma			1 (2%)	
Musculoskeletal System				
Skeletal muscle				(2)
Liposarcoma, metastatic, mesentery				1 (50%)
Sarcoma, metastatic, uncertain primary site				1 (50%)
Nervous System				
None				
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	5 (10%)	4 (8%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)			
Alveolar/bronchiolar carcinoma	6 (12%)	7 (14%)	6 (12%)	12 (24%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)	1 (2%)		
Carcinoma, metastatic, harderian gland	2 (4%)			
Carcinoma, metastatic, thyroid gland			1 (2%)	
Carcinoma, metastatic, uncertain primary site				1 (2%)
Hemangiosarcoma, metastatic, liver				1 (2%)
Hepatocellular carcinoma, metastatic, liver	3 (6%)	1 (2%)	4 (8%)	5 (10%)
Histiocytic sarcoma			1 (2%)	
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, uncertain primary site				2 (4%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung				2 (4%)
Pleura				(1)
Sarcoma, metastatic, uncertain primary site				1 (100%)
Special Senses System				
Harderian gland	(9)	(5)	(5)	(5)
Adenoma	6 (67%)	2 (40%)	4 (80%)	2 (40%)
Carcinoma	3 (33%)	1 (20%)	1 (20%)	1 (20%)
Bilateral, adenoma		2 (40%)		1 (20%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Carcinoma, metastatic, uncertain primary site				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Urinary bladder	(49)	(50)	(49)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant	3 (6%)	3 (6%)	4 (8%)	4 (8%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	43	39	37	42
Total primary neoplasms	69	64	52	75
Total animals with benign neoplasms	32	27	22	32
Total benign neoplasms	42	35	25	41
Total animals with malignant neoplasms	23	20	23	23
Total malignant neoplasms	27	29	27	34
Total animals with metastatic neoplasms	5	1	6	10
Total metastatic neoplasms	6	1	7	48
Total animals with malignant neoplasms of uncertain primary site				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 C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	384	421	476	588	606	635	642	649	665	674	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	031	023	032	040	048	008	035	055	047	021	001	003	004	009	011	013	014	015	022	029	034	037	042	043	045
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	A	+	A	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																	X								
Intestine small, duodenum	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Hepatocellular carcinoma	X			X	X		X				X					X									
Hepatocellular adenoma			X	X		X		X					X			X					X				
Hepatocellular adenoma, multiple														X	X							X			
Mesentery			+					+	+		+			+	+			+		+	+		+		
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth						+					+			+	+	+	+		+	+	+		+		
Cardiovascular System																									
Blood vessel		+																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma															X									X	
Adrenal medulla	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	A	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
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 Inhalation Study of Decalin: Chamber Control

Number of Days on Study	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	
Carcass ID Number	049	050	006	007	010	012	016	017	020	026	028	033	036	038	039	041	044	046	002	018	019	024	025	027	030	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous																										1
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma			X			X			X											X						10
Hepatocellular adenoma				X			X		X			X	X				X					X	X	X		16
Hepatocellular adenoma, multiple																X				X					X	6
Mesentery					+		+										+	+								14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue										+																1
Tooth	+				+	+	+	+		+	+	+			+	+		+	+					+		23
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcapsular, adenoma																										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X																						1
Parathyroid gland	+	+	+	+	M	M	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	384	421	476	588	606	635	642	649	665	674	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	031	023	032	040	048	008	035	050	047	021	001	003	004	009	011	013	014	015	022	029	034	037	042	043	045
Genital System																									
Coagulating gland													+												
Adenoma													X												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Lymph node						+																			
Lymph node, bronchial	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M
Lymph node, mandibular	+	+	+	+	+	M	+	M	M	+	+	+	M	M	M	M	M	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland										X															
Lymph node, mesenteric	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	M	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X											X						
Alveolar/bronchiolar adenoma, multiple																	X								
Alveolar/bronchiolar carcinoma								X						X				X							
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, harderian gland										X															
Hepatocellular carcinoma, metastatic, liver				X												X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	
Carcass ID Number	049	050	006	007	010	012	016	017	020	026	028	033	036	038	039	041	044	046	002	018	019	024	025	027	030	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Adenoma																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph node																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	42
Lymph node, mandibular	M	+	+	M	M	+	M	+	+	M	+	+	+	M	M	M	+	M	+	+	+	M	+	+	M	31
Carcinoma, metastatic, harderian gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	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
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X				X		X									X								6
Alveolar/bronchiolar adenoma, multiple										X																2
Alveolar/bronchiolar carcinoma					X									X											X	6
Alveolar/bronchiolar carcinoma, multiple				X															X							2
Carcinoma, metastatic, harderian gland																					X					2
Hepatocellular carcinoma, metastatic, liver			X																							3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	384	421	476	588	606	635	642	649	665	674	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	031	023	032	040	048	008	035	005	047	021	011	003	004	009	011	013	014	015	022	029	034	037	042	043	045
Special Senses System																									
Ear		+																							
Eye										+		+						+							
Harderian gland				+						+		+						+		+			+	+	
Adenoma				X								X						X					X	X	
Carcinoma										X										X					
Urinary System																									
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735		
Carcass ID Number	049	050	006	007	010	012	016	017	020	026	028	033	036	038	039	041	044	046	002	018	019	024	025	027	030	Total Tissues/ Tumors
Special Senses System																										
Ear																										1
Eye																										3
Harderian gland																					+		+			9
Adenoma																							X			6
Carcinoma																					X					3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant	X								X																	3

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	203	495	497	532	539	561	575	658	718	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734
Carcass ID Number	247	203	207	219	234	236	249	221	224	201	208	211	213	214	216	218	228	229	233	238	245	204	205	209	212
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	A	+	+	+	A	+	M	+	+	+	+	I	+	+	I	I	M	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangioma																									
Hemangiosarcoma																	X						X		
Hepatoblastoma																									X
Hepatocellular carcinoma			X		X	X		X									X								
Hepatocellular adenoma		X		X	X							X		X		X		X			X	X	X		
Hepatocellular adenoma, multiple																				X					
Mesentery		+		+								+				+	+	+	+						+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+			+	+	+	+		+			+		+			+	+	
Cardiovascular System																									
Blood vessel							+																		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	215	217	222	223	225	226	227	232	235	237	240	241	242	243	202	206	210	220	230	231	239	244	246	248	250	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	I	+	+	+	+	+	+	+	+	I	+	+	+	+	I	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma													X													1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangioma																								X		1
Hemangiosarcoma													X													3
Hepatoblastoma																										1
Hepatocellular carcinoma										X													X			7
Hepatocellular adenoma		X									X	X						X					X	X		16
Hepatocellular adenoma, multiple	X									X				X							X				X	6
Mesentery		+																+		+						11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth			+		+	+	+	+	+	+			+		+	+	+	+	+			+		+	+	26
Cardiovascular System																										
Blood vessel							+						+													3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma						X																				1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	M	+	+	+	+	M	+	+	I	+	M	+	+	+	M	+	M	+	+	+	+	M	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma																							X			1
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
Tissue NOS												+														1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	203	495	497	532	539	561	575	658	718	733	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	734
Carcass ID Number	247	203	207	219	234	236	249	221	224	201	208	211	213	214	216	218	228	229	233	238	245	204	205	209	212
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	+	+	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mandibular	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant																									
Lymph node, mediastinal	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	M	+	M	M	M	+	+	M	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X					X											
Thymus	+	+	I	+	+	+	+	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	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																							M		
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X		X					X			X				
Alveolar/bronchiolar carcinoma			X											X	X		X			X		X			
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																										
Eye																							+		
Harderian gland									+									+					+		
Adenoma									X									X							
Carcinoma																							X		
Bilateral, adenoma																									
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																						X		X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	734	734	734	734	74	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	215	217	222	223	225	226	227	232	235	237	240	241	242	243	202	206	210	220	230	231	239	244	246	248	250	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	M	M	+	+	+	M	36
Lymph node, mandibular	M	+	+	+	M	+	+	+	+	M	+	M	+	+	M	+	+	M	+	+	M	+	M	+	M	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Plasma cell tumor malignant							X																			1
Lymph node, mediastinal	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+	+	+	M	+	M	36
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma															X											3
Thymus	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Squamous cell papilloma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord													M													
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														5
Alveolar/bronchiolar carcinoma								X																		7
Alveolar/bronchiolar carcinoma, multiple				X																						1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																						+				1
Eye					+														+							3
Harderian gland					+						+															5
Adenoma																										2
Carcinoma																										1
Bilateral, adenoma					X						X															2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant													X													3

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	448	468	561	596	596	602	612	623	654	699	700	703	715	728	733	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	450	435	420	426	442	406	418	430	409	407	425	423	404	417	401	403	408	410	411	413	414	419	422	424	432
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	A	A	M	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Intestine small, jejunum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Intestine small, ileum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X	X	X			X																	
Hepatocellular carcinoma, multiple												X						X							
Hepatocellular adenoma		X											X											X	
Hepatocellular adenoma, multiple	X							X	X		X														
Histiocytic sarcoma																									
Mesentery											+						+			+	+				
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+							+		+		+			+	+	+	+	+	+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X		X																
Parathyroid gland	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Penis				+																					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	
Carcass ID Number	437	439	440	441	446	448	405	412	415	416	427	433	434	436	445	447	402	421	428	429	431	438	443	444	449	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	I	+	+	+	A	I	+	+	+	+	+	M	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma										X		X					X			X						8
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma		X		X				X		X	X							X								9
Hepatocellular adenoma, multiple																								X		5
Histiocytic sarcoma														X												1
Mesentery						+		+					+					+	+	+						10
Oral mucosa														M												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+			+	+	+	+					+	+				+		+		+	+	+			22
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Parathyroid gland	M	+	M	+	+	M	M	M	+	M	+	+	+	M	M	M	+	M	+	+	+	+	+	+	+	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma															X											1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												1
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	448	468	561	596	596	602	612	623	654	699	700	703	715	728	733	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	450	435	420	426	442	406	418	430	409	407	425	423	404	417	401	403	408	410	411	413	414	419	422	424	432
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node						+					+														
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Lymph node, mandibular	+	M	+	+	M	+	+	+	+	M	M	M	M	+	M	+	+	M	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mediastinal	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	M	+	M	+	M	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X					X									X	
Alveolar/bronchiolar carcinoma								X															X		
Carcinoma, metastatic, thyroid gland																									
Hepatocellular carcinoma, metastatic, liver				X	X																				
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									+
Harderian gland																									+
Adenoma																									X
Carcinoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	
Carcass ID Number	437	439	440	441	446	448	405	412	415	416	427	433	434	436	445	447	402	421	428	429	431	438	443	444	449	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												1
Lymph node			+																							3
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	M	+	+	+	M	+	M	+	40
Alveolar/bronchiolar carcinoma, metastatic, lung														X												1
Lymph node, mandibular	M	+	+	+	+	+	+	+	M	+	+	M	+	M	+	M	M	M	M	+	+	M	+	+	+	32
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	42
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord											M			M												
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland															X											1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													4
Alveolar/bronchiolar carcinoma		X						X						X						X						6
Carcinoma, metastatic, thyroid gland															X											1
Hepatocellular carcinoma, metastatic, liver																	X			X						4
Histiocytic sarcoma														X												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye									+																	2
Harderian gland				+					+											+				+		5
Adenoma									X											X				X		4
Carcinoma				X																						1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	448	468	561	596	596	602	612	623	654	699	700	703	715	728	733	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	450	435	420	426	442	406	418	430	409	407	425	423	404	417	401	403	408	410	411	413	414	419	422	424	432
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant				X		X														X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	
Carcass ID Number	437	439	440	441	446	448	405	412	415	416	427	433	434	436	445	447	402	421	428	429	431	438	443	444	449	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												1
Lymphoma malignant			X																							4

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	467	469	530	552	593	602	605	616	622	634	634	692	718	723	723	731	733	733	733	733	733	733	733	733	733
Carcass ID Number	632	644	609	646	614	603	620	611	648	629	635	641	630	606	616	631	601	610	617	618	622	624	628	633	634
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	A	A	A	+	A	A	+	A	A	+	+	A	+	+	+	M	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	A	+	+	A	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	A	A	A	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Hepatoblastoma													X												
Hepatocellular carcinoma				X	X	X	X		X			X			X				X				X		X
Hepatocellular adenoma							X		X	X			X		X	X		X		X					
Hepatocellular adenoma, multiple																	X								
Liposarcoma, metastatic, mesentery															X										
Sarcoma, metastatic, uncertain primary site												X													
Mesentery			+									+			+	+		+		+	+				+
Liposarcoma															X										
Sarcoma, metastatic, uncertain primary site												X													
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, mesentery															X										
Sarcoma, metastatic, uncertain primary site												X													X
Salivary glands	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									X
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, mesentery															X										
Tooth																+	+	+	+	+	+	+	+		+
Sarcoma, metastatic, uncertain primary site																									X
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Carcinoma, metastatic, uncertain primary site												X													
Hemangiosarcoma, metastatic, liver																							X		
Sarcoma, metastatic, uncertain primary site																									X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	
Carcass ID Number	636	637	639	643	647	649	602	604	605	607	608	613	615	619	623	625	627	638	640	642	645	650	612	621	626	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																							X			2
Hepatoblastoma																										1
Hepatocellular carcinoma																								X		11
Hepatocellular adenoma		X					X						X	X		X	X	X	X					X		17
Hepatocellular adenoma, multiple	X		X		X	X		X		X		X			X					X						10
Liposarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, uncertain primary site																										1
Mesentery	+	+		+	+							+	+			+										15
Liposarcoma																										1
Sarcoma, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liposarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, uncertain primary site																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liposarcoma, metastatic, mesentery																										1
Tooth	+	+	+		+	+	+		+		+		+		+				+						+	21
Sarcoma, metastatic, uncertain primary site																										1
Cardiovascular System																										
Blood vessel		+																								1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Carcinoma, metastatic, uncertain primary site																										1
Hemangiosarcoma, metastatic, liver																										1
Sarcoma, metastatic, uncertain primary site																										1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	467	469	530	552	593	602	605	616	622	634	634	692	718	723	723	731	733	733	733	733	733	733	733	733	733	733
Carcass ID Number	632	644	609	646	614	603	620	611	648	629	635	641	630	606	616	631	601	610	617	618	622	624	628	633	634
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									X
Subcapsular, adenoma										X												X			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									X
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X					X				
Parathyroid gland	M	+	+	M	A	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+
Pituitary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																										
Peritoneum																							+		
Hemangiosarcoma, metastatic, liver																							X		
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, mesentery															X										
Sarcoma, metastatic, uncertain primary site												X													
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma						X																X			
Hematopoietic System																										
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+																					
Lymph node, bronchial	+	+	+	+	A	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung		X	X																						
Liposarcoma, metastatic, mesentery															X										
Sarcoma, metastatic, uncertain primary site												X													X
Lymph node, mandibular	M	M	M	+	A	M	+	+	M	M	+	+	+	M	+	M	M	+	M	M	+	+	M	M	M
Liposarcoma, metastatic, mesentery															X										
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, mesentery															X										
Sarcoma, metastatic, uncertain primary site												X													X
Lymph node, mediastinal	M	+	+	+	A	+	M	M	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	M	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X															
Sarcoma, metastatic, uncertain primary site												X													X
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X										X		
Thymus	+	+	+	M	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+
Carcinoma, metastatic, uncertain primary site												X													

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735		
Carcass ID Number	636	637	639	643	647	649	602	604	605	607	608	613	615	619	623	625	627	638	640	642	645	650	612	621	626	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Subcapsular, adenoma																			X				X			4
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Parathyroid gland	+	+	+	M	+	+	M	+	M	+	+	M	M	+	+	I	+	+	+	+	M	+	M	+	M	32
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
Peritoneum																										1
Hemangiosarcoma, metastatic, liver																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, uncertain primary site																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																							X			3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																										1
Lymph node, bronchial	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	41
Alveolar/bronchiolar carcinoma, metastatic, lung																										2
Liposarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, uncertain primary site																										2
Lymph node, mandibular	M	M	M	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	M	M	M	M	M	M	M	22
Liposarcoma, metastatic, mesentery																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liposarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, uncertain primary site																										2
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	M	M	+	M	M	+	+	35
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Sarcoma, metastatic, uncertain primary site																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	I	+	40
Carcinoma, metastatic, uncertain primary site																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	467	469	530	552	593	602	605	616	622	634	634	692	718	723	723	731	733	733	733	733	733	733	733	733	733
Carcass ID Number	632	644	609	646	614	603	620	611	648	629	635	641	630	606	616	631	601	610	617	618	622	624	628	633	634
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+			+										
Liposarcoma, metastatic, mesentery															X										
Sarcoma, metastatic, uncertain primary site												X													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X																
Alveolar/bronchiolar carcinoma		X	X				X		X	X							X						X		
Carcinoma, metastatic, uncertain primary site												X													
Hemangiosarcoma, metastatic, liver																							X		
Hepatocellular carcinoma, metastatic, liver						X			X			X							X				X		
Liposarcoma, metastatic, mesentery															X										
Sarcoma, metastatic, uncertain primary site												X													X
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		X	X																						
Nose	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Pleura												+													
Sarcoma, metastatic, uncertain primary site												X													
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																				+					
Harderian gland	+										+									+					
Adenoma	X																								
Carcinoma																				X					
Bilateral, adenoma																									
Urinary System																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site												X													
Sarcoma, metastatic, uncertain primary site																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant				X					X						X										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	733	733	733	733	733	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735		
Carcass ID Number	636	637	639	643	647	649	602	604	605	607	608	613	615	619	623	625	627	638	640	642	645	650	612	621	626	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Liposarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												2
Alveolar/bronchiolar carcinoma					X										X						X		X		X	12
Carcinoma, metastatic, uncertain primary site																										1
Hemangiosarcoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										5
Liposarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, uncertain primary site																										2
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pleura																										1
Sarcoma, metastatic, uncertain primary site																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye																										1
Harderian gland								+							+											5
Adenoma								X																		2
Carcinoma																										1
Bilateral, adenoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uncertain primary site																										1
Sarcoma, metastatic, uncertain primary site																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																X										4

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	2/49 (4%)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted rate[b]	4.5%	2.2%	0.0%	9.0%
Terminal rate[c]	2/40 (5%)	1/41 (2%)	0/36 (0%)	3/34 (9%)
First incidence (days)	733 (T)	733 (T)	—[e]	634
Poly-3 test[d]	P=0.088	P=0.496N	P=0.235N	P=0.337
Harderian Gland: Adenoma				
Overall rate	6/50 (12%)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted rate	13.1%	8.9%	8.9%	6.7%
Terminal rate	5/40 (13%)	3/41 (7%)	4/36 (11%)	2/34 (6%)
First incidence (days)	588	718	733 (T)	467
Poly-3 test	P=0.277N	P=0.378N	P=0.379N	P=0.251N
Harderian Gland: Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.6%	2.2%	2.2%	2.3%
Terminal rate	2/40 (5%)	1/41 (2%)	1/36 (3%)	1/34 (3%)
First incidence (days)	674	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.392N	P=0.309N	P=0.309N	P=0.316N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	9/50 (18%)	5/50 (10%)	5/50 (10%)	4/50 (8%)
Adjusted rate	19.6%	11.1%	11.1%	8.9%
Terminal rate	7/40 (18%)	4/41 (10%)	5/36 (14%)	3/34 (9%)
First incidence (days)	588	718	733 (T)	467
Poly-3 test	P=0.189N	P=0.202N	P=0.203N	P=0.123N
Liver: Hemangiosarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted rate	2.2%	6.7%	0.0%	4.5%
Terminal rate	1/40 (3%)	3/41 (7%)	0/36 (0%)	2/34 (6%)
First incidence (days)	733 (T)	733 (T)	—	733 (T)
Poly-3 test	P=0.556	P=0.304	P=0.501N	P=0.492
Liver: Hepatocellular Adenoma				
Overall rate	22/50 (44%)	22/50 (44%)	14/50 (28%)	27/50 (54%)
Adjusted rate	46.7%	46.9%	29.5%	59.4%
Terminal rate	18/40 (45%)	19/41 (46%)	8/36 (22%)	21/34 (62%)
First incidence (days)	476	495	448	605
Poly-3 test	P=0.062	P=0.576	P=0.063N	P=0.151
Liver: Hepatocellular Carcinoma				
Overall rate	10/50 (20%)	7/50 (14%)	10/50 (20%)	11/50 (22%)
Adjusted rate	21.1%	14.9%	21.3%	23.6%
Terminal rate	6/40 (15%)	3/41 (7%)	5/36 (14%)	4/34 (12%)
First incidence (days)	384	497	561	552
Poly-3 test	P=0.298	P=0.300N	P=0.592	P=0.486
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	28/50 (56%)	26/50 (52%)	22/50 (44%)	34/50 (68%)
Adjusted rate	57.5%	53.7%	44.9%	72.2%
Terminal rate	21/40 (53%)	20/41 (49%)	12/36 (33%)	24/34 (71%)
First incidence (days)	384	495	448	552
Poly-3 test	P=0.026	P=0.431N	P=0.148N	P=0.094

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	10/50 (20%)	8/50 (16%)	10/50 (20%)	12/50 (24%)
Adjusted rate	21.1%	17.0%	21.3%	25.7%
Terminal rate	6/40 (15%)	4/41 (10%)	5/36 (14%)	4/34 (12%)
First incidence (days)	384	497	561	552
Poly-3 test	P=0.243	P=0.401N	P=0.592	P=0.391
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	28/50 (56%)	27/50 (54%)	22/50 (44%)	34/50 (68%)
Adjusted rate	57.5%	55.7%	44.9%	72.2%
Terminal rate	21/40 (53%)	21/41 (51%)	12/36 (33%)	24/34 (71%)
First incidence (days)	384	495	448	552
Poly-3 test	P=0.033	P=0.512N	P=0.148N	P=0.094
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	8/50 (16%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	17.6%	11.1%	8.9%	4.5%
Terminal rate	7/40 (18%)	5/41 (12%)	3/36 (8%)	1/34 (3%)
First incidence (days)	649	733 (T)	699	622
Poly-3 test	P=0.063N	P=0.283N	P=0.180N	P=0.048N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	8/50 (16%)	8/50 (16%)	6/50 (12%)	12/50 (24%)
Adjusted rate	17.6%	17.5%	13.2%	25.7%
Terminal rate	7/40 (18%)	7/41 (17%)	5/36 (14%)	7/34 (21%)
First incidence (days)	649	497	623	469
Poly-3 test	P=0.133	P=0.605N	P=0.389N	P=0.244
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/50 (30%)	13/50 (26%)	10/50 (20%)	13/50 (26%)
Adjusted rate	32.9%	28.4%	22.0%	27.8%
Terminal rate	14/40 (35%)	12/41 (29%)	8/36 (22%)	8/34 (24%)
First incidence (days)	649	497	623	469
Poly-3 test	P=0.460N	P=0.406N	P=0.173N	P=0.380N
Spleen: Hemangiosarcoma				
Overall rate	0/49 (0%)	3/50 (6%)	0/50 (0%)	2/49 (4%)
Adjusted rate	0.0%	6.7%	0.0%	4.6%
Terminal rate	0/40 (0%)	2/41 (5%)	0/36 (0%)	1/34 (3%)
First incidence (days)	—	718	—	718
Poly-3 test	P=0.411	P=0.121	—[f]	P=0.233
Testes: Adenoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	6.7%
Terminal rate	0/40 (0%)	0/41 (0%)	0/36 (0%)	2/34 (6%)
First incidence (days)	—	—	—	602
Poly-3 test	P=0.007	—	—	P=0.116
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	6/50 (12%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.2%	13.3%	4.4%	6.8%
Terminal rate	1/40 (3%)	5/41 (12%)	2/36 (6%)	2/34 (6%)
First incidence (days)	733 (T)	718	733 (T)	718
Poly-3 test	P=0.605N	P=0.055	P=0.498	P=0.297

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	6/50 (12%)	3/50 (6%)	3/50 (6%)
Adjusted rate	2.2%	13.3%	6.6%	6.8%
Terminal rate	1/40 (3%)	5/41 (12%)	2/36 (6%)	2/34 (6%)
First incidence (days)	733 (T)	718	596	718
Poly-3 test	P=0.582N	P=0.055	P=0.307	P=0.297
All Organs: Malignant Lymphoma				
Overall rate	3/50 (6%)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted rate	6.6%	6.7%	8.7%	8.9%
Terminal rate	2/40 (5%)	3/41 (7%)	2/36 (6%)	1/34 (3%)
First incidence (days)	635	733 (T)	596	552
Poly-3 test	P=0.437	P=0.657	P=0.504	P=0.495
All Organs: Benign Neoplasms				
Overall rate	32/50 (64%)	27/50 (54%)	22/50 (44%)	32/50 (64%)
Adjusted rate	68.0%	57.5%	45.5%	68.6%
Terminal rate	28/40 (70%)	23/41 (56%)	13/36 (36%)	24/34 (71%)
First incidence (days)	476	495	448	467
Poly-3 test	P=0.227	P=0.198N	P=0.019N	P=0.562
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	20/50 (40%)	23/50 (46%)	23/50 (46%)
Adjusted rate	47.7%	42.4%	48.4%	47.5%
Terminal rate	16/40 (40%)	15/41 (37%)	16/36 (44%)	12/34 (35%)
First incidence (days)	384	497	561	469
Poly-3 test	P=0.473	P=0.376N	P=0.556	P=0.571N
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	39/50 (78%)	37/50 (74%)	42/50 (84%)
Adjusted rate	87.9%	80.4%	74.0%	85.4%
Terminal rate	35/40 (88%)	32/41 (78%)	24/36 (67%)	29/34 (85%)
First incidence (days)	384	495	448	467
Poly-3 test	P=0.440	P=0.230N	P=0.065N	P=0.472N

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

Table C4a
Historical Incidence of Liver Neoplasms in Control Male B6C3F$_1$ Mice

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma	Hepatoblastoma
Historical Incidence in Controls Given NTP-2000 Diet[a]				
Acrylonitrile (gavage)	23/50	14/50	32/50	0/50
trans-Cinnamaldehyde (feed)	14/100	13/100	26/100	0/100
Citral (feed)	20/100	13/100	28/100	0/100
Decalin (inhalation)	22/50	10/50	28/50	0/50
p,p′-Dichlorodiphenyl sulfone (feed)	6/50	9/50	15/50	0/50
Dipropylene glycol (drinking water)	17/50	14/50	29/50	0/50
Elmiron® (gavage)	19/50	11/50	23/50	1/50
2,4-Hexadienal (gavage)	23/50	8/50	31/50	2/50
Indium phosphide (inhalation)	17/50	11/50	26/50	0/50
60-Hz Magnetic fields (whole body exposure)	30/100	19/100	46/100	2/100
Methacrylonitrile (gavage)	17/49	13/49	24/49	1/49
o-Nitrotoluene (feed)	18/60	12/60	27/60	1/60
p-Nitrotoluene (feed)	14/50	8/50	20/50	0/50
Riddelliine (gavage)	16/50	23/50	36/50	3/50
Sodium nitrite (drinking water)	19/50	9/50	24/50	5/50
Vanadium pentoxide (inhalation)	15/50	14/50	26/50	0/50
Overall Historical Incidence in Controls Given NTP-2000 Diet				
Total (%)	290/959 (30.2%)	201/959 (21.0%)	441/959 (46.0%)	15/959 (1.6%)
Mean ± standard deviation	31.9% ± 10.1%	22.1% ± 8.1%	48.4% ± 12.9%	1.7% ± 2.8%
Range	12%-46%	13%-46%	26%-72%	0%-10%

[a] Data as of January 30, 2002

TABLE C4b
Historical Incidence of Interstitial Cell Adenoma of the Testis in Control Male B6C3F$_1$ Mice

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Diet[a]	
Acrylonitrile (gavage)	0/50
trans-Cinnamaldehyde (feed)	1/100
Citral (feed)	1/100
Decalin (inhalation)	0/50
p,p′-Dichlorodiphenyl sulfone (feed)	1/50
Dipropylene glycol (drinking water)	3/50
Elmiron® (gavage)	0/50
2,4-Hexadienal (gavage)	1/50
Indium phosphide (inhalation)	2/50
60-Hz Magnetic fields (whole body exposure)	1/99
Methacrylonitrile (gavage)	0/49
o-Nitrotoluene (feed)	0/60
p-Nitrotoluene (feed)	0/50
Riddelliine (gavage)	0/50
Sodium nitrite (drinking water)	0/50
Vanadium pentoxide (inhalation)	0/50
Overall Historical Incidence in Controls Given NTP-2000 Diet	
Total (%)	10/958 (1.0%)
Mean ± standard deviation	1.1% ± 1.7%
Range	0%-6%

[a] Data as of January 30, 2002

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	100 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	7	7	5
Natural deaths	3	2	7	11
Survivors				
Died last week of study	1		1	1
Terminal sacrifice	39	41	35	33
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(40)	(41)	(40)
Degeneration, hyaline	1 (2%)			3 (8%)
Hyperplasia		1 (3%)		1 (3%)
Intestine large, colon	(49)	(48)	(49)	(49)
Hemorrhage				1 (2%)
Infiltration cellular, mixed cell				1 (2%)
Necrosis			1 (2%)	
Serosa, inflammation, chronic			1 (2%)	
Intestine large, cecum	(48)	(48)	(49)	(46)
Hemorrhage				1 (2%)
Infiltration cellular, mixed cell				1 (2%)
Inflammation, acute			1 (2%)	
Necrosis			1 (2%)	
Serosa, inflammation, granulomatous	1 (2%)			
Intestine small, duodenum	(47)	(48)	(47)	(43)
Inflammation, acute	1 (2%)			
Necrosis	1 (2%)			
Intestine small, jejunum	(46)	(48)	(47)	(43)
Infiltration cellular, mixed cell	1 (2%)			1 (2%)
Necrosis			1 (2%)	
Intestine small, ileum	(46)	(48)	(47)	(46)
Hyperplasia				1 (2%)
Infiltration cellular, mixed cell		1 (2%)		1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			1 (2%)
Basophilic focus	9 (18%)	6 (12%)	13 (26%)	13 (26%)
Clear cell focus	17 (34%)	21 (42%)	16 (32%)	21 (42%)
Eosinophilic focus	10 (20%)	9 (18%)	7 (14%)	19 (38%)
Erythrophagocytosis				9 (18%)
Fatty change	1 (2%)		3 (6%)	3 (6%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Infarct		1 (2%)		
Inflammation, granulomatous	5 (10%)	6 (12%)	9 (18%)	3 (6%)
Mixed cell focus				1 (2%)
Necrosis		1 (2%)	3 (6%)	19 (38%)
Syncytial alteration	26 (52%)	28 (56%)	36 (72%)	44 (88%)
Tension lipidosis	2 (4%)	5 (10%)		1 (2%)
Thrombosis			1 (2%)	
Vacuolization cytoplasmic		1 (2%)		
Bile duct, degeneration, hyaline				1 (2%)
Centrilobular, hypertrophy	2 (4%)		4 (8%)	36 (72%)
Centrilobular, necrosis			4 (8%)	2 (4%)

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

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Alimentary System (continued)				
Mesentery	(14)	(11)	(10)	(15)
Inflammation, granulomatous	3 (21%)	1 (9%)	2 (20%)	3 (20%)
Artery, inflammation, chronic active		1 (9%)		
Fat, necrosis	12 (86%)	9 (82%)	9 (90%)	12 (80%)
Pancreas	(49)	(50)	(50)	(49)
Atrophy	1 (2%)	1 (2%)		
Basophilic focus		1 (2%)	1 (2%)	
Cyst	1 (2%)			
Lipomatosis	1 (2%)	1 (2%)		
Stomach, forestomach	(49)	(50)	(49)	(50)
Hyperplasia, squamous	4 (8%)	4 (8%)	1 (2%)	9 (18%)
Inflammation, acute	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Inflammation, chronic active	1 (2%)			1 (2%)
Necrosis	1 (2%)	1 (2%)		4 (8%)
Stomach, glandular	(49)	(49)	(48)	(48)
Hyperplasia		1 (2%)		
Infiltration cellular, mixed cell		1 (2%)		
Mineralization	1 (2%)		1 (2%)	
Necrosis			2 (4%)	
Tooth	(23)	(26)	(22)	(21)
Inflammation, chronic active	1 (4%)			
Malformation	21 (91%)	26 (100%)	22 (100%)	20 (95%)
Dentine, incisor, dysplasia	1 (4%)			1 (5%)
Cardiovascular System				
Blood vessel	(1)	(3)		(1)
Inflammation, chronic active	1 (100%)	1 (33%)		
Heart	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Cardiomyopathy	9 (18%)	8 (16%)	7 (14%)	7 (14%)
Mineralization			1 (2%)	1 (2%)
Artery, inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Hyperplasia	23 (47%)	16 (32%)	13 (26%)	14 (28%)
Hypertrophy	37 (76%)	42 (84%)	30 (60%)	26 (52%)
Subcapsular, hyperplasia				1 (2%)
Adrenal medulla	(49)	(50)	(50)	(50)
Hyperplasia	3 (6%)			3 (6%)
Islets, pancreatic	(49)	(50)	(50)	(49)
Hypertrophy		2 (4%)		
Pituitary gland	(48)	(50)	(50)	(49)
Cyst		1 (2%)		1 (2%)
Pars distalis, hyperplasia	2 (4%)	1 (2%)	3 (6%)	3 (6%)
Pars intermedia, hyperplasia	1 (2%)			
Pars intermedia, hypertrophy		1 (2%)		
General Body System				
None				

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Inflammation, chronic				1 (2%)
Preputial gland	(49)	(49)	(50)	(50)
Ectasia	28 (57%)	24 (49%)	21 (42%)	22 (44%)
Hyperplasia, squamous				1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Prostate, NOS	(48)	(50)	(50)	(50)
Hyperplasia		2 (4%)		
Inflammation, chronic active			2 (4%)	
Artery, inflammation, chronic active		1 (2%)		
Seminal vesicle	(49)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)		
Interstitial cell, hyperplasia	2 (4%)			
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(48)
Angiectasis				1 (2%)
Thrombosis				1 (2%)
Lymph node	(1)		(3)	(1)
Iliac, infiltration cellular, plasma cell			1 (33%)	1 (100%)
Lymph node, mesenteric	(49)	(48)	(50)	(47)
Angiectasis	2 (4%)			
Infiltration cellular, plasma cell		2 (4%)	1 (2%)	2 (4%)
Infiltration cellular, mixed cell	2 (4%)			1 (2%)
Lymph node, mediastinal	(41)	(36)	(42)	(35)
Inflammation, granulomatous	1 (2%)			
Spleen	(49)	(50)	(50)	(49)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid				1 (2%)
Thymus	(44)	(44)	(42)	(40)
Necrosis		1 (2%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)		
Hyperplasia, basal cell				1 (2%)
Infiltration cellular, mixed cell				1 (2%)
Inflammation, acute			1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Lymphatic, angiectasis	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)		

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meninges, infiltration cellular, mononuclear cell			1 (2%)	
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Degeneration, hyaline				1 (2%)
Inflammation, acute			1 (2%)	
Lung	(50)	(50)	(50)	(50)
Inflammation, granulomatous	3 (6%)		2 (4%)	1 (2%)
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	5 (10%)	2 (4%)	2 (4%)	6 (12%)
Alveolus, infiltration cellular, histiocyte	1 (2%)	2 (4%)		
Nose	(50)	(50)	(50)	(48)
Inflammation, suppurative	1 (2%)	2 (4%)	4 (8%)	2 (4%)
Polyp, inflammatory		1 (2%)		
Thrombosis		2 (4%)		
Glands, dilatation	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Olfactory epithelium, atrophy	1 (2%)	1 (2%)	3 (6%)	
Sinus, foreign body	1 (2%)			
Trachea	(49)	(50)	(49)	(48)
Degeneration, hyaline				1 (2%)
Necrosis				1 (2%)
Special Senses System				
Eye	(3)	(3)	(2)	(1)
Cataract	2 (67%)			
Degeneration		1 (33%)		
Cornea, inflammation, chronic active		1 (33%)		
Harderian gland	(9)	(5)	(5)	(5)
Hyperplasia	1 (11%)			
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Cyst		1 (2%)		
Infarct	3 (6%)	2 (4%)	5 (10%)	1 (2%)
Metaplasia, osseous	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Mineralization			1 (2%)	
Nephropathy	47 (96%)	46 (92%)	47 (94%)	41 (84%)
Renal tubule, hyperplasia	1 (2%)			2 (4%)
Renal tubule, karyomegaly		1 (2%)	1 (2%)	

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF DECALIN

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TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	100 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	10	15	11	8
Natural deaths	2	7	3	6
Survivors				
Died last week of study				1
Terminal sacrifice	37	28	35	35
Pregnant	1			
Animals examined microscopically	49	50	50	50
Alimentary System				
Esophagus	(49)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Gallbladder	(41)	(40)	(40)	(38)
Hepatocholangiocarcinoma, metastatic, liver		1 (3%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (3%)	
Intestine large, cecum	(48)	(43)	(47)	(46)
Leiomyoma	1 (2%)			
Intestine small, duodenum	(48)	(43)	(47)	(47)
Polyp adenomatous				1 (2%)
Intestine small, ileum	(47)	(45)	(49)	(47)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Liver	(49)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Hepatoblastoma				1 (2%)
Hepatocellular carcinoma	4 (8%)	15 (30%)	6 (12%)	5 (10%)
Hepatocellular carcinoma, multiple		1 (2%)		
Hepatocellular adenoma	4 (8%)	11 (22%)	7 (14%)	14 (28%)
Hepatocellular adenoma, multiple	3 (6%)	2 (4%)	1 (2%)	3 (6%)
Hepatocholangiocarcinoma		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Sarcoma, metastatic, skin		1 (2%)		
Sarcoma, metastatic, uncertain primary site				1 (2%)
Mesentery	(17)	(18)	(12)	(18)
Hepatocholangiocarcinoma, metastatic, liver		1 (6%)		
Sarcoma, metastatic, skin		1 (6%)		
Pancreas	(49)	(47)	(50)	(49)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(49)	(49)	(50)	(47)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Squamous cell carcinoma		1 (2%)		1 (2%)
Stomach, glandular	(48)	(47)	(50)	(47)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Tongue	(1)			
Squamous cell carcinoma	1 (100%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Cardiovascular System				
Blood vessel			(2)	
Aorta, mast cell tumor malignant, metastatic, uncertain primary site			1 (50%)	
Heart	(49)	(50)	(50)	(50)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(49)
Subcapsular, adenoma	1 (2%)			
Adrenal medulla	(48)	(50)	(50)	(49)
Pheochromocytoma benign	2 (4%)		2 (4%)	1 (2%)
Islets, pancreatic	(49)	(47)	(50)	(49)
Adenoma	1 (2%)		1 (2%)	
Pituitary gland	(49)	(49)	(49)	(50)
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Pars distalis, adenoma	13 (27%)	8 (16%)	10 (20%)	17 (34%)
Pars intermedia, adenoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Thyroid gland	(49)	(49)	(50)	(47)
Follicular cell, adenoma	1 (2%)			
General Body System				
None				
Genital System				
Ovary	(49)	(49)	(49)	(48)
Carcinoma, metastatic, uterus		1 (2%)		
Cystadenoma	1 (2%)		3 (6%)	2 (4%)
Granulosa cell tumor malignant				1 (2%)
Granulosa cell tumor benign	1 (2%)		1 (2%)	1 (2%)
Granulosa-theca tumor malignant			1 (2%)	
Hemangioma	1 (2%)			
Hemangiosarcoma			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Luteoma	1 (2%)			
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Tubulostromal adenoma			1 (2%)	
Uterus	(49)	(49)	(50)	(49)
Carcinoma	1 (2%)	1 (2%)		
Hemangiosarcoma		1 (2%)		1 (2%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Polyp stromal			2 (4%)	3 (6%)
Sarcoma stromal				1 (2%)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(48)
Hemangiosarcoma			1 (2%)	1 (2%)
Lymph node	(5)	(2)	(4)	(1)
Mast cell tumor malignant, metastatic, uncertain primary site			1 (25%)	
Iliac, mast cell tumor malignant, metastatic, uncertain primary site			1 (25%)	
Lymph node, bronchial	(41)	(45)	(47)	(44)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Sarcoma, metastatic, uncertain primary site				1 (2%)
Lymph node, mandibular	(36)	(40)	(37)	(41)
Carcinoma, metastatic, harderian gland			1 (3%)	
Lymph node, mesenteric	(47)	(47)	(50)	(47)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Sarcoma, metastatic, uncertain primary site				1 (2%)
Lymph node, mediastinal	(43)	(42)	(43)	(46)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Osteosarcoma, metastatic, uncertain primary site				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Spleen	(49)	(47)	(50)	(48)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Thymus	(48)	(48)	(48)	(47)
Thymoma benign				1 (2%)
Integumentary System				
Mammary gland	(48)	(50)	(50)	(50)
Carcinoma	1 (2%)	2 (4%)	2 (4%)	
Skin	(49)	(50)	(50)	(50)
Basal cell carcinoma		1 (2%)		
Mast cell tumor benign				1 (2%)
Neural crest tumor			1 (2%)	
Squamous cell papilloma			1 (2%)	
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		1 (2%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)		1 (2%)
Subcutaneous tissue, sarcoma	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Subcutaneous tissue, schwannoma malignant			1 (2%)	

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Carcinoma, metastatic, uncertain primary site			1 (2%)	
Osteoma		1 (2%)		
Skeletal muscle		(2)		
Hepatocholangiocarcinoma, metastatic, liver		1 (50%)		
Nervous System				
Brain	(49)	(50)	(50)	(50)
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Respiratory System				
Larynx	(49)	(50)	(50)	(49)
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	4 (8%)		4 (8%)
Alveolar/bronchiolar carcinoma	6 (12%)	3 (6%)	1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland			1 (2%)	
Carcinoma, metastatic, uterus		1 (2%)		
Hemangiosarcoma, metastatic, liver				1 (2%)
Hemangiosarcoma, metastatic, skin		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)	2 (4%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Sarcoma, metastatic, uncertain primary site				1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Mediastinum, sarcoma, metastatic, skin		1 (2%)		
Nose	(49)	(50)	(50)	(49)
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Pleura	(1)			(1)
Sarcoma, metastatic, uncertain primary site				1 (100%)
Special Senses System				
Eye	(2)	(1)	(2)	
Carcinoma, metastatic, uncertain primary site			1 (50%)	
Harderian gland	(4)	(4)	(5)	(3)
Adenoma	3 (75%)	4 (100%)	2 (40%)	2 (67%)
Carcinoma	1 (25%)		3 (60%)	
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Mast cell tumor malignant, metastatic, uncertain primary site			1 (2%)	
Urinary bladder	(49)	(46)	(49)	(47)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Systemic Lesions				
Multiple organs[b]	(49)	(50)	(50)	(50)
Lymphoma malignant	11 (22%)	8 (16%)	13 (26%)	14 (28%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	39	40	42	41
Total primary neoplasms	63	70	67	84
Total animals with benign neoplasms	28	25	27	34
Total benign neoplasms	35	31	33	52
Total animals with malignant neoplasms	22	28	28	26
Total malignant neoplasms	28	39	33	32
Total animals with metastatic neoplasms	3	5	5	3
Total metastatic neoplasms	4	23	23	9
Total animals with malignant neoplasms of uncertain primary site			2	2
Total animals with uncertain neoplasms–benign or malignant			1	
Total uncertain neoplasms			1	

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	363	568	599	610	616	638	659	659	672	700	703	714	735	735	735	735	735	735	735	736	736	736	736	736
Carcass ID Number	117	111	135	132	148	101	140	150	120	131	102	105	103	104	106	115	129	136	144	146	107	113	116	118
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma		X																						
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma											X													
Hepatocellular adenoma																						X		
Hepatocellular adenoma, multiple																								
Mesentery		+					+					+	+		+			+	+		+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue								+																
Squamous cell carcinoma								X																
Tooth																						+		+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																	
Parathyroid gland	+	+	M	+	+	+	+	M	+	I	+	M	+	+	+	+	+	I	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X	X					X		X									X
Pars intermedia, adenoma																								
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 Inhalation Study of Decalin: Chamber Control

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	119	122	123	130	137	138	139	142	145	149	108	109	110	114	121	124	125	126	127	128	133	134	141	143	147	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	M	+	I	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma										X			X							X						4
Hepatocellular adenoma												X			X										X	4
Hepatocellular adenoma, multiple								X	X												X					3
Mesentery				+				+	+			+		+				+	+		+	+				17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Squamous cell carcinoma																										1
Tooth						+																		+		4
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcapsular, adenoma																								X		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign			X						X																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	M	+	+	M	+	+	M	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X			X	X	X			X	X										X			X		13
Pars intermedia, adenoma																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	363	568	599	610	616	638	659	659	672	700	703	714	735	735	735	735	735	735	735	736	736	736	736	736	736
Carcass ID Number	117	111	135	132	148	101	140	150	120	131	102	105	103	104	106	115	129	136	144	146	107	113	116	118
Genital System																									
Clitoral gland	M	+	+	+	+	M	+	+	+	I	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign																			X						
Hemangioma															X										
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+									+			+							+		
Lymph node, bronchial	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	M	M	M	+	+	M	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X												
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma												X			X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																				+				
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma				X						X				X		X					X				
Hepatocellular carcinoma, metastatic, liver																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																		+							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	119	122	123	130	137	138	139	142	145	149	108	109	110	114	121	124	125	126	127	128	133	134	141	143	147	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	I	+	40
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma															X											1
Granulosa cell tumor benign																										1
Hemangioma																										1
Luteoma	X																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																				X						1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										5
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	41
Lymph node, mandibular	+	+	+	+	+	M	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	M	M	+	+	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Peripheral nerve																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																							X			1
Alveolar/bronchiolar carcinoma													X													6
Hepatocellular carcinoma, metastatic, liver													X							X						2
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	363	568	599	610	616	638	659	659	672	700	703	714	735	735	735	735	735	735	735	736	736	736	736	736	736
Carcass ID Number	117	111	135	132	148	101	140	150	120	131	102	105	103	104	106	115	129	136	144	146	107	113	116	118
Special Senses System																									
Ear																									
Eye									+								+								
Harderian gland						+											+								
Adenoma						X											X								
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X	X				X	X					X			X							X		X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: Chamber Control

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	119	122	123	130	137	138	139	142	145	149	108	109	110	114	121	124	125	126	127	128	133	134	141	143	147	Total Tissues/ Tumors
Special Senses System																										
Ear											+															1
Eye																										2
Harderian gland	+																	+								4
Adenoma																		X								3
Carcinoma	X																									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant																			X			X	X			11

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	305	488	527	532	571	588	588	601	616	624	644	658	658	673	692	692	700	714	722	728	731	733	735	733	735
Carcass ID Number	341	328	342	331	343	313	350	323	325	334	318	317	322	348	302	309	329	327	330	303	311	308	310	312	345
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Gallbladder	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	I	+	A	A	I	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	I	+	+	+
Intestine large, cecum	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	A	A	+	+	+
Intestine small, duodenum	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	A	A	+	+	+
Intestine small, jejunum	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X							X	X	X		X	X			X			X		X	X		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma				X				X												X				X	X
Hepatocellular adenoma, multiple																		X							
Hepatocholangiocarcinoma															X										
Sarcoma, metastatic, skin																				X					
Mesentery				+		+						+			+				+	+				+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Sarcoma, metastatic, skin																				X					
Pancreas	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Squamous cell carcinoma												X													
Stomach, glandular	+	A	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Tooth																						+			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	+	+	+	+
Pituitary gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X			X											X				
Pars intermedia, adenoma																					X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	301	306	307	316	319	321	326	333	335	336	340	344	304	305	314	315	320	324	332	337	338	339	346	347	349	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Gallbladder	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hepatocholangiocarcinoma, metastatic, liver																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hepatocholangiocarcinoma, metastatic, liver																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma								X					X						X			X			X	15
Hepatocellular carcinoma, multiple																							X			1
Hepatocellular adenoma				X			X				X			X				X							X	11
Hepatocellular adenoma, multiple																								X		2
Hepatocholangiocarcinoma																										1
Sarcoma, metastatic, skin																										1
Mesentery				+	+			+			+				+		+			+			+	+	+	18
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver																										1
Tooth											+															2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X		X													X								8
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	305	488	527	532	571	588	588	601	616	624	644	658	658	673	692	692	700	714	722	728	731	733	735	735	735
Carcass ID Number	341	328	342	331	343	313	350	323	325	334	318	317	322	348	302	309	329	327	330	303	311	308	310	312	345
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																			X						
Hepatocholangiocarcinoma, metastatic, liver															X										
Uterus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Hemangiosarcoma																									
Hepatocholangiocarcinoma, metastatic, liver															X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+														+				
Lymph node, bronchial	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Lymph node, mandibular	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Spleen	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X								
Hepatocholangiocarcinoma, metastatic, liver															X										
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue, fibrous histiocytoma											X														
Subcutaneous tissue, hemangiosarcoma																	X								
Subcutaneous tissue, sarcoma						X														X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																								X	
Skeletal muscle															+				+						
Hepatocholangiocarcinoma, metastatic, liver															X										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	301	306	307	316	319	321	326	333	335	336	340	344	304	305	314	315	320	324	332	337	338	339	346	347	349	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	I	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	49
Carcinoma, metastatic, uterus																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Hemangiosarcoma	X																									1
Hepatocholangiocarcinoma, metastatic, liver																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, bronchial	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	M	40
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mediastinal	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	42
Hepatocholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																		X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma													X													1
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma																										1
Skeletal muscle																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	305	488	527	532	571	588	588	601	616	624	644	658	658	673	692	692	700	714	722	728	731	733	735	735	735
Carcass ID Number	341	328	342	331	343	313	350	323	325	334	318	317	322	348	302	309	329	327	330	303	311	308	310	312	345
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X																
Alveolar/bronchiolar carcinoma																							X		
Carcinoma, metastatic, uterus																			X						
Hemangiosarcoma, metastatic, skin																	X								
Hepatocellular carcinoma, metastatic, liver																							X		
Hepatocholangiocarcinoma, metastatic, liver															X										
Mediastinum, sarcoma, metastatic, skin																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+																			
Harderian gland						+						+													
Adenoma						X						X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Urinary bladder	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X	X		X												X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 25 ppm

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	301	306	307	316	319	321	326	333	335	336	340	344	304	305	314	315	320	324	332	337	338	339	346	347	349	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X												X	X				4
Alveolar/bronchiolar carcinoma																			X				X			3
Carcinoma, metastatic, uterus																										1
Hemangiosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinum, sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Harderian gland	+																					+				4
Adenoma	X																					X				4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant		X										X		X									X			8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	0	3	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	5	1	9	1	5	5	7	8	0	0	1	1	2	3	3	3	3	3	3	3	3	3	3	3
	3	6	1	4	2	2	2	2	6	0	0	0	4	3	4	5	5	5	5	5	5	6	6	6	6
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	1	4	1	5	4	0	2	2	4	2	2	3	0	4	3	0	1	2	2	3	3	0	0	0	0
	6	5	7	0	1	2	2	1	6	0	5	7	1	7	9	8	2	4	6	1	3	3	4	5	6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	A	A	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X			X					X													
Hepatocellular adenoma						X													X		X				
Hepatocellular adenoma, multiple													X												
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Mesentery			+												+	+		+			+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Tooth																									
Cardiovascular System																									
Blood vessel					+					+															
Aorta, mast cell tumor malignant, metastatic, uncertain primary site										X															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	M	+	M	I	+	+	+	+	+	+	M	+	I	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Pars distalis, adenoma			X								X											X	X		X
Pars intermedia, adenoma							X							X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	507	509	510	511	515	518	519	528	530	535	536	542	543	544	513	514	523	527	529	532	534	538	540	548	549	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	40
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X						X								X							6
Hepatocellular adenoma										X		X						X					X			7
Hepatocellular adenoma, multiple																										1
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Mesentery	+						+		+					+		+							+		+		12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Tooth																		+								1
Cardiovascular System																										
Blood vessel																										2
Aorta, mast cell tumor malignant, metastatic, uncertain primary site																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X																	X								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	M	38
Pituitary gland	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Pars distalis, adenoma				X	X									X		X					X					10
Pars intermedia, adenoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	003	356	511	594	612	652	652	672	686	700	700	710	714	723	734	735	735	735	735	735	735	736	736	736	736	736
Carcass ID Number	516	445	517	550	541	002	022	221	446	520	525	537	011	447	439	008	012	424	226	131	333	033	044	045	046
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	M	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																										
Granulosa cell tumor benign																										
Granulosa-theca tumor malignant																										
Hemangiosarcoma																										
Mast cell tumor malignant, metastatic, uncertain primary site										X																
Tubulostromal adenoma																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X																
Polyp stromal													X													
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Lymph node					+					+																
Mast cell tumor malignant, metastatic, uncertain primary site										X																
Iliac, mast cell tumor malignant, metastatic, uncertain primary site										X																
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X																
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	M	M	+	M	+	+	+	+	M	+	+	M	M	+
Carcinoma, metastatic, harderian gland																										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X																
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	M	+
Mast cell tumor malignant, metastatic, uncertain primary site										X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X			X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neural crest tumor																	X									
Squamous cell papilloma																										
Subcutaneous tissue, fibrosarcoma																				X						
Subcutaneous tissue, sarcoma		X													X											
Subcutaneous tissue, schwannoma malignant																		X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	507	509	510	511	515	518	519	528	530	535	536	542	543	544	513	514	523	527	529	532	534	538	540	548	549	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma	X											X					X									3
Granulosa cell tumor benign							X																			1
Granulosa-theca tumor malignant															X											1
Hemangiosarcoma										X																1
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Tubulostromal adenoma			X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Polyp stromal																				X						2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						1
Lymph node																		+				+				4
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Iliac, mast cell tumor malignant, metastatic, uncertain primary site																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Lymph node, mandibular	+	+	M	M	+	I	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	37
Carcinoma, metastatic, harderian gland																									X	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	43
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neural crest tumor																										1
Squamous cell papilloma																		X								1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																										2
Subcutaneous tissue, schwannoma malignant																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	0	3	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	5	1	9	1	5	5	7	8	0	0	1	1	2	3	3	3	3	3	3	3	3	3	3	3
	3	6	1	4	2	2	2	2	6	0	0	0	4	3	4	5	5	5	5	5	5	6	6	6	6
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	1	4	1	5	4	0	2	2	4	2	2	3	0	4	3	0	1	2	2	3	3	0	0	0	0
	6	5	7	0	1	2	2	1	6	0	5	7	1	7	9	8	2	4	6	1	3	3	4	5	6
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																	X								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma								X																	
Carcinoma, metastatic, harderian gland																									
Hepatocellular carcinoma, metastatic, liver							X																		
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear								+																	
Eye																	+								
Carcinoma, metastatic, uncertain primary site																	X								
Harderian gland									+											+					
Adenoma									X																
Carcinoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, uncertain primary site										X															
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant					X				X			X					X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 100 ppm

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	507	509	510	511	515	518	519	528	530	535	536	542	543	544	513	514	523	527	529	532	534	538	540	548	549	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, harderian gland																									X	1
Hepatocellular carcinoma, metastatic, liver											X															2
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye	+																									2
Carcinoma, metastatic, uncertain primary site																										1
Harderian gland	+																							+	+	5
Adenoma																								X		2
Carcinoma	X																								X	3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, uncertain primary site																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X				X						X		X	X						X	X	X	X	13

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	309	344	432	624	636	644	674	686	710	714	714	714	721	727	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	715	741	723	739	709	735	713	705	007	710	712	744	708	742	711	716	719	725	729	731	733	734	737	746	747
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	A	+	+	M	A	+	+	+	M	+	I	+	M	+	M	+	+	+	+	+	I
Intestine large, colon	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	A	+	A	+	+	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatoblastoma														X											
Hepatocellular carcinoma					X								X												
Hepatocellular adenoma										X	X							X							X
Hepatocellular adenoma, multiple													X						X						
Sarcoma, metastatic, uncertain primary site					X																				
Mesentery				+					+		+		+						+		+	+		+	
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site					X																				
Endocrine System																									
Adrenal cortex	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign						X																			
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	M	M	M	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X		X		X		X	X	X	X						X
Pars intermedia, adenoma																						X			
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	749	701	702	706	717	718	720	722	728	730	736	743	745	748	703	704	714	721	724	726	727	732	738	740	750	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous																				X						1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Hepatoblastoma																										1
Hepatocellular carcinoma															X				X		X					5
Hepatocellular adenoma	X			X					X	X	X					X		X			X	X			X	14
Hepatocellular adenoma, multiple														X												3
Sarcoma, metastatic, uncertain primary site																										1
Mesentery		+				+							+	+		+	+	+		+	+	+				18
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma														X												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth																+										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	I	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X				X		X		X	X						X			X		X	17
Pars intermedia, adenoma																	X									2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	47
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	309	344	432	624	636	644	674	686	710	714	714	714	721	727	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	715	741	723	739	709	735	713	705	707	710	712	744	708	742	711	716	719	725	729	731	733	734	737	746	747
Genital System																										
Clitoral gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Ovary	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma									X															X	
Granulosa cell tumor malignant																									
Granulosa cell tumor benign						X																			
Uterus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Polyp stromal																	X						X		
Sarcoma stromal																									
Hematopoietic System																										
Bone marrow	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node					+																				
Lymph node, bronchial	M	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Sarcoma, metastatic, uncertain primary site					X																				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+
Lymph node, mesenteric	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Sarcoma, metastatic, uncertain primary site					X																				
Lymph node, mediastinal	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+
Osteosarcoma, metastatic, uncertain primary site								X																	
Sarcoma, metastatic, uncertain primary site					X																				
Spleen	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Thymoma benign										X															
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor benign																									
Subcutaneous tissue, fibrous histiocytoma																						X			
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+																							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	749	701	702	706	717	718	720	722	728	730	736	743	745	748	703	704	714	721	724	726	727	732	738	740	750	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	48
Cystadenoma																										2
Granulosa cell tumor malignant									X																	1
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma										X																1
Polyp stromal			X																							3
Sarcoma stromal																	X									1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																						X				1
Lymph node																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	44
Sarcoma, metastatic, uncertain primary site																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	M	+	+	M	M	41
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, metastatic, uncertain primary site																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Osteosarcoma, metastatic, uncertain primary site																										1
Sarcoma, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma						X				X																2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor benign														X												1
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, hemangiosarcoma																						X				1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	309	344	432	624	636	644	674	686	710	714	714	714	721	727	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	715	741	723	739	709	735	713	705	707	710	712	744	708	742	711	716	719	725	729	731	733	734	737	746	747
Respiratory System																										
Larynx	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X				X												
Alveolar/bronchiolar carcinoma																										
Hemangiosarcoma, metastatic, liver																										
Sarcoma, metastatic, uncertain primary site					X																					
Nose	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura					+																					
Sarcoma, metastatic, uncertain primary site					X																					
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland					+																					
Adenoma					X																					
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant				X	X	X		X					X						X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Decalin: 400 ppm

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	749	701	002	006	017	018	020	022	028	030	036	043	045	048	003	004	014	021	024	026	027	032	038	040	050	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X		X																					4
Alveolar/bronchiolar carcinoma																X										1
Hemangiosarcoma, metastatic, liver								X																		1
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura																										1
Sarcoma, metastatic, uncertain primary site																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland															+							+				3
Adenoma															X											2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X	X			X	X				X						X			X		X			14

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Harderian Gland: Adenoma				
Overall rate[a]	3/49 (6%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate[b]	6.7%	9.2%	4.4%	4.4%
Terminal rate[c]	2/37 (5%)	2/28 (7%)	1/35 (3%)	1/36 (3%)
First incidence (days)	638	588	686	636
Poly-3 test[d]	P=0.342N	P=0.478	P=0.499N	P=0.493N
Harderian Gland: Carcinoma				
Overall rate	1/49 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.2%	0.0%	6.7%	0.0%
Terminal rate	1/37 (3%)	0/28 (0%)	3/35 (9%)	0/36 (0%)
First incidence (days)	735 (T)	—[e]	735 (T)	—
Poly-3 test	P=0.386N	P=0.510N	P=0.307	P=0.497N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/49 (8%)	4/50 (8%)	5/50 (10%)	2/50 (4%)
Adjusted rate	8.9%	9.2%	11.1%	4.4%
Terminal rate	3/37 (8%)	2/28 (7%)	4/35 (11%)	1/36 (3%)
First incidence (days)	638	588	686	636
Poly-3 test	P=0.225N	P=0.621	P=0.501	P=0.330N
Liver: Hepatocellular Adenoma				
Overall rate	7/49 (14%)	13/50 (26%)	8/50 (16%)	17/50 (34%)
Adjusted rate	15.6%	29.7%	17.6%	37.2%
Terminal rate	7/37 (19%)	9/28 (32%)	6/35 (17%)	14/36 (39%)
First incidence (days)	735 (T)	532	652	714
Poly-3 test	P=0.024	P=0.089	P=0.511	P=0.016
Liver: Hepatocellular Carcinoma				
Overall rate	4/49 (8%)	16/50 (32%)	6/50 (12%)	5/50 (10%)
Adjusted rate	8.9%	35.5%	13.1%	10.9%
Terminal rate	3/37 (8%)	7/28 (25%)	3/35 (9%)	3/36 (8%)
First incidence (days)	703	488	594	636
Poly-3 test	P=0.115N	P=0.002	P=0.383	P=0.513
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	11/49 (22%)	27/50 (54%)	14/50 (28%)	20/50 (40%)
Adjusted rate	24.5%	58.4%	30.3%	43.5%
Terminal rate	10/37 (27%)	15/28 (54%)	9/35 (26%)	16/36 (44%)
First incidence (days)	703	488	594	636
Poly-3 test	P=0.339	P<0.001	P=0.351	P=0.043
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	4/49 (8%)	16/50 (32%)	6/50 (12%)	6/50 (12%)
Adjusted rate	8.9%	35.5%	13.1%	13.1%
Terminal rate	3/37 (8%)	7/28 (25%)	3/35 (9%)	3/36 (8%)
First incidence (days)	703	488	594	636
Poly-3 test	P=0.198N	P=0.002	P=0.383	P=0.383
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	11/49 (22%)	27/50 (54%)	14/50 (28%)	21/50 (42%)
Adjusted rate	24.5%	58.4%	30.3%	45.6%
Terminal rate	10/37 (27%)	15/28 (54%)	9/35 (26%)	16/36 (44%)
First incidence (days)	703	488	594	636
Poly-3 test	P=0.250	P<0.001	P=0.351	P=0.027

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/49 (2%)	4/50 (8%)	0/50 (0%)	4/50 (8%)
Adjusted rate	2.2%	9.3%	0.0%	8.8%
Terminal rate	1/37 (3%)	3/28 (11%)	0/35 (0%)	2/36 (6%)
First incidence (days)	735 (T)	616	—	714
Poly-3 test	P=0.217	P=0.166	P=0.499N	P=0.184
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	6/49 (12%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	13.2%	7.1%	2.2%	2.2%
Terminal rate	4/37 (11%)	3/28 (11%)	0/35 (0%)	1/36 (3%)
First incidence (days)	610	735 (T)	672	735 (T)
Poly-3 test	P=0.071N	P=0.274N	P=0.056N	P=0.055N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	7/49 (14%)	7/50 (14%)	1/50 (2%)	5/50 (10%)
Adjusted rate	15.4%	16.3%	2.2%	11.0%
Terminal rate	5/37 (14%)	6/28 (21%)	0/35 (0%)	3/36 (8%)
First incidence (days)	610	616	672	714
Poly-3 test	P=0.367N	P=0.572	P=0.030N	P=0.376N
Ovary: Cystadenoma				
Overall rate	1/49 (2%)	0/49 (0%)	3/49 (6%)	2/48 (4%)
Adjusted rate	2.2%	0.0%	6.8%	4.5%
Terminal rate	1/37 (3%)	0/27 (0%)	3/35 (9%)	1/35 (3%)
First incidence (days)	735 (T)	—	735 (T)	710
Poly-3 test	P=0.353	P=0.515N	P=0.301	P=0.497
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	13/49 (27%)	8/49 (16%)	10/49 (20%)	17/50 (34%)
Adjusted rate	28.7%	18.3%	22.3%	37.2%
Terminal rate	11/37 (30%)	4/28 (14%)	8/34 (24%)	14/36 (39%)
First incidence (days)	659	532	511	714
Poly-3 test	P=0.059	P=0.181N	P=0.326N	P=0.258
Skin (Subcutaneous Tissue): Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma				
Overall rate	2/49 (4%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.5%	6.9%	6.5%	4.4%
Terminal rate	1/37 (3%)	0/28 (0%)	1/35 (3%)	1/36 (3%)
First incidence (days)	714	588	356	714
Poly-3 test	P=0.499N	P=0.485	P=0.510	P=0.689N
Uterus: Stromal Polyp				
Overall rate	0/49 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	4.4%	6.6%
Terminal rate	0/37 (0%)	0/28 (0%)	1/35 (3%)	3/36 (8%)
First incidence (days)	—	—	714	735 (T)
Poly-3 test	P=0.049	—[f]	P=0.239	P=0.121
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	0/49 (0%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	4.4%	8.8%
Terminal rate	0/37 (0%)	0/28 (0%)	1/35 (3%)	4/36 (11%)
First incidence (days)	—	—	714	735 (T)
Poly-3 test	P=0.013	—	P=0.239	P=0.062

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
All Organs: Hemangiosarcoma				
Overall rate	1/49 (2%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	2.2%	4.7%	6.6%	8.8%
Terminal rate	0/37 (0%)	1/28 (4%)	2/35 (6%)	4/36 (11%)
First incidence (days)	714	700	700	735 (T)
Poly-3 test	P=0.171	P=0.483	P=0.307	P=0.182
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/49 (4%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	4.5%	4.7%	6.6%	8.8%
Terminal rate	1/37 (3%)	1/28 (4%)	2/35 (6%)	4/36 (11%)
First incidence (days)	714	700	700	735 (T)
Poly-3 test	P=0.260	P=0.676	P=0.503	P=0.343
All Organs: Malignant Lymphoma				
Overall rate	11/49 (22%)	8/50 (16%)	13/50 (26%)	14/50 (28%)
Adjusted rate	23.4%	18.2%	28.4%	29.9%
Terminal rate	6/37 (16%)	4/28 (14%)	10/35 (29%)	9/36 (25%)
First incidence (days)	363	588	612	624
Poly-3 test	P=0.190	P=0.361N	P=0.378	P=0.317
All Organs: Benign Neoplasms				
Overall rate	28/49 (57%)	25/50 (50%)	27/50 (54%)	34/50 (68%)
Adjusted rate	60.4%	54.6%	57.8%	73.0%
Terminal rate	23/37 (62%)	15/28 (54%)	20/35 (57%)	26/36 (72%)
First incidence (days)	568	532	511	636
Poly-3 test	P=0.046	P=0.357N	P=0.479N	P=0.138
All Organs: Malignant Neoplasms				
Overall rate	22/49 (45%)	28/50 (56%)	29/50 (58%)	26/50 (52%)
Adjusted rate	45.9%	59.3%	60.5%	55.5%
Terminal rate	13/37 (35%)	12/28 (43%)	18/35 (51%)	19/36 (53%)
First incidence (days)	363	488	356	624
Poly-3 test	P=0.427	P=0.133	P=0.109	P=0.235
All Organs: Benign or Malignant Neoplasms				
Overall rate	39/49 (80%)	40/50 (80%)	43/50 (86%)	41/50 (82%)
Adjusted rate	81.4%	83.8%	87.8%	87.0%
Terminal rate	30/37 (81%)	22/28 (79%)	29/35 (83%)	31/36 (86%)
First incidence (days)	363	488	356	624
Poly-3 test	P=0.327	P=0.486	P=0.278	P=0.320

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

TABLE D4a
Historical Incidence of Liver Neoplasms in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma	Hepatoblastoma
Historical Incidence in Controls Given NTP-2000 Diet[a]				
Acrylonitrile (gavage)	14/50	7/50	20/50	0/50
trans-Cinnamaldehyde (feed)	7/99	3/99	9/99	0/99
Citral (feed)	8/99	4/99	12/99	0/99
Decalin (inhalation)	7/50	4/50	11/50	0/50
p,p′-Dichlorodiphenyl sulfone (feed)	4/50	3/50	6/50	0/50
Dipropylene glycol (drinking water)	11/50	7/50	17/50	0/50
Elmiron® (gavage)	7/50	3/50	10/50	0/50
2,4-Hexadienal (gavage)	11/50	3/50	13/50	0/50
Indium phosphide (inhalation)	12/50	6/50	18/50	0/50
60-Hz Magnetic fields (whole body exposure)	17/98	6/98	22/98	0/98
Methacrylonitrile (gavage)	9/50	2/50	10/50	0/50
o-Nitrotoluene (feed)	7/60	2/60	9/60	0/60
p-Nitrotoluene (feed)	6/49	3/49	8/49	0/49
Riddelliine (gavage)	9/49	8/49	16/49	0/49
Sodium nitrite (drinking water)	9/50	2/50	10/50	0/50
Vanadium pentoxide (inhalation)	6/50	6/50	12/50	0/50
Overall Historical Incidence in Controls Given NTP-2000 Diet				
Total (%)	144/954 (15.1%)	69/954 (7.2%)	203/954 (21.3%)	0/954
Mean ± standard deviation	15.9% ± 6.1%	7.8% ± 4.4%	22.6% ± 9.1%	
Range	7%-28%	3%-16%	9%-40%	

[a] Data as of January 30, 2002

TABLE D4b
Historical Incidence of Uterine Neoplasms in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls		
	Stromal Polyp	Stromal Sarcoma	Stromal Polyp or Stromal Sarcoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
Acrylonitrile (gavage)	0/50	0/50	0/50
trans-Cinnamaldehyde (feed)	1/100	0/100	1/100
Citral (feed)	2/99	0/99	2/99
Decalin (inhalation)	0/50	0/50	0/50
p,p′-Dichlorodiphenyl sulfone (feed)	1/50	0/50	1/50
Dipropylene glycol (drinking water)	0/50	0/50	0/50
Elmiron® (gavage)	3/50	1/50	3/50
2,4-Hexadienal (gavage)	0/50	1/50	0/50
Indium phosphide (inhalation)	0/50	0/50	0/50
60-Hz Magnetic fields (whole body exposure)	1/100	0/100	1/100
Methacrylonitrile (gavage)	0/50	0/50	0/50
o-Nitrotoluene (feed)	2/60	0/60	2/60
p-Nitrotoluene (feed)	3/50	0/50	3/50
Riddelliine (gavage)	0/50	0/50	0/50
Sodium nitrite (drinking water)	0/50	0/50	0/50
Vanadium pentoxide (inhalation)	2/50	0/50	2/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	15/959 (1.6%)	2/959 (0.2%)	15/959 (1.6%)
Mean ± standard deviation	1.6% ± 2.2%	0.3% ± 0.7%	1.6% ± 2.2%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of January 30, 2002

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	100 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	10	15	11	8
Natural deaths	2	7	3	6
Survivors				
Died last week of study				1
Terminal sacrifice	37	28	35	35
Pregnant	1			
Animals examined microscopically	49	50	50	50
Alimentary System				
Esophagus	(49)	(50)	(50)	(50)
Hyperplasia, squamous	1 (2%)			
Inflammation, chronic active	2 (4%)			
Intestine large, rectum	(49)	(47)	(49)	(48)
Necrosis		1 (2%)		
Intestine small, duodenum	(48)	(43)	(47)	(47)
Inflammation, acute				1 (2%)
Necrosis			1 (2%)	1 (2%)
Intestine small, jejunum	(48)	(45)	(48)	(45)
Infiltration cellular, mixed cell		1 (2%)		
Necrosis	1 (2%)			
Intestine small, ileum	(47)	(45)	(49)	(47)
Infiltration cellular, mixed cell		2 (4%)		
Inflammation, granulomatous				1 (2%)
Necrosis	1 (2%)			
Liver	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)		1 (2%)	1 (2%)
Basophilic focus	8 (16%)	7 (14%)	6 (12%)	3 (6%)
Clear cell focus	2 (4%)	2 (4%)	4 (8%)	1 (2%)
Cyst		1 (2%)		
Eosinophilic focus	8 (16%)	6 (12%)	11 (22%)	11 (22%)
Fatty change	2 (4%)		2 (4%)	2 (4%)
Hematopoietic cell proliferation		2 (4%)		3 (6%)
Infarct	1 (2%)	2 (4%)		
Infiltration cellular, mast cell	1 (2%)			
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation, granulomatous	16 (33%)	11 (22%)	16 (32%)	16 (32%)
Mitotic alteration		1 (2%)	1 (2%)	
Mixed cell focus		1 (2%)		
Necrosis			1 (2%)	1 (2%)
Tension lipidosis		3 (6%)		4 (8%)
Thrombosis	1 (2%)			
Vacuolization cytoplasmic		1 (2%)		1 (2%)
Bile duct, cyst		1 (2%)		
Centrilobular, degeneration	1 (2%)			
Centrilobular, necrosis		1 (2%)		2 (4%)
Oval cell, hyperplasia			1 (2%)	

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

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Alimentary System (continued)				
Mesentery	(17)	(18)	(12)	(18)
Inflammation, granulomatous	2 (12%)			2 (11%)
Thrombosis		1 (6%)		
Fat, hemorrhage		1 (6%)		
Fat, necrosis	16 (94%)	16 (89%)	11 (92%)	16 (89%)
Pancreas	(49)	(47)	(50)	(49)
Angiectasis				1 (2%)
Atrophy	1 (2%)		1 (2%)	
Basophilic focus	1 (2%)		1 (2%)	
Lipomatosis	1 (2%)			
Necrosis	1 (2%)			
Salivary glands	(49)	(50)	(50)	(50)
Degeneration	1 (2%)			
Stomach, forestomach	(49)	(49)	(50)	(47)
Hyperplasia, squamous	5 (10%)	1 (2%)	6 (12%)	2 (4%)
Inflammation, acute	1 (2%)		1 (2%)	2 (4%)
Stomach, glandular	(48)	(47)	(50)	(47)
Infiltration cellular, mixed cell	1 (2%)			
Mineralization		2 (4%)	3 (6%)	1 (2%)
Necrosis	1 (2%)		1 (2%)	
Tooth	(4)	(2)	(1)	(1)
Inflammation, chronic active		1 (50%)		
Malformation	3 (75%)	1 (50%)	1 (100%)	1 (100%)
Dentine, incisor, dysplasia	1 (25%)			
Cardiovascular System				
Blood vessel			(2)	
Aorta, mineralization			1 (50%)	
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy	8 (16%)	10 (20%)	13 (26%)	8 (16%)
Inflammation, chronic active		1 (2%)		
Mineralization			1 (2%)	1 (2%)
Atrium, inflammation, acute		1 (2%)		
Atrium, thrombosis				1 (2%)
Capillary, hyperplasia			1 (2%)	
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(49)
Hyperplasia	6 (12%)	7 (14%)	5 (10%)	5 (10%)
Hypertrophy	3 (6%)	8 (16%)	2 (4%)	6 (12%)
Necrosis			1 (2%)	
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	1 (2%)			
Subcapsular, hyperplasia	1 (2%)	1 (2%)		
Adrenal medulla	(48)	(50)	(50)	(49)
Hyperplasia	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Islets, pancreatic	(49)	(47)	(50)	(49)
Hyperplasia			1 (2%)	
Pituitary gland	(49)	(49)	(49)	(50)
Pars distalis, angiectasis	1 (2%)	1 (2%)		
Pars distalis, hyperplasia	20 (41%)	20 (41%)	20 (41%)	12 (24%)
Pars intermedia, hyperplasia	2 (4%)			
Pars intermedia, hypertrophy			1 (2%)	1 (2%)

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Endocrine System (continued)				
Thyroid gland	(49)	(49)	(50)	(47)
Cyst	1 (2%)			
Follicular cell, hyperplasia	1 (2%)	2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Ovary	(49)	(49)	(49)	(48)
Angiectasis		2 (4%)	1 (2%)	1 (2%)
Cyst	16 (33%)	11 (22%)	8 (16%)	10 (21%)
Hyperplasia, tubular	1 (2%)	1 (2%)	1 (2%)	
Inflammation, granulomatous		1 (2%)		
Thrombosis		1 (2%)		
Uterus	(49)	(49)	(50)	(49)
Angiectasis	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Hyperplasia, cystic	3 (6%)	3 (6%)	5 (10%)	
Inflammation, suppurative	1 (2%)			
Necrosis	1 (2%)			
Thrombosis				1 (2%)
Endometrium, hyperplasia, cystic	7 (14%)	5 (10%)	4 (8%)	8 (16%)
Lymphatic, cyst				1 (2%)
Hematopoietic System				
Lymph node	(5)	(2)	(4)	(1)
Lumbar, angiectasis			1 (25%)	
Renal, angiectasis	2 (40%)			
Lymph node, bronchial	(41)	(45)	(47)	(44)
Infiltration cellular, plasma cell		1 (2%)	1 (2%)	
Lymph node, mandibular	(36)	(40)	(37)	(41)
Hyperplasia, lymphoid		1 (3%)		
Infiltration cellular, mast cell	1 (3%)			
Lymph node, mesenteric	(47)	(47)	(50)	(47)
Angiectasis		1 (2%)	2 (4%)	2 (4%)
Ectasia		1 (2%)		
Infiltration cellular, plasma cell	1 (2%)	1 (2%)		
Inflammation, granulomatous		1 (2%)		1 (2%)
Lymph node, mediastinal	(43)	(42)	(43)	(46)
Congestion				1 (2%)
Infiltration cellular, plasma cell		1 (2%)		
Spleen	(49)	(47)	(50)	(48)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)		1 (2%)
Infiltration cellular, mast cell	1 (2%)			
Necrosis				1 (2%)
Thymus	(48)	(48)	(48)	(47)
Necrosis		1 (2%)		2 (4%)

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Integumentary System				
Mammary gland	(48)	(50)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Skin	(49)	(50)	(50)	(50)
Hyperplasia, basal cell				1 (2%)
Infiltration cellular, mixed cell	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active				1 (2%)
Inflammation, granulomatous			1 (2%)	
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Fibrous osteodystrophy	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Skeletal muscle		(2)		
Necrosis, fatty		1 (50%)		
Nervous System				
Brain	(49)	(50)	(50)	(50)
Meninges, infiltration cellular, mononuclear cell			1 (2%)	1 (2%)
Respiratory System				
Larynx	(49)	(50)	(50)	(49)
Inflammation, acute			1 (2%)	
Mineralization			1 (2%)	
Lung	(49)	(50)	(50)	(50)
Congestion			1 (2%)	
Hemorrhage			1 (2%)	1 (2%)
Inflammation, granulomatous			3 (6%)	
Mineralization			1 (2%)	
Thrombosis		1 (2%)		
Alveolar epithelium, hyperplasia	4 (8%)	2 (4%)	3 (6%)	4 (8%)
Alveolus, infiltration cellular, histiocyte	3 (6%)		1 (2%)	3 (6%)
Artery, inflammation, chronic				1 (2%)
Bronchiole, hyperplasia		1 (2%)		1 (2%)
Nose	(49)	(50)	(50)	(49)
Inflammation, suppurative	3 (6%)	1 (2%)		1 (2%)
Glands, dilatation			1 (2%)	5 (10%)
Olfactory epithelium, atrophy			1 (2%)	2 (4%)
Respiratory epithelium, metaplasia, squamous				1 (2%)
Sinus, foreign body		1 (2%)		1 (2%)
Trachea	(49)	(49)	(50)	(49)
Inflammation, acute			1 (2%)	
Mineralization			1 (2%)	
Special Senses System				
Eye	(2)	(1)	(2)	
Cornea, inflammation, chronic active	1 (50%)	1 (100%)	1 (50%)	
Harderian gland	(4)	(4)	(5)	(3)
Hyperplasia				1 (33%)

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Decalin

	Chamber Control	25 ppm	100 ppm	400 ppm
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Amyloid deposition		1 (2%)		1 (2%)
Infarct	4 (8%)	2 (4%)		
Metaplasia, osseous	4 (8%)	1 (2%)	1 (2%)	3 (6%)
Nephropathy	45 (92%)	40 (80%)	40 (80%)	41 (82%)
Pelvis, dilatation	1 (2%)			
Renal tubule, hyperplasia	1 (2%)			
Renal tubule, necrosis				1 (2%)
Renal tubule, vacuolization cytoplasmic			1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1987). Decalin was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA1535 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of decalin. The high dose was limited by toxicity. All trials were repeated at the same or a higher S9 factor.

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

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 3-month toxicity study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in up to 10 animals per exposure group; 1,000 erythrocytes were counted to determine the percentage of polychromatic (immature) erythrocytes (PCEs) among the total erythrocyte population.

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 exposed group and the chamber control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single exposed group is less than or equal to 0.025 divided by the number of exposed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Results of the 3-month study were accepted without repeat tests, because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

EVALUATION PROTOCOL

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among

aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

RESULTS

Decalin (1 to 10,000 µg/plate) was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535 with or without Aroclor-induced rat or hamster liver S9 enzymes (Table E1). No induction of micronuclei in peripheral blood NCEs was observed in female mice exposed to 25 to 400 ppm decalin for 3 months by inhalation (Table E2). In contrast to the negative results in females, a small but statistically significant increase in the frequency of micronucleated NCEs was noted in peripheral blood of male mice. A slight increase over the exposure range in the percentage of PCEs was seen in males and females; all values, however, were within the normal range.

TABLE E1
Mutagenicity of Decalin in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] –S9 Trial 1	–S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA100	0	97 ± 3.0	115 ± 5.4	122 ± 3.7	132 ± 5.1	111 ± 2.2	129 ± 7.3
	1		112 ± 1.7				
	3	93 ± 2.0	110 ± 5.8				
	10	97 ± 4.0	98 ± 3.8	107 ± 5.0		103 ± 11.1	
	33	87 ± 3.5	111 ± 6.5	93 ± 2.7		114 ± 5.9	
	100	91 ± 3.7	109 ± 7.3	97 ± 2.3	142 ± 3.5	105 ± 2.3	134 ± 6.5
	333	69 ± 6.9[c,d]		101 ± 10.8	144 ± 8.1	104 ± 0.7	141 ± 12.8
	1,000			84 ± 2.3[c]	125 ± 4.7	87 ± 12.7[c]	123 ± 4.1
	3,333				111 ± 6.8		107 ± 3.6
	10,000				80 ± 9.6[c]		98 ± 4.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[e]		900 ± 50.9	752 ± 15.3	354 ± 11.1	415 ± 10.5	328 ± 12.4	366 ± 7.6

Strain	Dose (µg/plate)	–S9 Trial 1	–S9 Trial 2	–S9 Trial 3	+hamster S9 10%	+hamster S9 30%
TA1535	0	9 ± 0.9	13 ± 1.3	11 ± 1.2	12 ± 1.2	9 ± 2.0
	1			11 ± 0.7		
	3	7 ± 0.9	17 ± 1.8	10 ± 0.6		
	10	7 ± 0.9	16 ± 0.9	9 ± 1.3	10 ± 1.3	
	33	7 ± 2.0	16 ± 3.5	12 ± 2.3	10 ± 1.2	
	100	6 ± 1.0	13 ± 1.7	9 ± 1.5	13 ± 2.1	10 ± 0.7
	333	9 ± 0.9	12 ± 1.2[c]	8 ± 0.7[c]	12 ± 1.2	10 ± 1.5
	1,000	Toxic			11 ± 1.7	6 ± 0.6
	3,333	Toxic				7 ± 0.9
	10,000	Toxic				5 ± 2.1[c]
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		851 ± 15.6	704 ± 83.3	613 ± 9.2	188 ± 14.8	198 ± 14.3

Strain	Dose (µg/plate)	+rat S9 10%	+rat S9 30%
TA1535 (continued)	0	10 ± 1.5	10 ± 1.8
	10	11 ± 1.5	
	33	13 ± 0.9	
	100	11 ± 2.2	8 ± 1.9
	333	12 ± 0.9	8 ± 1.0
	1,000	10 ± 0.6	9 ± 0.9
	3,333		8 ± 1.5
	10,000		5 ± 1.0[c]
Trial summary		Negative	Negative
Positive control		135 ± 10.1	138 ± 8.4

TABLE E1
Mutagenicity of Decalin in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate –S9 Trial 1	–S9 Trial 2	–S9 Trial 3	+hamster S9 10%	+hamster S9 30%
TA97	0	103 ± 3.4	124 ± 10.6	132 ± 4.9	141 ± 16.6	109 ± 14.8
	1			143 ± 12.9		
	3	84 ± 6.4	123 ± 6.4	135 ± 6.7		
	10	88 ± 1.5	137 ± 4.3	111 ± 14.4		
	33	86 ± 6.7	133 ± 3.5	98 ± 8.7		
	100	82 ± 5.0	103 ± 7.5	115 ± 1.5	148 ± 6.7	111 ± 9.9
	333	54 ± 0.7[c]	98 ± 3.7[c]	115 ± 8.1	152 ± 6.5	125 ± 1.5
	1,000	Toxic			155 ± 4.2	121 ± 14.3
	3,333	Toxic			147 ± 8.5	110 ± 17.1
	6,666				134 ± 11.8	
	10,000	Toxic			88 ± 1.7[c]	89 ± 8.7
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		392 ± 11.9	329 ± 18.9	447 ± 4.4	324 ± 14.2	409 ± 8.5

		+rat S9 10%	+rat S9 30%
TA97 (continued)	0	141 ± 3.5	102 ± 7.1
	100	156 ± 4.1	104 ± 3.2
	333	158 ± 1.9	103 ± 5.0
	1,000	155 ± 4.0	115 ± 3.3
	3,333	153 ± 4.7	118 ± 3.1
	6,666	144 ± 9.4[c]	
	10,000	112 ± 15.5[c]	95 ± 7.8
Trial summary		Negative	Negative
Positive control		355 ± 8.9	374 ± 10.7

		–S9 Trial 1	–S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA98	0	20 ± 1.5	17 ± 2.6	18 ± 3.2	24 ± 1.8	19 ± 1.3	21 ± 2.0
	1		17 ± 2.0				
	3	19 ± 1.9	16 ± 0.3				
	10	14 ± 0.6	18 ± 0.3	17 ± 2.1		18 ± 2.6	
	33	16 ± 0.6	15 ± 3.2	18 ± 0.3		24 ± 0.7	
	100	14 ± 1.7	17 ± 1.5	13 ± 1.3	21 ± 1.5	19 ± 3.3	23 ± 2.2
	333	13 ± 3.8[c]	10 ± 4.5[c,d]	18 ± 0.7	24 ± 5.2	14 ± 3.0	17 ± 1.2
	1,000			16 ± 3.2	24 ± 1.7	19 ± 4.0	19 ± 3.2
	3,333				20 ± 2.4		16 ± 1.9
	10,000				13 ± 2.2		13 ± 2.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		236 ± 7.2	275 ± 11.4	142 ± 10.1	328 ± 21.0	196 ± 12.3	187 ± 15.1

[a] Study performed at SRI International. The detailed protocol is presented by Zeiger *et al*. (1987). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] Precipitate seen on plate
[e] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Inhalation of Decalin for 3 Months[a]

Concentration (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male				
Chamber control	10	0.55 ± 0.16		1.8
25	10	0.45 ± 0.16	0.6727	1.8
50	10	1.00 ± 0.15	0.0529	2.0
100	10	1.00 ± 0.22	0.0529	1.9
200	10	1.25 ± 0.20	0.0098	1.9
400	9	1.33 ± 0.20	0.0060	2.6
		P=0.001[d]		
Female				
Chamber control	9	0.67 ± 0.20		1.6
25	10	0.50 ± 0.11	0.7500	1.8
50	10	0.70 ± 0.19	0.4506	1.6
100	10	0.35 ± 0.13	0.9160	1.5
200	10	0.30 ± 0.08	0.9495	2.0
400	10	0.40 ± 0.12	0.8711	2.0
		P=0.917		

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by MacGregor *et al*. (1990). NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the chamber controls, significant at P≤0.005 (ILS, 1990)
[d] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)

APPENDIX F
CLINICAL PATHOLOGY RESULTS

TABLE F1 **Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin** 244
TABLE F2 **Hematology Data for Mice in the 3-Month Inhalation Study of Decalin** 251

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male						
Hematology						
Hematocrit (%)						
Day 3	45.7 ± 0.3	46.3 ± 0.3	46.0 ± 0.5	45.2 ± 0.4	45.3 ± 0.3	46.4 ± 0.6
Day 23	47.3 ± 0.3	47.9 ± 0.5	47.7 ± 0.3	47.4 ± 0.4	47.5 ± 0.4	47.4 ± 0.2
Week 14	46.7 ± 0.3	46.4 ± 0.3	47.0 ± 0.5	46.4 ± 0.5	46.3 ± 0.4	45.9 ± 0.4
Packed red cell volume (mL/dL)						
Day 3	44.0 ± 0.4	44.5 ± 0.4	44.5 ± 0.6	43.0 ± 0.4	43.4 ± 0.4	45.1 ± 0.7
Day 23	46.6 ± 0.4	47.4 ± 0.5	47.1 ± 0.4	46.6 ± 0.4	47.2 ± 0.3	46.7 ± 0.3
Week 14	46.0 ± 0.3	46.3 ± 0.3	46.3 ± 0.4	45.8 ± 0.4	46.2 ± 0.5	45.8 ± 0.2
Hemoglobin (g/dL)						
Day 3	13.8 ± 0.1	14.1 ± 0.2	13.8 ± 0.2	13.5 ± 0.1	13.7 ± 0.1	14.1 ± 0.2
Day 23	15.3 ± 0.2	15.4 ± 0.2	15.3 ± 0.1	15.1 ± 0.1	15.2 ± 0.1	15.1 ± 0.1
Week 14	15.5 ± 0.1	15.5 ± 0.1	15.3 ± 0.1	15.4 ± 0.1	15.4 ± 0.1	15.3 ± 0.1
Erythrocytes (10^6/µL)						
Day 3	6.84 ± 0.07	6.90 ± 0.07	6.96 ± 0.12	6.70 ± 0.08	6.73 ± 0.07	7.04 ± 0.12
Day 23	7.84 ± 0.07	7.81 ± 0.11	7.83 ± 0.09	7.67 ± 0.12	7.82 ± 0.09	7.68 ± 0.08
Week 14	8.31 ± 0.07	8.33 ± 0.06	8.26 ± 0.05	8.22 ± 0.08	8.30 ± 0.09	8.12 ± 0.04
Reticulocytes (10^6/µL)						
Day 3	0.28 ± 0.03	0.26 ± 0.03	0.28 ± 0.04	0.47 ± 0.03**	0.46 ± 0.04**	0.38 ± 0.03**
Day 23	0.26 ± 0.01	0.30 ± 0.02	0.28 ± 0.02	0.29 ± 0.01	0.28 ± 0.02	0.29 ± 0.01
Week 14	0.19 ± 0.09	0.16 ± 0.01	0.18 ± 0.10	0.16 ± 0.02	0.18 ± 0.01	0.19 ± 0.01
Nucleated erythrocytes/100 leukocytes						
Week 14	0.10 ± 0.10	0.30 ± 0.15	0.10 ± 0.10	0.00 ± 0.00	0.40 ± 0.31	0.20 ± 0.20
Mean cell volume (fL)						
Day 3	64.5 ± 0.5	64.5 ± 0.3	63.8 ± 0.3	64.2 ± 0.3	64.6 ± 0.4	64.1 ± 0.3
Day 23	59.5 ± 0.6	60.6 ± 0.5	60.1 ± 0.5	60.6 ± 0.7	60.6 ± 0.7	60.7 ± 0.3
Week 14	55.3 ± 0.4	55.4 ± 0.4	56.1 ± 0.3	55.8 ± 0.3	55.6 ± 0.3	56.3 ± 0.3
Mean cell hemoglobin (pg)						
Day 3	20.2 ± 0.1	20.4 ± 0.2	19.9 ± 0.2	20.1 ± 0.1	20.3 ± 0.1	20.0 ± 0.2
Day 23	19.5 ± 0.2	19.8 ± 0.2	19.6 ± 0.2	19.7 ± 0.2	19.5 ± 0.3	19.7 ± 0.2
Week 14	18.7 ± 0.1	18.6 ± 0.1	18.6 ± 0.1	18.8 ± 0.1	18.5 ± 0.1	18.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 3	31.4 ± 0.2	31.6 ± 0.2	31.1 ± 0.2	31.3 ± 0.1	31.5 ± 0.2	31.2 ± 0.2
Day 23	32.9 ± 0.2	32.6 ± 0.2	32.6 ± 0.1	32.5 ± 0.1	32.3 ± 0.1	32.4 ± 0.2
Week 14	33.8 ± 0.3	33.4 ± 0.2	33.1 ± 0.4	33.7 ± 0.3	33.4 ± 0.4	33.3 ± 0.3
Platelets (10^3/µL)						
Day 3	873.4 ± 16.4	848.0 ± 14.3	857.5 ± 8.8	871.5 ± 17.4	889.7 ± 22.4	855.8 ± 23.8
Day 23	673.7 ± 20.7	649.1 ± 19.9	665.0 ± 21.1	712.4 ± 12.5	711.0 ± 13.8	752.9 ± 18.7*
Week 14	615.6 ± 20.4	655.6 ± 18.0	653.9 ± 18.4	619.8 ± 17.4	660.2 ± 18.4	638.3 ± 14.2
Leukocytes (10^3/µL)						
Day 3	9.19 ± 0.47	8.73 ± 0.54	8.56 ± 0.45	8.52 ± 0.33	9.26 ± 0.59	9.09 ± 0.38
Day 23	10.65 ± 0.75	10.20 ± 0.43	10.16 ± 0.58	11.82 ± 0.36	11.23 ± 0.48	10.98 ± 0.64
Week 14	5.31 ± 0.30	5.46 ± 0.53	5.67 ± 0.30	6.45 ± 0.51	6.76 ± 0.49	6.15 ± 0.39
Segmented neutrophils (10^3/µL)						
Day 3	0.89 ± 0.12	0.88 ± 0.06	0.66 ± 0.08	0.99 ± 0.11	1.00 ± 0.11	0.96 ± 0.13
Day 23	0.68 ± 0.09	0.69 ± 0.05	0.68 ± 0.08	0.82 ± 0.07	1.03 ± 0.13*	0.91 ± 0.13*
Week 14	0.95 ± 0.10	0.87 ± 0.10	1.01 ± 0.09	1.00 ± 0.11	1.05 ± 0.11	0.98 ± 0.06

Table F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male (continued)						
Hematology (continued)						
Bands ($10^3/\mu L$)						
Day 3	0.01 ± 0.01	0.00 ± 0.00	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes ($10^3/\mu L$)						
Day 3	7.82 ± 0.35	7.62 ± 0.52	7.56 ± 0.50	7.03 ± 0.30	7.77 ± 0.54	7.51 ± 0.43
Day 23	9.68 ± 0.64	9.23 ± 0.38	9.15 ± 0.48	10.65 ± 0.36	9.80 ± 0.41	9.57 ± 0.55
Week 14	4.25 ± 0.25	4.37 ± 0.45	4.55 ± 0.29	5.34 ± 0.48	5.57 ± 0.43	5.05 ± 0.35
Monocytes ($10^3/\mu L$)						
Day 3	0.43 ± 0.06	0.16 ± 0.05	0.27 ± 0.03	0.46 ± 0.06	0.47 ± 0.11	0.59 ± 0.08
Day 23	0.21 ± 0.04	0.21 ± 0.03	0.25 ± 0.04	0.28 ± 0.03	0.32 ± 0.03**	0.41 ± 0.08**
Week 14	0.04 ± 0.02	0.05 ± 0.03	0.08 ± 0.02	0.06 ± 0.02	0.09 ± 0.04	0.05 ± 0.02
Basophils ($10^3/\mu L$)						
Day 3	0.000 ± 0.000	0.008 ± 0.008	0.000 ± 0.000	0.000 ± 0.000	0.008 ± 0.008	0.000 ± 0.000
Day 23	0.048 ± 0.007	0.041 ± 0.004	0.046 ± 0.008	0.037 ± 0.005	0.044 ± 0.005	0.054 ± 0.005
Week 14	0.009 ± 0.009	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.006 ± 0.006
Eosinophils ($10^3/\mu L$)						
Day 3	0.05 ± 0.02	0.06 ± 0.02	0.04 ± 0.02	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Day 23	0.03 ± 0.00	0.03 ± 0.00	0.04 ± 0.01	0.03 ± 0.00	0.03 ± 0.01	0.03 ± 0.00
Week 14	0.06 ± 0.02	0.08 ± 0.02	0.03 ± 0.01	0.05 ± 0.02	0.06 ± 0.02	0.06 ± 0.02
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 3	7.5 ± 0.4	8.6 ± 0.3*	7.8 ± 0.7	8.4 ± 0.4	9.2 ± 0.5*	10.8 ± 0.8**
Day 23	10.3 ± 0.3	9.1 ± 0.5	8.9 ± 0.3*	8.5 ± 0.4**	9.1 ± 0.3	10.5 ± 0.4
Week 14	13.3 ± 0.4	14.0 ± 0.3	14.0 ± 0.4	14.9 ± 0.3*	14.2 ± 0.5	13.5 ± 0.2
Creatinine (mg/dL)						
Day 3	0.67 ± 0.02	0.69 ± 0.01	0.66 ± 0.02	0.69 ± 0.02	0.68 ± 0.01	0.71 ± 0.02
Day 23	0.79 ± 0.02	0.81 ± 0.02	0.76 ± 0.02[b]	0.77 ± 0.02	0.76 ± 0.02	0.78 ± 0.01
Week 14	0.89 ± 0.02	0.95 ± 0.04	0.92 ± 0.03	0.96 ± 0.02	0.96 ± 0.03	0.97 ± 0.02
Total protein (g/dL)						
Day 3	5.7 ± 0.0	5.7 ± 0.1	5.7 ± 0.1	5.6 ± 0.1	5.6 ± 0.1	5.9 ± 0.1
Day 23	6.3 ± 0.1	6.3 ± 0.0	6.3 ± 0.1	6.3 ± 0.1	6.3 ± 0.0	6.5 ± 0.1
Week 14	6.8 ± 0.1	6.8 ± 0.1	6.7 ± 0.0	6.7 ± 0.0	6.8 ± 0.1	6.9 ± 0.1
Albumin (g/dL)						
Day 3	3.4 ± 0.1	3.5 ± 0.0	3.4 ± 0.1	3.5 ± 0.1	3.5 ± 0.0	3.5 ± 0.0
Day 23	3.9 ± 0.0	3.9 ± 0.1	3.9 ± 0.1	3.8 ± 0.0	3.9 ± 0.1	3.9 ± 0.0
Week 14	4.4 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	4.2 ± 0.1*	4.4 ± 0.1	4.4 ± 0.1
Globulin (g/dL)						
Day 3	2.3 ± 0.1	2.2 ± 0.1	2.2 ± 0.0	2.2 ± 0.1	2.1 ± 0.1	2.4 ± 0.1
Day 23	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.1
Week 14	2.4 ± 0.1	2.4 ± 0.1	2.3 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	2.6 ± 0.1
Albumin/globulin ratio						
Day 3	1.5 ± 0.1	1.6 ± 0.0	1.5 ± 0.0	1.6 ± 0.1	1.7 ± 0.1	1.5 ± 0.0
Day 23	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.5 ± 0.0
Week 14	1.9 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	1.7 ± 0.1

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male (continued)						
Clinical Chemistry (continued)						
Alanine aminotransferase (IU/L)						
Day 3	60 ± 1	59 ± 2	54 ± 1*	54 ± 1*	53 ± 1**	54 ± 1**
Day 23	51 ± 2	49 ± 5*	45 ± 3**	36 ± 1**	36 ± 1**	35 ± 1**
Week 14	66 ± 3	60 ± 3	69 ± 6	59 ± 2	49 ± 3**	47 ± 2**
Alkaline phosphatase (IU/L)						
Day 3	785 ± 16	753 ± 10	732 ± 19*	750 ± 12*	688 ± 16**	709 ± 11**
Day 23	502 ± 11	486 ± 11	474 ± 15	453 ± 11*	449 ± 8**	458 ± 14*
Week 14	326 ± 6	314 ± 9	335 ± 10	320 ± 9	303 ± 10	300 ± 7
Creatine kinase (IU/L)						
Day 3	373 ± 53	387 ± 57	399 ± 47	368 ± 53	287 ± 17	341 ± 31
Day 23	701 ± 116	355 ± 39*[b]	755 ± 267	460 ± 52	495 ± 85	284 ± 40**
Week 14	145 ± 19	123 ± 18	187 ± 42	163 ± 34	183 ± 46	139 ± 14
Sorbitol dehydrogenase (IU/L)						
Day 3	13 ± 1	14 ± 1	13 ± 0	14 ± 1	14 ± 1	13 ± 0
Day 23	9 ± 1	12 ± 1	14 ± 2	9 ± 1	10 ± 1	12 ± 0
Week 14	16 ± 1	18 ± 1	18 ± 1	17 ± 1	15 ± 1	16 ± 1
Bile acids (µmol/L)						
Day 3	31.7 ± 1.1	39.2 ± 2.9*	39.7 ± 1.9**	42.3 ± 1.9**	38.8 ± 1.7**	43.0 ± 1.2**
Day 23	37.7 ± 4.3	43.0 ± 7.8	38.1 ± 4.8[b]	43.1 ± 2.9	40.7 ± 1.7	42.0 ± 2.9
Week 14	24.4 ± 0.8	26.3 ± 1.0	32.5 ± 2.3**	30.9 ± 1.1**	28.6 ± 1.4	28.5 ± 1.8
Urinalysis						
Creatinine (mg/dL)	70.20 ± 12.12	65.90 ± 11.87	59.00 ± 11.41	58.00 ± 12.32	49.00 ± 6.83	62.90 ± 11.03
Glucose (mg/dL)	10 ± 2	11 ± 2	10 ± 3	12 ± 3	12 ± 2	12 ± 2
Glucose/creatinine ratio	0.15 ± 0.04	0.18 ± 0.02*	0.21 ± 0.06*	0.20 ± 0.01**	0.29 ± 0.07**	0.21 ± 0.02**
Protein (mg/dL)	82 ± 12	90 ± 13	98 ± 17	100 ± 20	82 ± 12	101 ± 18
Protein/creatinine ratio	1.24 ± 0.06	1.48 ± 0.09*	1.71 ± 0.05**	1.79 ± 0.10**	1.65 ± 0.08**	1.63 ± 0.07**
Alkaline phosphatase (IU/L)	222.7 ± 26.4	260.7 ± 48.2	255.7 ± 41.9	233.2 ± 42.2	180.2 ± 25.9	175.0 ± 25.0
Alkaline phosphatase/ creatinine ratio	3.63 ± 0.38	4.15 ± 0.29	4.60 ± 0.27	4.32 ± 0.27	3.64 ± 0.19	2.97 ± 0.17
Aspartate aminotransferase (IU/L)	10.60 ± 1.84	46.60 ± 8.17**	53.40 ± 11.61**	56.00 ± 11.87**	46.10 ± 8.73**	57.50 ± 11.82**
Aspartate aminotransferase/ creatinine ratio	0.15 ± 0.01	0.73 ± 0.04**	0.90 ± 0.04**	1.00 ± 0.08**	0.89 ± 0.06**	0.88 ± 0.06**
Lactate dehydrogenase (IU/L)	29.90 ± 5.55	77.90 ± 12.69**	88.60 ± 18.68**	95.30 ± 18.60**	77.50 ± 12.88**	102.00 ± 20.57**
Lactate dehydrogenase/ creatinine ratio	0.41 ± 0.02	1.25 ± 0.07**	1.49 ± 0.08**	1.73 ± 0.12**	1.52 ± 0.10**	1.57 ± 0.08**
γ-Glutamyltransferase (IU/L)	1,787 ± 283	1,659 ± 247	1,596 ± 278	1,530 ± 271	1,278 ± 180	1,318 ± 223
γ-Glutamyltransferase/ creatinine ratio	26.62 ± 1.21	26.69 ± 1.23	28.29 ± 1.21	28.21 ± 1.49	26.12 ± 0.85	21.66 ± 0.95
N-acetyl-β-D-glucosaminidase (IU/L)	12.38 ± 1.53[b]	16.51 ± 2.77	17.72 ± 2.86	17.45 ± 3.25	13.63 ± 2.11	17.93 ± 3.09
N-acetyl-β-D-glucosaminidase/ creatinine ratio	0.17 ± 0.01[b]	0.26 ± 0.01**	0.33 ± 0.03**	0.32 ± 0.02**	0.27 ± 0.01**	0.29 ± 0.01**
Volume (mL/16 hr)	12.3 ± 2.6	14.4 ± 3.1	14.9 ± 2.4	15.6 ± 2.6	19.3 ± 3.3	15.9 ± 3.6
Specific gravity	1.018 ± 0.003	1.017 ± 0.003	1.016 ± 0.003	1.017 ± 0.003	1.015 ± 0.002	1.019 ± 0.004

TABLE F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Female						
Hematology						
Hematocrit (%)						
Day 3	46.5 ± 0.5	46.4 ± 0.5	46.4 ± 0.4	47.2 ± 0.3	46.8 ± 0.6	47.0 ± 0.3
Day 23	47.4 ± 0.4	47.4 ± 0.6	46.9 ± 0.2	47.4 ± 0.4	47.1 ± 0.5	46.2 ± 0.5
Week 14	44.3 ± 0.6	44.7 ± 0.3	44.4 ± 0.6	44.3 ± 0.3	44.5 ± 0.4	44.1 ± 0.5
Packed red cell volume (mL/dL)						
Day 3	45.2 ± 0.6	45.6 ± 0.4	45.3 ± 0.5	45.7 ± 0.5	45.7 ± 0.8	46.0 ± 0.3
Day 23	47.0 ± 0.5	47.6 ± 0.5	47.4 ± 0.3	47.0 ± 0.3	47.2 ± 0.6	46.3 ± 0.6
Week 14	44.3 ± 0.4	44.2 ± 0.3	43.8 ± 0.6	43.6 ± 0.4	44.2 ± 0.4	44.0 ± 0.5
Hemoglobin (g/dL)						
Day 3	14.4 ± 0.2	14.5 ± 0.1	14.4 ± 0.2	14.7 ± 0.2	14.6 ± 0.2	14.5 ± 0.2
Day 23	15.6 ± 0.1	15.7 ± 0.2	15.5 ± 0.1	15.5 ± 0.1	15.5 ± 0.1	15.3 ± 0.2
Week 14	15.5 ± 0.2	15.5 ± 0.1	15.5 ± 0.2	15.3 ± 0.1	15.5 ± 0.1	15.4 ± 0.1
Erythrocytes (10^6/µL)						
Day 3	7.01 ± 0.10	7.08 ± 0.08	7.10 ± 0.11	7.20 ± 0.10	7.20 ± 0.14	7.26 ± 0.08
Day 23	7.65 ± 0.09	7.70 ± 0.10	7.77 ± 0.08	7.76 ± 0.08	7.79 ± 0.12	7.71 ± 0.14
Week 14	7.56 ± 0.08	7.53 ± 0.05	7.43 ± 0.13	7.42 ± 0.07	7.51 ± 0.07	7.47 ± 0.07
Reticulocytes (10^6/µL)						
Day 3	0.14 ± 0.02	0.26 ± 0.03**	0.23 ± 0.02**	0.29 ± 0.02**	0.32 ± 0.03**	0.31 ± 0.02**
Day 23	0.16 ± 0.01	0.16 ± 0.01	0.15 ± 0.01	0.18 ± 0.01	0.17 ± 0.01	0.21 ± 0.02
Week 14	0.17 ± 0.01	0.14 ± 0.01	0.17 ± 0.02	0.18 ± 0.01	0.17 ± 0.01	0.17 ± 0.01
Nucleated erythrocytes/100 leukocytes						
Week 14	0.10 ± 0.10	0.00 ± 0.00	0.50 ± 0.22	0.30 ± 0.21	0.20 ± 0.13	0.30 ± 0.15
Mean cell volume (fL)						
Day 3	64.5 ± 0.3	64.6 ± 0.3	63.9 ± 0.4	63.3 ± 0.3*	63.6 ± 0.3*	63.5 ± 0.3
Day 23	61.4 ± 0.4	61.7 ± 0.5	61.0 ± 0.5	60.6 ± 0.4	60.6 ± 0.3	60.2 ± 0.4
Week 14	58.6 ± 0.2	58.6 ± 0.2	59.0 ± 0.4	58.8 ± 0.1	58.8 ± 0.2	58.8 ± 0.2
Mean cell hemoglobin (pg)						
Day 3	20.6 ± 0.1	20.4 ± 0.1	20.3 ± 0.1	20.4 ± 0.1	20.3 ± 0.1	20.0 ± 0.2
Day 23	20.4 ± 0.1	20.4 ± 0.2	19.9 ± 0.2	20.0 ± 0.2	20.0 ± 0.2	19.9 ± 0.2
Week 14	20.5 ± 0.1	20.6 ± 0.1	20.8 ± 0.1	20.6 ± 0.1	20.6 ± 0.1	20.7 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 3	31.9 ± 0.2	31.7 ± 0.1	31.7 ± 0.1	32.1 ± 0.1	31.9 ± 0.2	31.6 ± 0.2
Day 23	33.2 ± 0.1	33.1 ± 0.1	32.7 ± 0.2	33.0 ± 0.1	32.9 ± 0.2	33.2 ± 0.2
Week 14	35.0 ± 0.1	35.0 ± 0.1	35.3 ± 0.1	35.1 ± 0.1	35.0 ± 0.2	35.1 ± 0.2
Platelets (10^3/µL)						
Day 3	820.6 ± 25.2	822.1 ± 24.6	792.0 ± 14.8	795.7 ± 23.6	814.5 ± 16.7	765.9 ± 17.4
Day 23	605.2 ± 13.4	607.7 ± 9.6	615.8 ± 13.3	640.7 ± 17.7*	655.2 ± 14.5*	668.2 ± 17.3**
Week 14	582.5 ± 11.0	561.3 ± 11.8	611.4 ± 39.6	607.0 ± 30.1	557.6 ± 7.5	585.0 ± 12.1
Leukocytes (10^3/µL)						
Day 3	9.68 ± 0.40	10.17 ± 0.31	9.74 ± 0.51	10.90 ± 0.62	10.22 ± 0.69	9.47 ± 0.53
Day 23	12.86 ± 0.33	12.35 ± 0.40	12.71 ± 0.43	13.00 ± 0.49	12.62 ± 0.41	12.48 ± 0.45
Week 14	4.97 ± 0.42	4.46 ± 0.29	5.44 ± 0.56	5.62 ± 0.57	4.70 ± 0.22	4.66 ± 0.40
Segmented neutrophils (10^3/µL)						
Day 3	0.83 ± 0.09	0.92 ± 0.07	0.71 ± 0.10	1.20 ± 0.16	0.92 ± 0.10	1.00 ± 0.15
Day 23	0.93 ± 0.05	0.88 ± 0.10	1.00 ± 0.08	1.22 ± 0.12	1.22 ± 0.13	1.15 ± 0.09
Week 14	0.74 ± 0.06	0.73 ± 0.08	0.82 ± 0.12	0.79 ± 0.12	0.67 ± 0.05	0.78 ± 0.10

Table F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Female (continued)						
Hematology (continued)						
Bands ($10^3/\mu L$)						
Day 3	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes ($10^3/\mu L$)						
Day 3	8.60 ± 0.39	8.90 ± 0.32	8.70 ± 0.57	9.26 ± 0.53	8.86 ± 0.63	8.04 ± 0.55
Day 23	11.57 ± 0.32	11.11 ± 0.32	11.25 ± 0.41	11.27 ± 0.41	10.87 ± 0.33	10.77 ± 0.37
Week 14	4.07 ± 0.34	3.64 ± 0.25	4.54 ± 0.48	4.67 ± 0.45	3.92 ± 0.19	3.76 ± 0.36
Monocytes ($10^3/\mu L$)						
Day 3	0.20 ± 0.04	0.27 ± 0.06	0.31 ± 0.10	0.38 ± 0.07	0.37 ± 0.12	0.34 ± 0.11
Day 23	0.28 ± 0.02	0.26 ± 0.05	0.37 ± 0.06	0.41 ± 0.04	0.44 ± 0.07	0.44 ± 0.03*
Week 14	0.11 ± 0.03	0.06 ± 0.02	0.06 ± 0.02	0.09 ± 0.03	0.08 ± 0.02	0.07 ± 0.02
Basophils ($10^3/\mu L$)						
Day 3	0.011 ± 0.011	0.000 ± 0.000	0.000 ± 0.000	0.009 ± 0.009	0.018 ± 0.012	0.000 ± 0.000
Day 23	0.048 ± 0.004	0.062 ± 0.012	0.046 ± 0.006	0.057 ± 0.009	0.051 ± 0.007	0.058 ± 0.009
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)						
Day 3	0.03 ± 0.02	0.06 ± 0.03	0.03 ± 0.02	0.05 ± 0.02	0.06 ± 0.03	0.07 ± 0.03
Day 23	0.04 ± 0.00	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.05 ± 0.01
Week 14	0.05 ± 0.02	0.03 ± 0.01	0.02 ± 0.01	0.08 ± 0.03	0.03 ± 0.01	0.05 ± 0.01
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 3	9.8 ± 0.4	8.9 ± 0.3	9.2 ± 0.5	9.8 ± 0.5	9.8 ± 0.7	10.8 ± 0.5
Day 23	11.2 ± 0.4	10.9 ± 0.5	10.1 ± 0.4	9.6 ± 0.3*	10.1 ± 0.4	11.0 ± 0.5
Week 14	14.4 ± 0.4	13.5 ± 0.5	14.2 ± 0.5	13.7 ± 0.4	13.7 ± 0.7	12.9 ± 0.5
Creatinine (mg/dL)						
Day 3	0.65 ± 0.03	0.70 ± 0.02	0.64 ± 0.02	0.67 ± 0.03	0.70 ± 0.02	0.74 ± 0.02*
Day 23	0.70 ± 0.02	0.72 ± 0.01	0.66 ± 0.02	0.71 ± 0.01	0.74 ± 0.02	0.70 ± 0.02
Week 14	0.85 ± 0.02	0.86 ± 0.02	0.85 ± 0.03	0.85 ± 0.03	0.85 ± 0.02	0.85 ± 0.03
Total protein (g/dL)						
Day 3	6.1 ± 0.1	5.8 ± 0.1	5.8 ± 0.0	5.8 ± 0.0	5.9 ± 0.0	5.9 ± 0.1
Day 23	6.0 ± 0.1	6.1 ± 0.1	5.9 ± 0.1	6.0 ± 0.1	6.2 ± 0.1	6.1 ± 0.1
Week 14	6.8 ± 0.1	6.8 ± 0.1	6.8 ± 0.1	6.7 ± 0.1	6.8 ± 0.1	6.8 ± 0.1
Albumin (g/dL)						
Day 3	4.0 ± 0.0	3.9 ± 0.1	4.0 ± 0.1	3.9 ± 0.1	4.0 ± 0.1	4.0 ± 0.0
Day 23	3.9 ± 0.0	4.1 ± 0.1	3.9 ± 0.1	3.9 ± 0.0	4.1 ± 0.1	4.0 ± 0.1
Week 14	4.4 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.4 ± 0.1
Globulin (g/dL)						
Day 3	2.1 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	2.0 ± 0.1
Day 23	2.1 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	2.1 ± 0.0	2.1 ± 0.1	2.1 ± 0.1
Week 14	2.4 ± 0.1	2.4 ± 0.0	2.4 ± 0.1	2.4 ± 0.1	2.5 ± 0.1	2.4 ± 0.1
Albumin/globulin ratio						
Day 3	2.0 ± 0.1	2.1 ± 0.1	2.2 ± 0.1	2.0 ± 0.1	2.1 ± 0.1	2.1 ± 0.1
Day 23	1.9 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	1.8 ± 0.0	2.0 ± 0.1	1.9 ± 0.1
Week 14	1.8 ± 0.1	1.8 ± 0.0	1.9 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1

Table F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Female (continued)						
Clinical Chemistry (continued)						
Alanine aminotransferase (IU/L)						
Day 3	50 ± 2	48 ± 1	50 ± 2	48 ± 1	45 ± 1*	43 ± 1**
Day 23	44 ± 2	41 ± 2	42 ± 2	42 ± 1	37 ± 1**	35 ± 1**
Week 14	71 ± 4	68 ± 4	69 ± 3	56 ± 4**	56 ± 4*	51 ± 2**
Alkaline phosphatase (IU/L)						
Day 3	644 ± 13	624 ± 11	625 ± 12	596 ± 10**	600 ± 16*	557 ± 11**
Day 23	410 ± 9	418 ± 17	393 ± 12	406 ± 9	385 ± 7	365 ± 12**
Week 14	284 ± 6	266 ± 11	297 ± 8	288 ± 11	297 ± 7	266 ± 8
Creatine kinase (IU/L)						
Day 3	516 ± 103	481 ± 51	394 ± 49	577 ± 91	475 ± 74	556 ± 93
Day 23	211 ± 21[b]	307 ± 80	458 ± 87	398 ± 74	287 ± 50	388 ± 71
Week 14	163 ± 35	216 ± 70	163 ± 30	137 ± 24	172 ± 39	158 ± 34
Sorbitol dehydrogenase (IU/L)						
Day 3	13 ± 1	13 ± 1	12 ± 0	12 ± 1	14 ± 1	13 ± 1
Day 23	12 ± 1	13 ± 0	11 ± 1	12 ± 1	13 ± 0	11 ± 0
Week 14	18 ± 1	16 ± 0	18 ± 1	16 ± 1	15 ± 1	15 ± 1
Bile acids (μmol/L)						
Day 3	23.8 ± 2.8	31.4 ± 2.7*	29.9 ± 2.2*	34.6 ± 3.3**	39.2 ± 1.7**	37.7 ± 3.1**
Day 23	22.1 ± 2.0	30.7 ± 3.2*	34.1 ± 4.0**	27.6 ± 2.0*	35.7 ± 6.6**	30.3 ± 1.0**
Week 14	25.8 ± 2.2	26.5 ± 5.4	24.1 ± 2.0	22.5 ± 1.3	22.8 ± 1.6	23.4 ± 1.5
Urinalysis						
Creatinine (mg/dL)	40.10 ± 3.46	31.60 ± 4.29	35.10 ± 3.43	39.80 ± 4.84	38.50 ± 5.12	33.70 ± 3.90
Glucose (mg/dL)	4 ± 0	4 ± 1	4 ± 1	5 ± 1	4 ± 1	4 ± 1
Glucose/creatinine ratio	0.11 ± 0.00	0.12 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.10 ± 0.01
Protein (mg/dL)	3 ± 0	3 ± 1	3 ± 1	4 ± 1	3 ± 0	3 ± 0
Protein/creatinine ratio	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.09 ± 0.01
Alkaline phosphatase (IU/L)	95.0 ± 12.8	84.1 ± 13.5	87.3 ± 9.9	99.6 ± 10.6	103.9 ± 12.9	75.6 ± 5.3
Alkaline phosphatase/ creatinine ratio	2.31 ± 0.17	2.61 ± 0.13	2.48 ± 0.08	2.58 ± 0.19	2.77 ± 0.16	2.40 ± 0.18
Aspartate aminotransferase (IU/L)	1.20 ± 0.36	1.40 ± 0.22	2.00 ± 0.30	2.00 ± 0.30	2.50 ± 0.31**	2.10 ± 0.35*
Aspartate aminotransferase/ creatinine ratio	0.03 ± 0.01	0.05 ± 0.00	0.06 ± 0.01**	0.05 ± 0.01*	0.07 ± 0.01**	0.07 ± 0.02**
Lactate dehydrogenase (IU/L)	18.00 ± 2.10	21.50 ± 2.70	26.60 ± 3.63*	30.90 ± 2.76**	35.90 ± 4.46**	33.30 ± 4.20**
Lactate dehydrogenase/ creatinine ratio	0.48 ± 0.07	0.70 ± 0.05*	0.75 ± 0.05**	0.82 ± 0.06**	0.95 ± 0.03**	1.02 ± 0.10**
γ-Glutamyltransferase (IU/L)	455 ± 56	389 ± 61	404 ± 37	473 ± 67	562 ± 88	351 ± 38
γ-Glutamyltransferase/ creatinine ratio	11.28 ± 0.86	12.21 ± 1.17	12.05 ± 1.15	11.90 ± 0.86	14.49 ± 0.84	10.76 ± 0.93

Table F1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Female (continued)						
Urinalysis (continued)						
N-acetyl-β-D-glucosaminidase (IU/L)	5.21 ± 0.58	4.24 ± 0.75	5.52 ± 0.63	5.67 ± 0.71	5.47 ± 0.80	4.58 ± 0.61
N-acetyl-β-D-glucosaminidase/ creatinine ratio	0.13 ± 0.00	0.13 ± 0.01	0.16 ± 0.02*	0.14 ± 0.00	0.14 ± 0.01	0.13 ± 0.01
Volume (mL/16 hr)	10.9 ± 1.0	15.0 ± 2.0	12.9 ± 1.1	12.0 ± 1.4	12.9 ± 1.6	14.0 ± 1.8
Specific gravity	1.013 ± 0.001	1.011 ± 0.002	1.012 ± 0.001	1.014 ± 0.001	1.015 ± 0.002	1.014 ± 0.002

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

Table F2
Hematology Data for Mice in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
Male						
n	10	10	10	10	10	10
Hematocrit (%)	49.8 ± 0.5	50.0 ± 0.4	48.7 ± 0.7	49.2 ± 0.3	49.0 ± 0.3	48.6 ± 0.5
Packed red cell volume (mL/dL)	48.4 ± 0.4	48.7 ± 0.4	47.2 ± 0.5	47.8 ± 0.2	47.4 ± 0.2	47.1 ± 0.4*
Hemoglobin (g/dL)	15.9 ± 0.1	16.0 ± 0.1	15.5 ± 0.2	15.7 ± 0.1	15.7 ± 0.1	15.6 ± 0.1
Erythrocytes (10^6/µL)	10.02 ± 0.07	10.01 ± 0.07	9.69 ± 0.14	9.87 ± 0.04	9.74 ± 0.07*	9.73 ± 0.07**
Reticulocytes (10^6/µL)	0.13 ± 0.03	0.12 ± 0.01	0.14 ± 0.02	0.18 ± 0.02	0.16 ± 0.02	0.13 ± 0.02
Nucleated erythrocytes/ 100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	48.1 ± 0.2	48.8 ± 0.1	48.9 ± 0.5	48.4 ± 0.2	48.7 ± 0.3	48.3 ± 0.2
Mean cell hemoglobin (pg)	15.9 ± 0.1	16.0 ± 0.1	16.0 ± 0.1	15.9 ± 0.1	16.1 ± 0.1	16.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.9 ± 0.2	32.8 ± 0.2	32.8 ± 0.1	32.9 ± 0.2	33.2 ± 0.2	33.1 ± 0.2
Platelets (10^3/µL)	732.3 ± 10.2	729.3 ± 9.9	696.1 ± 15.8	720.1 ± 14.8	734.5 ± 10.1	719.7 ± 19.0
Leukocytes (10^3/µL)	3.00 ± 0.38	2.88 ± 0.33	2.35 ± 0.23	2.95 ± 0.24	2.87 ± 0.23	3.00 ± 0.33
Segmented neutrophils (10^3/µL)	0.38 ± 0.06	0.34 ± 0.05	0.28 ± 0.03	0.39 ± 0.04	0.40 ± 0.05	0.53 ± 0.07
Bands (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/µL)	2.60 ± 0.32	2.45 ± 0.28	2.04 ± 0.21	2.52 ± 0.21	2.41 ± 0.19	2.38 ± 0.26
Monocytes (10^3/µL)	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.03 ± 0.02
Basophils (10^3/µL)	0.000 ± 0.000	0.002 ± 0.002	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)	0.01 ± 0.01	0.07 ± 0.02*	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.06 ± 0.02*
Female						
n	9	10	10	10	10	10
Hematocrit (%)	49.4 ± 0.4	50.3 ± 0.4	49.0 ± 0.4	49.1 ± 0.2	48.3 ± 0.3	48.9 ± 0.4
Packed red cell volume (mL/dL)	47.4 ± 0.4	47.7 ± 0.3	46.5 ± 0.4	46.8 ± 0.2	45.9 ± 0.2**	46.4 ± 0.4*
Hemoglobin (g/dL)	16.3 ± 0.1	16.3 ± 0.1	16.1 ± 0.2	16.1 ± 0.1	15.7 ± 0.1**	16.0 ± 0.1*
Erythrocytes (10^6/µL)	9.79 ± 0.07	9.78 ± 0.08	9.58 ± 0.09	9.69 ± 0.04	9.50 ± 0.05*	9.69 ± 0.09
Reticulocytes (10^6/µL)	0.11 ± 0.03	0.09 ± 0.02	0.12 ± 0.02	0.12 ± 0.02	0.14 ± 0.03	0.14 ± 0.02
Nucleated erythrocytes/ 100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	48.3 ± 0.2	48.8 ± 0.2	48.7 ± 0.2	48.3 ± 0.2	48.2 ± 0.1	48.0 ± 0.0
Mean cell hemoglobin (pg)	16.7 ± 0.1	16.7 ± 0.1	16.8 ± 0.1	16.6 ± 0.1	16.6 ± 0.1	16.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.4 ± 0.2	34.2 ± 0.1	34.6 ± 0.1	34.4 ± 0.2	34.3 ± 0.2	34.5 ± 0.2
Platelets (10^3/µL)	707.4 ± 17.9	674.4 ± 7.7	687.4 ± 11.4	690.1 ± 10.4	716.4 ± 10.9	732.4 ± 10.5
Leukocytes (10^3/µL)	2.93 ± 0.17	3.10 ± 0.27	3.51 ± 0.33	3.42 ± 0.32	2.83 ± 0.14	3.52 ± 0.18
Segmented neutrophils (10^3/µL)	0.29 ± 0.05	0.42 ± 0.06	0.36 ± 0.05	0.33 ± 0.04	0.30 ± 0.05	0.48 ± 0.05
Bands (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/µL)	2.57 ± 0.17	2.63 ± 0.22	3.11 ± 0.28	3.01 ± 0.29	2.48 ± 0.12	2.97 ± 0.19
Monocytes (10^3/µL)	0.03 ± 0.01	0.00 ± 0.00*	0.02 ± 0.01	0.03 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.004 ± 0.004
Eosinophils (10^3/µL)	0.05 ± 0.01	0.05 ± 0.01	0.02 ± 0.01	0.06 ± 0.01	0.03 ± 0.01	0.06 ± 0.02

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Ratios were calculated and statistical tests were performed on unrounded data.

APPENDIX G
RENAL TOXICITY RESULTS

TABLE G1 Renal Toxicity Data for Male F344/N Rats in the 2-Week Inhalation Study of Decalin . . . 254
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TABLE G1
Renal Toxicity Data for Male F344/N Rats in the 2-Week Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	5	5	5	5	5	5
cis-2-Decalone (µg/g kidney)	—[b]	13.920 ± 0.758	17.680 ± 1.304	16.740 ± 1.200	14.700 ± 0.869	8.290 ± 0.682
trans-2-Decalone (µg/g kidney)	—	8.534 ± 0.561	11.740 ± 0.842	12.720 ± 0.941	13.180 ± 0.887	8.352 ± 0.666
(*cis* + *trans*)-2-Decalone (µg/g kidney)	—	22.460 ± 1.320	29.440 ± 2.135	29.440 ± 2.150	27.880 ± 1.753	16.660 ± 1.335
cis-2-Decalone (%)	—	62.040 ± 0.301	60.100 ± 0.173	56.820 ± 0.180	52.800 ± 0.293	49.780 ± 0.447
trans-2-Decalone (%)	—	37.960 ± 0.301	39.900 ± 0.173	43.180 ± 0.180	47.200 ± 0.293	50.220 ± 0.447
cis-/*trans*-2-Decalone ratio	—	1.634 ± 0.020	1.506 ± 0.011	1.316 ± 0.011	1.120 ± 0.014	0.992 ± 0.017
Cells labeled	64.60 ± 6.12	46.60 ± 5.98	54.80 ± 8.81	95.00 ± 10.70	105.4 ± 6.9*	120.4 ± 12.2*
Cells counted	2,083 ± 39	2,082 ± 13	2,125 ± 25	2,061 ± 20	2,077 ± 23	2,065 ± 21
Labeling index	0.031 ± 0.003	0.022 ± 0.003	0.026 ± 0.004	0.046 ± 0.005	0.051 ± 0.003*	0.058 ± 0.005*
α2u-Globulin (ng/µg soluble protein)	48.03 ± 7.12[c]	217.5 ± 49.79*	211.8 ± 38.30*[c]	238.4 ± 40.9*	368.0 ± 80.0**	931.8 ± 123.9**

* Significantly different (P≤0.05) from the chamber control by Shirley's test
** P≤0.01
[a] Data are presented as mean ± standard error.
[b] One or more values were below the limit of detection or were between the limit of detection and the experimental limit of quantification; group mean was declared indeterminate and no statistical tests were performed for this parameter.
[c] n=4

TABLE G2
Renal Toxicity Data for Male NBR Rats in the 2-Week Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	5	5	5	5	5	5
Cells labeled	33.600 ± 3.501	37.600 ± 1.749	33.600 ± 3.544	34.600 ± 3.280	29.600 ± 2.561	32.400 ± 5.221
Cells counted	2,097.40 ± 21.33	2,126.20 ± 35.33	2,138.80 ± 34.18	2,090.40 ± 28.69	2,183.00 ± 24.17	2,081.20 ± 20.71
Labeling index	0.016 ± 0.002	0.018 ± 0.001	0.016 ± 0.002	0.017 ± 0.002	0.014 ± 0.001	0.016 ± 0.002

[a] Data are presented as mean ± standard error.

TABLE G3
Renal Toxicity Data for F344/N Rats in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n						
Week 2	5	5	5	5	5	5
Week 6	5	5	5	5	5	5
Week 14	10	10	10	10	10	10
Male						
Urine volume (mL/16 hr)						
Week 2	12.3 ± 2.1	15.6 ± 2.2	18.9 ± 3.4	20.5 ± 1.5	21.0 ± 1.9	15.6 ± 1.8
Week 6	13.3 ± 1.7	13.5 ± 4.1	16.8 ± 3.5	25.9 ± 4.6	26.2 ± 3.5	17.1 ± 2.9
Week 14	12.3 ± 2.6	14.4 ± 3.1	14.9 ± 2.4	15.6 ± 2.6	19.3 ± 3.3	15.9 ± 3.6
Creatinine (mg/dL)						
Week 2	25.00 ± 3.76	22.20 ± 2.15	19.40 ± 4.65	14.00 ± 1.14*	14.20 ± 1.32	19.40 ± 1.97
Week 6	38.20 ± 7.61	50.40 ± 16.44	33.40 ± 8.57	23.60 ± 3.44	22.00 ± 3.36	32.20 ± 7.24
Week 14	70.20 ± 12.12	65.90 ± 11.87	59.00 ± 11.41	58.00 ± 12.32	49.00 ± 6.83	62.90 ± 11.03
cis-Decalin (µg/g kidney)						
Week 2	—[b]	0.188 ± 0.036	0.304 ± 0.071	0.565 ± 0.142	1.318 ± 0.241[c]	2.596 ± 0.272
Week 6	—	2.196 ± 0.197	4.124 ± 0.478	6.346 ± 0.351	10.930 ± 0.495	14.640 ± 0.973
Week 14	—	2.448 ± 0.205	3.691 ± 0.200	5.677 ± 0.372	9.328 ± 0.358	13.545 ± 0.753
trans-Decalin (µg/g kidney)						
Week 2	—	0.373 ± 0.076	0.582 ± 0.149	0.965 ± 0.248	2.148 ± 0.434[c]	3.996 ± 0.405
Week 6	—	5.138 ± 0.460	9.172 ± 1.034	13.020 ± 0.665	20.020 ± 0.843	24.300 ± 1.678
Week 14	—	6.159 ± 0.494	9.182 ± 0.484	12.759 ± 0.822	18.390 ± 0.675	24.560 ± 1.352
(*cis* + *trans*)-Decalin (µg/g kidney)						
Week 2	—	0.561 ± 0.112	0.887 ± 0.220	1.529 ± 0.388	3.465 ± 0.675[c]	6.590 ± 0.679
Week 6	—	7.334 ± 0.658	13.310 ± 1.526	19.380 ± 1.003	30.960 ± 1.323	38.960 ± 2.673
Week 14	—	8.607 ± 0.699	12.861 ± 0.680	18.440 ± 1.199	27.710 ± 1.030	38.120 ± 2.102
cis-Decalin (%)						
Week 2	—	33.740 ± 0.610	35.040 ± 0.865	37.220 ± 0.523	38.375 ± 0.637[c]	39.360 ± 0.181
Week 6	—	29.940 ± 0.024	30.960 ± 0.075	32.720 ± 0.146	35.300 ± 0.224	37.600 ± 0.167
Week 14	—	28.370 ± 0.097	28.640 ± 0.093	30.790 ± 0.081	33.630 ± 0.105	35.550 ± 0.120
trans-Decalin (%)						
Week 2	—	66.260 ± 0.610	64.900 ± 0.856	62.840 ± 0.499	61.625 ± 0.637[c]	60.680 ± 0.183
Week 6	—	70.060 ± 0.024	68.980 ± 0.153	67.200 ± 0.114	64.660 ± 0.232	62.340 ± 0.175
Week 14	—	71.630 ± 0.097	71.360 ± 0.093	69.210 ± 0.081	66.370 ± 0.105	64.450 ± 0.120
cis-/*trans*-Decalin ratio						
Week 2	—	0.510 ± 0.014	0.541 ± 0.021	0.593 ± 0.013	0.623 ± 0.017[c]	0.649 ± 0.005
Week 6	—	0.428 ± 0.001	0.449 ± 0.002	0.487 ± 0.003	0.546 ± 0.006	0.603 ± 0.004
Week 14	—	0.396 ± 0.002	0.402 ± 0.002	0.445 ± 0.002	0.507 ± 0.002	0.551 ± 0.003
Decalol (µg/mL)						
Week 2	—	19.20 ± 2.35	30.98 ± 4.43[c]	73.92 ± 10.76	123.2 ± 8.3	331.4 ± 45.2
Week 6	—	25.16 ± 4.81	35.50 ± 4.36	61.10 ± 19.18	79.5 ± 18.2	243.4 ± 15.5
Decalol (ng/µg creatinine)						
Week 2	—	85.90 ± 5.65	207.4 ± 13.9	527.2 ± 58.4	893.0 ± 87.1	1,710 ± 122
Week 6	—	62.70 ± 10.54	125.2 ± 24.0	236.4 ± 42.1	288.0 ± 24.2[c]	865.4 ± 127.7
Decalol excreted (µg/16 hr)						
Week 2	—	278.8 ± 15.0	640.6 ± 64.6	1,465 ± 141	2,549 ± 183	4,962 ± 437
Week 6	—	268.2 ± 44.2	550.6 ± 86.0	1,238 ± 144	1,895 ± 284	4,016 ± 518
cis-2-Decalone (µg/g kidney)						
Week 2	—	1.339 ± 0.295	1.284 ± 0.376	1.163 ± 0.076[c]	1.184 ± 0.259	1.710 ± 0.172
Week 6	—	11.850 ± 1.146	17.460 ± 2.092	18.240 ± 0.518	17.180 ± 1.066	12.786 ± 1.263
Week 14	—	13.082 ± 0.818	18.510 ± 0.880	20.650 ± 0.919	21.490 ± 0.646	16.940 ± 0.790
trans-2-Decalone (µg/g kidney)						
Week 2	—	0.614 ± 0.138	0.750 ± 0.199	0.713 ± 0.130	0.977 ± 0.234	1.504 ± 0.177
Week 6	—	5.456 ± 0.637	8.520 ± 1.120	10.080 ± 0.312	12.426 ± 0.972	10.402 ± 0.967
Week 14	—	6.849 ± 0.465	10.480 ± 0.530	13.270 ± 0.618	15.500 ± 0.499	13.730 ± 0.632

Table G3
Renal Toxicity Data for F344/N Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n						
Week 2	5	5	5	5	5	5
Week 6	5	5	5	5	5	5
Week 14	10	10	10	10	10	10
Male (continued)						
(*cis* + *trans*)-2-Decalone (µg/g kidney)						
Week 2	—	1.953 ± 0.432	2.032 ± 0.573	1.714 ± 0.301	2.160 ± 0.493	3.214 ± 0.347
Week 6	—	17.300 ± 1.780	26.000 ± 3.226	28.340 ± 0.761	29.620 ± 2.016	23.180 ± 2.201
Week 14	—	19.940 ± 1.280	28.990 ± 1.399	33.930 ± 1.527	37.022 ± 1.140	30.680 ± 1.391
cis-2-Decalone (%)						
Week 2	—	68.700 ± 0.365	62.280 ± 0.811	58.640 ± 0.611	55.400 ± 0.759	53.420 ± 0.495
Week 6	—	68.620 ± 0.565	67.400 ± 0.559	64.380 ± 0.640	58.160 ± 0.466	55.120 ± 0.517
Week 14	—	65.710 ± 0.282	63.870 ± 0.257	60.900 ± 0.255	58.100 ± 0.238	55.190 ± 0.380
trans-2-Decalone (%)						
Week 2	—	31.300 ± 0.365	37.720 ± 0.811	41.360 ± 0.611	44.600 ± 0.759	46.580 ± 0.495
Week 6	—	31.380 ± 0.565	32.600 ± 0.559	35.620 ± 0.640	41.840 ± 0.466	44.880 ± 0.517
Week 14	—	34.290 ± 0.282	36.130 ± 0.257	39.100 ± 0.255	41.900 ± 0.238	44.810 ± 0.380
cis-/*trans*-2-Decalone ratio						
Week 2	—	2.196 ± 0.035	1.656 ± 0.060	1.420 ± 0.034	1.242 ± 0.039	1.146 ± 0.022
Week 6	—	2.192 ± 0.055	2.070 ± 0.051	1.812 ± 0.050	1.390 ± 0.028	1.228 ± 0.025
Week 14	—	1.918 ± 0.023	1.768 ± 0.019	1.559 ± 0.017	1.386 ± 0.014	1.233 ± 0.020
Cells labeled						
Week 2	74.8 ± 4.2	93.6 ± 3.7*	86.6 ± 5.8*	94.4 ± 5.3*	92.4 ± 5.5*	107.6 ± 9.4**
Week 6	69.8 ± 3.3	97.6 ± 3.4**	106.8 ± 1.9**	98.4 ± 5.3**	110.6 ± 5.9**	129.0 ± 7.2**
Week 14[d]	64.6 ± 4.2	98.4 ± 1.2*	80.8 ± 6.4	89.2 ± 5.6	96.8 ± 5.0**	95.2 ± 4.1*
Cells counted						
Week 2	2,254 ± 87	2,243 ± 36	2,206 ± 67	2,206 ± 37	2,207 ± 56	2,188 ± 35
Week 6	2,201 ± 69	2,314 ± 34	2,217 ± 42	2,124 ± 39	2,197 ± 55	2,183 ± 39
Week 14[d]	2,118 ± 31	2,184 ± 41	2,185 ± 63	2,184 ± 30	2,144 ± 36	2,127 ± 52
Labeling index (%)						
Week 2	3.33 ± 0.21	4.17 ± 0.13*	3.94 ± 0.28	4.27 ± 0.20**	4.20 ± 0.29*	4.90 ± 0.34**
Week 6	3.17 ± 0.11	4.22 ± 0.13**	4.82 ± 0.11**	4.64 ± 0.26**	5.03 ± 0.23**	5.91 ± 0.28**
Week 14[d]	3.05 ± 0.19	4.51 ± 0.10**	3.70 ± 0.28*	4.08 ± 0.23*	4.51 ± 0.18**	4.48 ± 0.15**
Soluble protein (g/dL)						
Week 2	2 ± 0	2 ± 0	2 ± 0	2 ± 0	2 ± 0	2 ± 0
Week 6	3 ± 0	2 ± 0	2 ± 0	2 ± 0	2 ± 0	2 ± 0
Week 14[d]	2 ± 0	3 ± 0	3 ± 0	3 ± 0	3 ± 0	3 ± 0
α2u-Globulin (mg/g kidney)						
Week 2	0.15 ± 0.09	0.39 ± 0.15	0.44 ± 0.20	0.52 ± 0.26	0.84 ± 0.19**	2.72 ± 1.59**
Week 6	2.51 ± 1.31	6.17 ± 1.26	7.71 ± 3.96	5.31 ± 1.18	7.57 ± 0.90*	15.18 ± 5.69**
Week 14[d]	2.86 ± 0.72	4.09 ± 1.10	10.94 ± 6.16	7.30 ± 1.56*	13.77 ± 3.68**	10.20 ± 5.06*
α2u-Globulin (ng/µg soluble protein)						
Week 2	3.65 ± 2.42	9.98 ± 3.99	12.3 ± 5.54	14.8 ± 7.30	23.9 ± 5.24**	64.5 ± 34.3**
Week 6	52.8 ± 28.8	126 ± 17.5	149 ± 67.8	102 ± 17.9	153 ± 15.8**	310 ± 94.3**
Week 14[d]	60.4 ± 17.5	75.2 ± 17.8	184 ± 97.7	143 ± 38.3	251 ± 69.2**	192 ± 93.4*

TABLE G3
Renal Toxicity Data for F344/N Rats in the 3-Month Inhalation Study of Decalin

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n						
Week 2	5	5	5	5	5	5
Week 6	5	5	5	5	5	5
Week 14	10	10	10	10	10	10
Female						
Urine volume (mL/16 hr)						
Week 2	20.6 ± 3.2	19.5 ± 1.7	16.4 ± 3.2	15.8 ± 1.4	19.6 ± 4.3	25.5 ± 2.1
Week 6	11.9 ± 1.9	19.1 ± 4.6	13.9 ± 3.3	11.7 ± 2.6	18.7 ± 3.1	15.2 ± 3.0
Week 14	10.9 ± 1.0	15.0 ± 2.0	12.9 ± 1.1	12.0 ± 1.4	12.9 ± 1.6	14.0 ± 1.8
Creatinine (mg/dL)						
Week 2	14.00 ± 2.49	12.80 ± 1.16	17.00 ± 2.59	15.60 ± 1.89	15.40 ± 3.83	9.20 ± 0.74
Week 6	30.20 ± 4.15	17.75 ± 3.84[c]	23.25 ± 3.04[c]	24.50 ± 3.57[c]	17.25 ± 1.70[c]	23.00 ± 4.14
Week 14	40.10 ± 3.46	31.60 ± 4.29	35.10 ± 3.43	39.80 ± 4.84	38.50 ± 5.12	33.70 ± 3.90
cis-Decalin (µg/g kidney)						
Week 14	—	0.058 ± 0.004	0.138 ± 0.020	0.226 ± 0.026	0.367 ± 0.060	0.649 ± 0.058
trans-Decalin (µg/g kidney)						
Week 14	—	0.070 ± 0.005[e]	0.163 ± 0.025	0.276 ± 0.031	0.460 ± 0.078	0.810 ± 0.076
(*cis* + *trans*)-Decalin (µg/g kidney)						
Week 14	—	0.126 ± 0.009	0.301 ± 0.045	0.501 ± 0.057	0.828 ± 0.139	1.459 ± 0.134
cis-Decalin (%)						
Week 14	—	46.350 ± 0.645	46.290 ± 0.593	44.960 ± 0.249	44.570 ± 0.344	44.610 ± 0.207
trans-Decalin (%)						
Week 14	—	53.650 ± 0.645	53.710 ± 0.593	55.040 ± 0.249	55.430 ± 0.344	55.390 ± 0.207
cis-/*trans*-Decalin ratio						
Week 14	—	0.867 ± 0.023	0.864 ± 0.022	0.818 ± 0.008	0.805 ± 0.011	0.806 ± 0.007
Decalol (µg/mL)						
Week 2	—	24.10 ± 1.49	63.30 ± 15.41	112.9 ± 10.4	223.3 ± 50.5	242.8 ± 24.7
Week 6	—	35.90 ± 11.96	62.03 ± 11.87[c]	191.5 ± 41.7	165.0 ± 20.4[c]	493.0 ± 92.8
Decalol (ng/µg creatinine)						
Week 2	—[c]	191.8 ± 14.5	351.4 ± 41.0	734.4 ± 44.4	1,470 ± 99	2,628 ± 125
Week 6	—	132.0 ± 10.6	274.6 ± 17.1	579.0 ± 54.9	971.2 ± 91.6	2,120 ± 62
Decalol excreted (µg/16 hr)						
Week 2	—[c]	462.2 ± 17.8	853.8 ± 68.6	1,732 ± 73	3,557 ± 196	5,978 ± 193
Week 6	—	474.2 ± 62.3	980.2 ± 75.3	1,827 ± 192	3,527 ± 308	6,401 ± 344

* Significantly different (P≤0.05) from the chamber control group by Dunn's or Shirley's test
** P≤0.01
[a] Data are presented as mean ± standard error. Statistical tests were performed on unrounded data.
[b] One or more values were below the limit of detection or were between the limit of detection and the experimental limit of quantification; group mean was declared indeterminate and no statistical tests were performed at this time point.
[c] n=4
[d] n=5
[e] n=9

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

TABLE H1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 2-Week Inhalation Study of Decalin 260
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TABLE H4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Inhalation Study of Decalin 263
TABLE H5 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Inhalation Study of Decalin 264

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 2-Week Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	5	5	5	5	5	5
Male						
Necropsy body wt	245 ± 5	241 ± 5	252 ± 5	244 ± 6	246 ± 5	244 ± 5
R. Kidney						
Absolute	0.804 ± 0.025	0.838 ± 0.016	0.912 ± 0.034**	0.896 ± 0.025**	0.992 ± 0.014**	0.968 ± 0.026**
Relative	3.290 ± 0.091	3.480 ± 0.034	3.622 ± 0.104**	3.676 ± 0.062**	4.032 ± 0.067**	3.973 ± 0.074**
Liver						
Absolute	8.296 ± 0.188	8.354 ± 0.208	9.408 ± 0.355*	9.500 ± 0.460*	9.758 ± 0.338**	10.212 ± 0.400**
Relative	33.9 ± 0.6	34.7 ± 0.4	37.4 ± 1.1	39.0 ± 1.6*	39.6 ± 0.6**	42.0 ± 2.2**
Lung						
Absolute	1.360 ± 0.061	1.304 ± 0.047	1.324 ± 0.041	1.338 ± 0.057	1.332 ± 0.044	1.422 ± 0.038
Relative	5.559 ± 0.200	5.415 ± 0.177	5.261 ± 0.129	5.486 ± 0.163	5.411 ± 0.163	5.854 ± 0.253
Female						
Necropsy body wt	161 ± 5	162 ± 2	163 ± 4	160 ± 5	157 ± 3	154 ± 4
R. Kidney						
Absolute	0.574 ± 0.026	0.618 ± 0.015	0.596 ± 0.010	0.614 ± 0.019	0.590 ± 0.013	0.606 ± 0.021
Relative	3.574 ± 0.103	3.808 ± 0.094	3.662 ± 0.045	3.849 ± 0.117	3.759 ± 0.046	3.927 ± 0.050**
Liver						
Absolute	5.052 ± 0.152	5.540 ± 0.170*	5.506 ± 0.050*	5.700 ± 0.134**	5.734 ± 0.066**	5.826 ± 0.246**
Relative	31.5 ± 1.0	34.1 ± 0.8*	33.9 ± 0.6*	35.7 ± 0.6**	36.6 ± 0.5**	37.7 ± 0.8**
Lung						
Absolute	1.040 ± 0.059	1.016 ± 0.050	1.024 ± 0.044	0.968 ± 0.017	0.978 ± 0.022	0.962 ± 0.039
Relative	6.484 ± 0.319	6.258 ± 0.302	6.279 ± 0.175	6.095 ± 0.308	6.232 ± 0.090	6.230 ± 0.115

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

Table H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male NBR Rats in the 2-Week Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	5	5	5	5	5	5
Necropsy body wt	276 ± 6	267 ± 6	275 ± 5	279 ± 8	277 ± 7	272 ± 7
R. Kidney						
Absolute	0.880 ± 0.026	0.900 ± 0.031	0.912 ± 0.018	0.970 ± 0.025	0.906 ± 0.023	0.916 ± 0.015
Relative	3.192 ± 0.052	3.376 ± 0.082	3.322 ± 0.065	3.476 ± 0.030*	3.278 ± 0.071	3.371 ± 0.039
Liver						
Absolute	8.702 ± 0.380	8.552 ± 0.221	9.496 ± 0.282	9.846 ± 0.365*	10.380 ± 0.396**	10.918 ± 0.356**
Relative	31.6 ± 1.1	32.1 ± 0.8	34.6 ± 0.9*	35.3 ± 0.7**	37.5 ± 1.0**	40.1 ± 0.7**
Lung						
Absolute	1.482 ± 0.018	1.502 ± 0.055	1.474 ± 0.028	1.504 ± 0.053	1.496 ± 0.030	1.516 ± 0.051
Relative	5.383 ± 0.075	5.631 ± 0.115	5.367 ± 0.070	5.384 ± 0.070	5.414 ± 0.095	5.569 ± 0.065

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

TABLE H3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	302 ± 5	306 ± 9	295 ± 6	290 ± 4	311 ± 6	303 ± 5
Heart						
Absolute	0.833 ± 0.009	0.831 ± 0.024	0.794 ± 0.012	0.772 ± 0.012	0.845 ± 0.034	0.804 ± 0.013
Relative	2.761 ± 0.039	2.719 ± 0.033	2.699 ± 0.047	2.667 ± 0.033	2.707 ± 0.065	2.657 ± 0.039
R. Kidney						
Absolute	0.913 ± 0.020	0.966 ± 0.034	0.961 ± 0.021	0.943 ± 0.019	1.050 ± 0.033**	1.094 ± 0.025**
Relative	3.021 ± 0.046	3.156 ± 0.047*	3.261 ± 0.042**	3.254 ± 0.034**	3.367 ± 0.051**	3.612 ± 0.060**
Liver						
Absolute	9.398 ± 0.132	9.919 ± 0.408	9.881 ± 0.204	9.510 ± 0.212	10.537 ± 0.320**	10.450 ± 0.202**
Relative	31.1 ± 0.3	32.3 ± 0.6	33.6 ± 0.6**	32.8 ± 0.3**	33.8 ± 0.5**	34.5 ± 0.4**
Lung						
Absolute	1.439 ± 0.051	1.469 ± 0.065	1.374 ± 0.046	1.410 ± 0.051	1.560 ± 0.053	1.445 ± 0.045
Relative	4.753 ± 0.108	4.801 ± 0.136	4.661 ± 0.121	4.860 ± 0.132	5.009 ± 0.132	4.765 ± 0.098
R. Testis						
Absolute	1.349 ± 0.014	1.355 ± 0.023	1.294 ± 0.023	1.292 ± 0.018	1.373 ± 0.020	1.345 ± 0.020
Relative	4.469 ± 0.058	4.450 ± 0.095	4.392 ± 0.047	4.465 ± 0.057	4.420 ± 0.083	4.444 ± 0.054
Thymus						
Absolute	0.275 ± 0.007	0.277 ± 0.012	0.274 ± 0.016	0.267 ± 0.009	0.295 ± 0.010	0.274 ± 0.010
Relative	0.912 ± 0.024	0.905 ± 0.031	0.926 ± 0.047	0.921 ± 0.021	0.949 ± 0.033	0.905 ± 0.035
Female						
Necropsy body wt	177 ± 3	174 ± 2	182 ± 2	181 ± 4	175 ± 3	173 ± 4
Heart						
Absolute	0.567 ± 0.011	0.570 ± 0.009	0.582 ± 0.008	0.594 ± 0.016	0.579 ± 0.013	0.588 ± 0.019
Relative	3.203 ± 0.067	3.284 ± 0.032	3.199 ± 0.047	3.278 ± 0.032	3.300 ± 0.035	3.404 ± 0.070**
R. Kidney						
Absolute	0.608 ± 0.015	0.616 ± 0.010	0.638 ± 0.009	0.645 ± 0.014	0.632 ± 0.013	0.624 ± 0.012
Relative	3.432 ± 0.076	3.552 ± 0.060	3.507 ± 0.045	3.566 ± 0.052	3.606 ± 0.049	3.618 ± 0.053
Liver						
Absolute	5.379 ± 0.073	5.193 ± 0.058	5.805 ± 0.214	5.810 ± 0.266	5.607 ± 0.166	5.790 ± 0.145
Relative	30.4 ± 0.7	29.9 ± 0.2	31.8 ± 0.9	32.0 ± 0.8	31.9 ± 0.5	33.5 ± 0.3**
Lung						
Absolute	0.994 ± 0.016	0.999 ± 0.016	1.015 ± 0.025	1.031 ± 0.034	1.017 ± 0.021	1.004 ± 0.036
Relative	5.614 ± 0.098	5.762 ± 0.106	5.571 ± 0.099	5.687 ± 0.107	5.803 ± 0.091	5.813 ± 0.166
Thymus						
Absolute	0.231 ± 0.005	0.224 ± 0.005	0.229 ± 0.009	0.230 ± 0.013	0.225 ± 0.010	0.218 ± 0.006
Relative	1.305 ± 0.034	1.293 ± 0.029	1.259 ± 0.048	1.265 ± 0.060	1.282 ± 0.044	1.264 ± 0.027

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

TABLE H4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	25.9 ± 0.2	26.2 ± 0.7	26.2 ± 0.5	26.2 ± 0.7	25.6 ± 0.9	24.9 ± 0.7
R. Kidney						
Absolute	0.218 ± 0.004	0.230 ± 0.004	0.220 ± 0.005	0.240 ± 0.006	0.230 ± 0.020	0.222 ± 0.010
Relative	8.404 ± 0.126	8.794 ± 0.197	8.403 ± 0.143	9.178 ± 0.104	8.911 ± 0.474	8.907 ± 0.179
Liver						
Absolute	1.314 ± 0.035	1.374 ± 0.054	1.408 ± 0.030	1.490 ± 0.051	1.590 ± 0.133*	1.710 ± 0.092**
Relative	50.6 ± 1.2	52.4 ± 0.7	53.8 ± 0.5	56.9 ± 0.8*	61.6 ± 2.9**	68.5 ± 1.8**
Lung						
Absolute	0.182 ± 0.006	0.194 ± 0.004	0.194 ± 0.007	0.186 ± 0.004	0.188 ± 0.009	0.190 ± 0.009
Relative	7.013 ± 0.194	7.418 ± 0.183	7.405 ± 0.173	7.117 ± 0.098	7.322 ± 0.111	7.631 ± 0.268
Female						
n	5	5	5	5	5	3
Necropsy body wt	22.2 ± 0.5	22.2 ± 0.4	22.5 ± 0.6	22.7 ± 0.6	22.4 ± 0.3	23.6 ± 0.1
R. Kidney						
Absolute	0.156 ± 0.007	0.156 ± 0.002	0.158 ± 0.006	0.164 ± 0.005	0.160 ± 0.005	0.167 ± 0.003
Relative	7.033 ± 0.199	7.048 ± 0.164	7.007 ± 0.155	7.211 ± 0.083	7.144 ± 0.173	7.062 ± 0.127
Liver						
Absolute	1.110 ± 0.042	1.192 ± 0.026	1.186 ± 0.054	1.286 ± 0.055**	1.350 ± 0.039**	1.587 ± 0.015**
Relative	50.0 ± 1.0	53.8 ± 0.8	52.5 ± 1.0	56.5 ± 1.4**	60.3 ± 1.4**	67.2 ± 0.8**
Lung						
Absolute	0.170 ± 0.007	0.174 ± 0.005	0.182 ± 0.006	0.174 ± 0.006	0.186 ± 0.012	0.190 ± 0.015
Relative	7.671 ± 0.253	7.870 ± 0.328	8.076 ± 0.154	7.652 ± 0.163	8.309 ± 0.496	8.054 ± 0.667

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

TABLE H5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	37.4 ± 0.9	37.2 ± 0.9	37.1 ± 1.1	37.0 ± 0.9	37.0 ± 0.9	36.1 ± 0.6
Heart						
Absolute	0.160 ± 0.004	0.174 ± 0.006	0.165 ± 0.006	0.166 ± 0.006	0.161 ± 0.006	0.171 ± 0.008
Relative	4.288 ± 0.120	4.685 ± 0.161	4.454 ± 0.144	4.488 ± 0.122	4.339 ± 0.103	4.740 ± 0.215
R. Kidney						
Absolute	0.304 ± 0.007	0.308 ± 0.005	0.310 ± 0.008	0.314 ± 0.007	0.302 ± 0.010	0.297 ± 0.011
Relative	8.146 ± 0.204	8.319 ± 0.241	8.385 ± 0.212	8.509 ± 0.213	8.162 ± 0.211	8.239 ± 0.291
Liver						
Absolute	1.472 ± 0.031	1.508 ± 0.048	1.551 ± 0.071	1.572 ± 0.054	1.666 ± 0.051*	1.760 ± 0.048**
Relative	39.4 ± 0.7	40.5 ± 0.7	41.7 ± 1.0	42.4 ± 0.7*	45.0 ± 1.1**	48.8 ± 1.1**
Lung						
Absolute	0.211 ± 0.003	0.223 ± 0.014	0.232 ± 0.012	0.235 ± 0.014	0.219 ± 0.005	0.221 ± 0.009
Relative	5.652 ± 0.093	5.986 ± 0.331	6.267 ± 0.308	6.327 ± 0.267	5.933 ± 0.160	6.124 ± 0.234
R. Testis						
Absolute	0.114 ± 0.004	0.107 ± 0.004	0.112 ± 0.003	0.112 ± 0.004	0.110 ± 0.002	0.106 ± 0.003
Relative	3.066 ± 0.112	2.895 ± 0.133	3.027 ± 0.112	3.034 ± 0.112	2.996 ± 0.097	2.923 ± 0.075
Thymus						
Absolute	0.037 ± 0.002	0.034 ± 0.002	0.031 ± 0.002	0.035 ± 0.002	0.037 ± 0.002	0.032 ± 0.003
Relative	0.986 ± 0.046	0.923 ± 0.043	0.847 ± 0.045	0.945 ± 0.050	0.989 ± 0.049	0.888 ± 0.072
Female						
Necropsy body wt	30.8 ± 0.8	30.1 ± 0.6	33.2 ± 1.0	30.6 ± 0.8	33.0 ± 1.1	30.4 ± 0.8
Heart						
Absolute	0.145 ± 0.004	0.145 ± 0.002	0.145 ± 0.003	0.144 ± 0.004	0.153 ± 0.006	0.138 ± 0.002
Relative	4.743 ± 0.192	4.832 ± 0.099	4.385 ± 0.075	4.726 ± 0.164	4.671 ± 0.191	4.570 ± 0.128
R. Kidney						
Absolute	0.202 ± 0.005	0.209 ± 0.004	0.210 ± 0.005	0.202 ± 0.004	0.202 ± 0.004	0.195 ± 0.006
Relative	6.601 ± 0.236	6.953 ± 0.119	6.354 ± 0.117	6.624 ± 0.162	6.167 ± 0.160	6.438 ± 0.149
Liver						
Absolute	1.385 ± 0.040	1.382 ± 0.044	1.497 ± 0.035	1.489 ± 0.028	1.692 ± 0.046**	1.627 ± 0.060**
Relative	45.1 ± 1.0	45.9 ± 0.9	45.3 ± 0.7	48.8 ± 0.8**	51.5 ± 1.2**	53.5 ± 0.8**
Lung						
Absolute	0.226 ± 0.007	0.222 ± 0.006	0.227 ± 0.009	0.231 ± 0.009	0.242 ± 0.009	0.225 ± 0.004
Relative	7.374 ± 0.250	7.397 ± 0.230	6.869 ± 0.238	7.613 ± 0.428	7.363 ± 0.212	7.442 ± 0.155
Thymus						
Absolute	0.047 ± 0.003	0.048 ± 0.002	0.049 ± 0.002	0.044 ± 0.004	0.048 ± 0.002	0.046 ± 0.002
Relative	1.537 ± 0.080	1.583 ± 0.046	1.464 ± 0.061	1.445 ± 0.115	1.443 ± 0.046	1.511 ± 0.055

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

APPENDIX I
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE I1 Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Inhalation Study of Decalin 266
TABLE I2 Estrous Cycle Characterization for Female Rats in the 3-Month Inhalation Study of Decalin 266
TABLE I3 Summary of Reproductive Tissue Evaluations for Male Mice in the 3-Month Inhalation Study of Decalin 267
TABLE I4 Estrous Cycle Characterization for Female Mice in the 3-Month Inhalation Study of Decalin 267

TABLE I1
Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	302 ± 5	290 ± 4	311 ± 6	303 ± 5
L. Cauda epididymis	0.170 ± 0.005	0.166 ± 0.020	0.162 ± 0.006	0.155 ± 0.003
L. Epididymis	0.446 ± 0.008	0.446 ± 0.024	0.438 ± 0.003	0.425 ± 0.010
L. Testis	1.43 ± 0.01	1.38 ± 0.02	1.44 ± 0.02	1.42 ± 0.02
Spermatid measurements				
Spermatid heads (10^7/g testis)	121 ± 13	125 ± 7	131 ± 13	119 ± 12
Spermatid heads (10^7/testis)	158 ± 18	157 ± 10	173 ± 19	154 ± 15
Spermatid heads (10^7/g cauda epididymis)	786 ± 35	709 ± 67	723 ± 18	803 ± 44
Spermatid heads (10^7/cauda epididymis)	133 ± 6	110 ± 8	117 ± 5	124 ± 7
Epididymal sperm motility (%)	97.9 ± 1.4	97.3 ± 1.2[b]	96.1 ± 1.2	97.8 ± 1.1

[a] Data are presented as mean ± standard error. There were no significant trends in spermatid measurements or epididymal sperm motility by Jonckheere's test; pairwise differences from the chamber control group are not significant by Dunnett's test (body and tissue weights) or by Dunn's test (spermatid measurements and epididymal sperm motility).
[b] n=9

TABLE I2
Estrous Cycle Characterization for Female Rats in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
n	10	10	10	10
Necropsy body wt (g)	177 ± 3	181 ± 4	175 ± 3	173 ± 4
Estrous cycle length (days)	4.90 ± 0.19	5.05 ± 0.12	5.00 ± 0.00	5.20 ± 0.13
Estrous stages (% of cycle)				
Diestrus	43.3	38.3	45.0	42.5
Proestrus	15.0	20.0	17.5	15.0
Estrus	22.5	22.5	20.0	21.7
Metestrus	19.2	19.2	17.5	20.8

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.

TABLE I3
Summary of Reproductive Tissue Evaluations for Male Mice in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	37.4 ± 0.9	37.0 ± 0.9	37.0 ± 0.9	36.1 ± 0.6
L. Cauda epididymis	0.0174 ± 0.0014	0.0180 ± 0.0013	0.0194 ± 0.0016	0.0192 ± 0.0020
L. Epididymis	0.0576 ± 0.0038	0.0593 ± 0.0033	0.0612 ± 0.0056	0.0567 ± 0.0040
L. Testis	0.1181 ± 0.0033	0.1139 ± 0.0034	0.1175 ± 0.0028	0.1079 ± 0.0036
Spermatid and sperm measurements				
Spermatid heads (10^7/g testis)	225 ± 13	209 ± 11	198 ± 18	189 ± 14
Spermatid heads (10^7/testis)	21.77 ± 0.96▲▲▲	19.45 ± 0.87	18.67 ± 1.73	16.14 ± 0.97**
Spermatid heads (10^7/g cauda epididymis)	1,213 ± 75	1,353 ± 120	1,047 ± 119	993 ± 178
Spermatid heads (10^7/cauda epididymis)	20.92 ± 1.77	23.28 ± 1.01	19.08 ± 1.65	17.72 ± 2.39
Epididymal sperm motility (%)	84.86 ± 1.26	86.11 ± 1.04	86.86 ± 1.31	82.68 ± 2.16[b]

▲▲▲Significant exposure concentration-related decrease (P≤0.001) by Jonckheere's test
** Significantly different (P≤0.01) from the chamber control group by Shirley's test
[a] Data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body and tissue weights) or by Dunn's test (spermatid heads per g testis, per g cauda epididymis, and per cauda epididymis; epididymal sperm motility).
[b] n=9

TABLE I4
Estrous Cycle Characterization for Female Mice in the 3-Month Inhalation Study of Decalin[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
n	10	10	10	10
Necropsy body wt (g)	30.8 ± 0.8	30.6 ± 0.8	33.0 ± 1.1	30.4 ± 0.8
Estrous cycle length (days)	4.00 ± 0.00	4.40 ± 0.40	4.20 ± 0.08*	4.00 ± 0.00[b]
Estrous stages (% of cycle)				
Diestrus	25.8	30.8	30.0	25.8
Proestrus	23.3	22.5	23.3	20.8
Estrus	25.8	23.3	24.2	34.2
Metestrus	25.0	23.3	22.5	19.2

* Significantly different (P≤0.05) from the chamber control group by Dunn's test
[a] Necropsy body weights and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group for body weight are not significant by Dunnett's test. By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in one of 10 animals.

APPENDIX J
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

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CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

Procurement and Characterization of Decalin

Decalin was obtained in three lots [07347LG and 12426EN (Sigma Aldrich Fluka Bulk Chemicals, St. Louis, MO) and 00334HR (Aldrich Chemical Company, Inc., Milwaukee, WI)]. For the 2-week and 3-month studies, lots 07347LG and 12426EN were combined and assigned a new lot number (13359). Lot 00334HR was used during the 2-year studies. Identity and purity analyses on lots 07347LG and 12426EN were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC), and on the combined lot and lot 00334HR by the study laboratory. Reports on analyses performed in support of the decalin studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a colorless liquid, was identified as decalin by the analytical chemistry laboratory (lots 07347LG, 12426EN) and Chemir/Polytech Laboratories, Inc. (Maryland Heights, MO; lots 13359 and 00334HR), using infrared and nuclear magnetic resonance (NMR) spectroscopy. In addition, the identities of lots 07347LG, 12426EN were confirmed by the analytical chemistry laboratory as decalin using gas chromatography/mass spectrometry (GC/MS) by system A (Table J1). Infrared and NMR spectra were consistent with the structure of decalin and the literature spectra (*Sadtler Standard Spectra*) (Figures J1 and J2). GC/MS spectra were consistent with NBS library spectra for the two isomers of decalin, *cis* and *trans*.

The purities of lots 07347LG, 12426EN were determined by the analytical chemistry laboratory using potentiometric titration and GC systems B, C, and D, respectively. The purities of lots 13359 and 00334HR were determined by the study laboratory using GC system E. In addition, Chemir/Polytech determined purity by elemental analyses (lots 13359 and 00334HR) and Karl Fischer titration was used to determine the moisture content of lot 00334HR. Samples for potentiometric titration were titrated directly in glacial acetic acid:chloroform (60:40) with standardized 0.1 N sodium thiosulfate and a platinum redox combination electrode and a pH meter (lot 00334HR).

For lot 07347LG, GC indicated two major peaks and seven impurities with a combined area of 0.39% relative to the combined major peak area. The *cis*/*trans* ratio was 25:75. No peroxides were detected with potentiometric titration. The overall purity was determined to be greater than 99%.

For lot 12426EN, GC indicated two major peaks and one impurity with an area of 0.3% relative to the combined major peak area. The *cis*/*trans* ratio was 37:63. No peroxides were detected with potentiometric titration. The overall purity was determined to be greater than 99%.

For lot 13359, GC indicated two major peaks and one impurity with an area of approximately 0.35% relative to the combined major peak area. The impurity was identified as tetralin by GC/MS similar to system A. The *cis*/*trans* ratio was 35:65. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for decalin; oxygen, nitrogen, and sulfur were also detected at concentrations less than 0.5%. The overall purity was determined to be greater than 99%.

For lot 00334HR, GC system D indicated two major peaks and one impurity with an area of 0.5% of the total integrated area. The *cis*/*trans* ratio was 42:57. GC indicated two major peaks and two impurities with areas of 0.1% and 0.49% (identified as tetralin) of the combined major peak areas. The isomer ratio was 42:58 *cis*:*trans*. Potentiometric titration detected 0.57 mEq/kg peroxides. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for decalin; oxygen was detected at a concentration of .91%; nitrogen and sulfur were detected at concentrations less than 0.5%. Karl Fischer titration indicated 73 ± 3.6 ppm water. The overall purity was determined to be greater than 99%.

The bulk chemical was stored at room temperature, in metal drums under a nitrogen headspace. The stability of decalin was monitored throughout the studies with GC; no degradation of the bulk chemical was detected.

Vapor Generation and Exposure System

A diagram of the vapor generation and delivery system used in the studies is shown in Figure J3. The design of the system was influenced by the relatively high boiling point for decalin (approximately 190° C) and the need to reach high concentrations of a multicomponent chemical without altering the composition of the bulk material. As a result, test material entering the generation system was completely vaporized, and the vapor transport lines and all dilution air, except individual chamber inlet flows, were heated.

Decalin was pumped through a preheater and then into the top of a heated glass column filled with glass beads to increase the surface area for evaporation. Heated nitrogen entering the column from below vaporized the chemical as it conveyed it out of the generator. Generator output was controlled by the delivery rate of the chemical metering pump.

Because the vapor leaving the generator was above room temperature, it was transported to the exposure room at an elevated temperature to prevent condensation. In the exposure room, the vapor was mixed with additional heated air before it entered a short vapor distribution manifold. Concentration in the manifold was determined by the chemical pump rate, nitrogen flow rate, and dilution air flow rate. All three components were monitored by the exposure operator. The pressure in the distribution manifold was kept fixed to ensure constant flows through the manifold and into the chambers. In the 2-year study, reduced vapor concentration was delivered to the 25-ppm chamber by mixing part of the vapor in the manifold with a metered amount of additional compressed air.

Electronically actuated metering valves controlled flow to each chamber. In addition, a three-way valve, mounted upstream of all chamber flow-control valves, directed all vapor to the exposure chamber exhaust until the generation system was stable and exposures were ready to proceed. When the exposure started, the three-way valve was opened to allow the flow of vapor to reach the chamber metering valves. Each metering valve, which was in the "off" position when exposures were not being conducted for that chamber, automatically opened to the established setting and allowed vapor to flow through individual temperature-controlled delivery lines to each exposure chamber. The vapor was then injected into the chamber inlet duct where it was further diluted with conditioned chamber air to achieve the desired exposure concentration.

The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that decalin vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

Vapor Concentration Monitoring

Summaries of the chamber vapor concentrations are given in Tables J2 through J4. The decalin concentrations in the exposure chambers were monitored by an on-line gas chromatograph (system F). Samples were drawn from each exposure chamber approximately every 24 minutes using a 12-port stream select valve (VALCO Instruments Company, Houston, TX). The on-line gas chromatograph was checked throughout the day for instrument drift against an on-line standard of decalin in nitrogen supplied by a diffusion tube standard generator (Model 360, Thermo Environmental Instruments, Franklin, MA). The on-line gas chromatograph was calibrated monthly by a comparison of chamber concentration data to data from grab samples, which were collected with charcoal sampling tubes (ORBO™-101, Supelco, Bellefonte, PA), extracted with toluene containing 1-phenylhexane as an internal

standard, and analyzed by an off-line gas chromatograph (system G). The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of decalin containing 1-phenylhexane as an internal standard in toluene.

Chamber Atmosphere Characterization

Buildup and decay rates for chamber vapor concentrations were determined with animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. For rats and mice in the 2-week studies, T_{90} values ranged from 7 to 18 minutes; T_{10} values ranged from 8 to 16 minutes except in the 25 ppm chamber, for which a T_{10} value was not determined because the chamber concentration had only reached approximately 13% of the initial concentration after 65 minutes, when monitoring was stopped. For rats and mice in the 3-month studies, T_{90} values ranged from 7 to 22 minutes; T_{10} values ranged from 11 to 25 minutes. In the 2-year rat study, T_{90} values ranged from 9 to 15 minutes; T_{10} values ranged from 12 to 23 minutes. In the 2-year mouse study, T_{90} values ranged from 8 to 13 minutes; T_{10} values ranged from 12 to 16 minutes. A T_{90} value of 12 minutes was selected for the studies.

The uniformity of decalin vapor concentration in the inhalation exposure chambers without animals was evaluated before the 3-month and 2-year studies began; concentration uniformity with animals present in the chambers was also measured once during the 2-week studies, once during the 3-month studies, and every 3 months during the 2-year studies. The vapor concentration was measured using the on-line gas chromatograph with the automatic 12-port sample valve disabled to allow continuous monitoring from a single input line. Samples were collected from several positions in each chamber. Chamber concentration uniformity was maintained throughout the studies.

The persistence of decalin in the chamber after vapor delivery ended was determined by monitoring the concentration overnight in the 400 ppm chamber in the 2-week, 3-month, and 2-year studies with animals present in the chambers. In the 2-week studies, the concentration decreased to less than 1% of the target concentration within 141 minutes. In the 3-month studies, the concentration decreased to less than 1% of the target concentration within 68 minutes. In the 2-year studies, the concentration decreased to less than 1% of the target concentration within 65 minutes.

The stability of decalin in the distribution line, 25 and 400 ppm exposure chambers, and generator reservoir was monitored during the studies. Exposure chamber and distribution line samples were collected once during the 2-week, 3-month, and 2-year studies with animals present and were analyzed with GC using system H or similar systems. Commercial standards of potential degradation products and impurities were obtained from Aldrich. No evidence of degradation was detected, and no impurities were detected that were not present in the bulk material. Generator reservoir samples were collected during and after the 2-week and 3-month studies and were analyzed by GC using system H or similar systems. No evidence of degradation of the test chemical in the generator reservoir was found. The results indicated that decalin was stable for 336 days in the generator reservoir.

TABLE J1
Gas Chromatography Systems Used in the Inhalation Studies of Decalin[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Electron impact ionization	DB-5, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific, Folsom, CA)	Helium at 1.2 mL/minute	50° C for 0.5 minutes, then 15° C/minute to 280° C, held for 2 minutes
System B			
Flame ionization	DB-1, 15 m × 0.25 mm, 0.25-µm film (J&W Scientific)	Helium at 0.76 mL/minute	From 50° C to 90° C at 2° C/minute
System C			
Flame ionization	DB-1, 13 m × 0.25 mm, 1.0-µm film (J&W Scientific)	Helium at 0.96 mL/minute	From 50° C to 90° C at 2° C/minute, held at 90° C for 10 minutes
System D			
Flame ionization	DB-1, 30 m × 0.32 mm, 0.25-µm film (J&W Scientific)	Helium at 1.1 mL/minute	From 50° C to 90° C at 2° C/minute, held at 90° C for 10 minutes
System E			
Flame ionization	Rtx-5, 30 m × 0.25 mm, 1-µm film (Restek, Bellefonte, PA)	Helium at 1.0 mL/minute	50° C for 1 minute, then 10° C/minute to 200° C
System F			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5-µm film (J&W Scientific)	Nitrogen at 2.0 mL/minute	Isothermal at 140° C
System G			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5-µm film (J&W Scientific)	Helium at 6 PSI head pressure	60° C for 1 minute, then 16° C/minute to 200° C
System H			
Flame ionization	DB-5, 30 m × 0.25 mm, 1-µm film (J&W Scientific)	Helium at 24 PSI head pressure	50° C for 1 minute, then 4° C/minute to 300° C

[a] Gas chromatographs were manufactured by Hewlett Packard (Palo Alto, CA) except system D, which was manufactured by Varian (Palo Alto, CA).

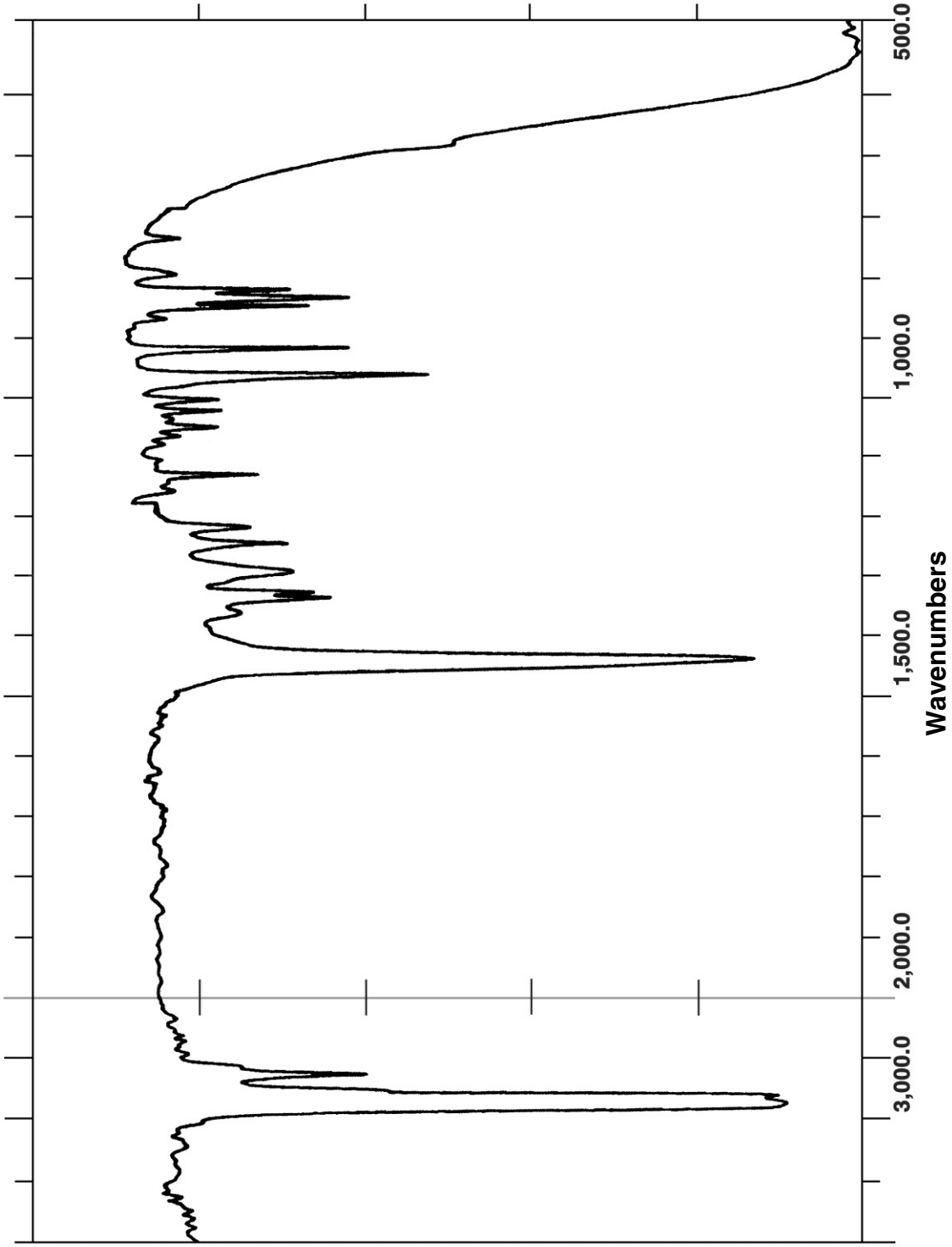

FIGURE J1
Infrared Absorption Spectrum of Decalin

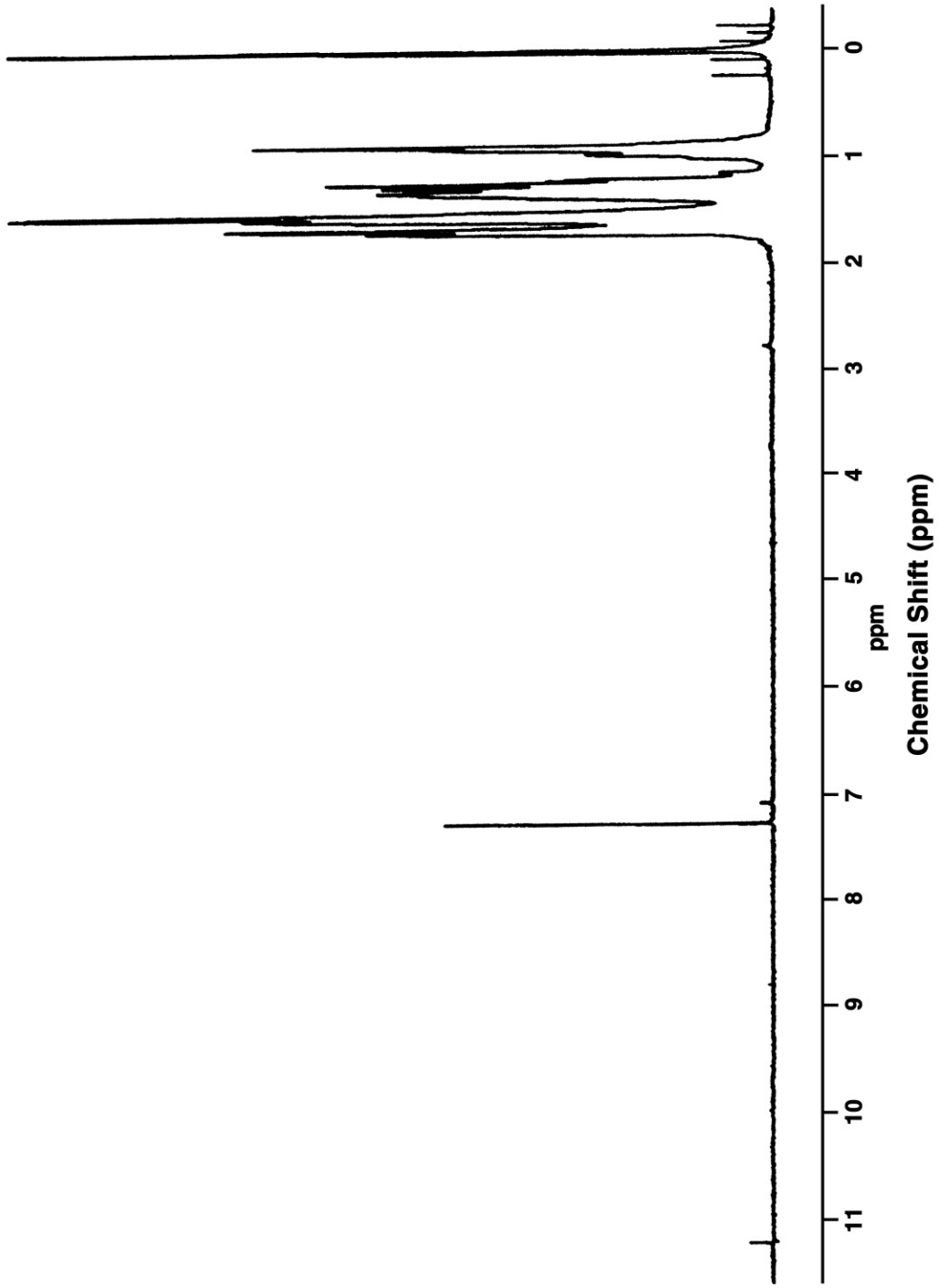

FIGURE J2
Nuclear Magnetic Resonance Spectrum of Decalin

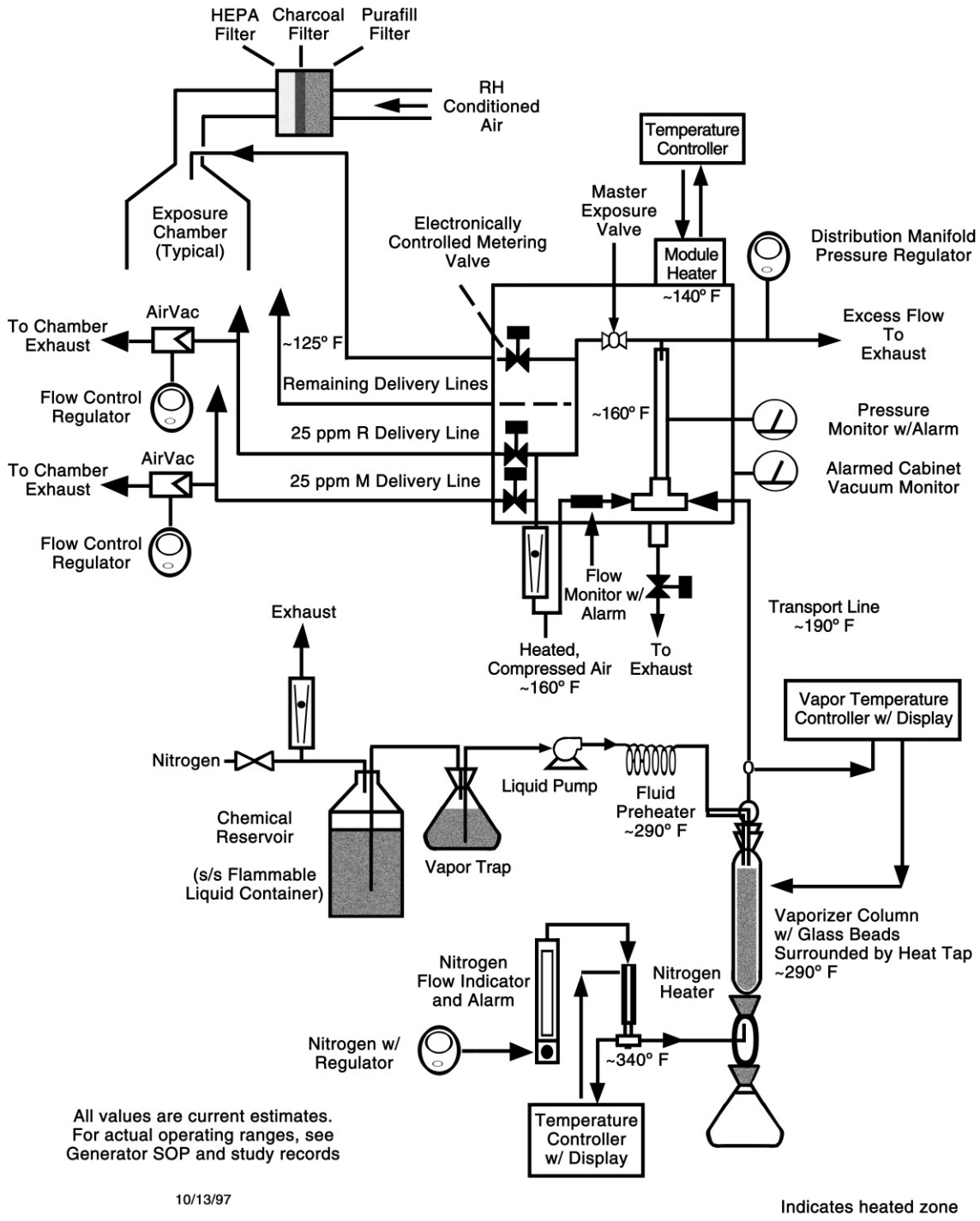

FIGURE J3
Schematic of the Vapor Generation and Delivery System in the Inhalation Studies of Decalin

TABLE J2
Summary of Chamber Concentrations in the 2-Week Inhalation Studies of Decalin

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
25	171	24.9 ± 2.1
50	193	49.6 ± 3.8
100	192	99.0 ± 6.3
200	189	200 ± 12
400	174	396 ± 28
Mouse Chambers		
25	183	24.9 ± 2.1
50	205	49.7 ± 3.7
100	205	99.0 ± 6.2
200	205	200 ± 12
400	186	397 ± 27

[a] Mean ± standard deviation

TABLE J3
Summary of Chamber Concentrations in the 3-Month Inhalation Studies of Decalin

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
25	978	24.3 ± 2.3
50	909	49.8 ± 4.4
100	908	100 ± 5.5
200	907	198 ± 10
400	907	399 ± 21
Mouse Chambers		
25	1,008	24.3 ± 2.2
50	938	49.8 ± 4.4
100	936	100 ± 5.5
200	936	198 ± 10
400	936	399 ± 21

[a] Mean ± standard deviation

TABLE J4
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Decalin

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
25	7,344	25.1 ± 1.1
50	7,548	49.8 ± 2.6
100	7,338	99.5 ± 4.5
400	7,553	402 ± 18
Mouse Chambers		
25	7,330	25.0 ± 1.2
100	7,586	100 ± 4.3
400	7,557	402 ± 18

[a] Mean ± standard deviation

APPENDIX K
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

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TABLE K2 Vitamins and Minerals in NTP-2000 Rat and Mouse Ration 280
TABLE K3 Nutrient Composition of NTP-2000 Rat and Mouse Ration 281
TABLE K4 Contaminant Levels in NTP-2000 Rat and Mouse Ration 282

TABLE K1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

TABLE K2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

Table K3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.1 ± 0.37	12.5 – 13.8	23
Crude fat (% by weight)	8.1 ± 0.25	7.6 – 8.6	23
Crude fiber (% by weight)	9.3 ± 0.71	7.9 – 10.3	23
Ash (% by weight)	5.0 ± 0.16	4.7 – 5.3	23
Amino Acids (% of total diet)			
Arginine	0.731 ± 0.050	0.670 – 0.800	8
Cystine	0.224 ± 0.012	0.210 – 0.240	8
Glycine	0.684 ± 0.041	0.620 – 0.740	8
Histidine	0.333 ± 0.018	0.310 – 0.350	8
Isoleucine	0.524 ± 0.046	0.430 – 0.590	8
Leucine	1.061 ± 0.061	0.960 – 1.130	8
Lysine	0.708 ± 0.056	0.620 – 0.790	8
Methionine	0.401 ± 0.035	0.350 – 0.460	8
Phenylalanine	0.598 ± 0.036	0.540 – 0.640	8
Threonine	0.501 ± 0.051	0.430 – 0.590	8
Tryptophan	0.126 ± 0.014	0.110 – 0.150	8
Tyrosine	0.390 ± 0.056	0.280 – 0.460	8
Valine	0.640 ± 0.049	0.550 – 0.690	8
Essential Fatty Acids (% of total diet)			
Linoleic	3.97 ± 0.284	3.59 – 4.54	8
Linolenic	0.30 ± 0.042	0.21 – 0.35	8
Vitamins			
Vitamin A (IU/kg)	5,469 ± 1,227	3,280 – 7,790	23
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	82.2 ± 14.08	62.2 – 107.0	8
Thiamine (ppm)[b]	7.5 ± 0.90	6.1 – 9.3	23
Riboflavin (ppm)	5.6 ± 1.12	4.20 – 7.70	8
Niacin (ppm)	74.3 ± 5.94	66.4 – 85.8	8
Pantothenic acid (ppm)	22.5 ± 3.96	17.4 – 29.1	8
Pyridoxine (ppm)[b]	9.04 ± 2.37	6.4 – 12.4	8
Folic acid (ppm)	1.64 ± 0.38	1.26 – 2.32	8
Biotin (ppm)	0.333 ± 0.15	0.225 – 0.704	8
Vitamin B_{12} (ppb)	68.7 ± 63.0	18.3 – 174.0	8
Choline (ppm)[b]	3,155 ± 325	2,700 – 3,790	8
Minerals			
Calcium (%)	0.964 ± 0.036	0.903 – 1.030	23
Phosphorus (%)	0.546 ± 0.023	0.498 – 0.582	23
Potassium (%)	0.659 ± 0.022	0.627 – 0.691	8
Chloride (%)	0.357 ± 0.027	0.300 – 0.392	8
Sodium (%)	0.189 ± 0.019	0.160 – 0.212	8
Magnesium (%)	0.199 ± 0.009	0.185 – 0.213	8
Sulfur (%)	0.178 ± 0.021	0.153 – 0.209	8
Iron (ppm)	160 ± 14.7	135 – 177	8
Manganese (ppm)	50.3 ± 4.82	42.1 – 56.0	8
Zinc (ppm)	50.7 ± 6.59	43.3 – 61.1	8
Copper (ppm)	6.29 ± 0.828	5.08 – 7.59	8
Iodine (ppm)	0.461 ± 0.187	0.233 – 0.843	8
Chromium (ppm)	0.542 ± 0.128	0.330 – 0.707	7
Cobalt (ppm)	0.23 ± 0.049	0.20 – 0.30	7

[a] From formulation
[b] As hydrochloride (thiamine and pyridoxine) or chloride (choline)

TABLE K4
Contaminant Levels in NTP-2000 Rat and Mouse Rationa

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.20 ± 0.138	0.10 – 0.50	23
Cadmium (ppm)	0.04 ± 0.002	0.04 – 0.05	23
Lead (ppm)	0.09 ± 0.038	0.06 – 0.25	23
Mercury (ppm)	<0.02		23
Selenium (ppm)	0.18 ± 0.034	0.13 – 0.28	23
Aflatoxins (ppb)	<5.00		23
Nitrate nitrogen (ppm)[c]	15.2 ± 8.18	9.04 – 39.6	23
Nitrite nitrogen (ppm)[c]	<0.61		23
BHA (ppm)[d]	1.1 ± 0.38	1.0 – 2.5	23
BHT (ppm)[d]	1.0 ± 0.14	1.0 – 1.7	23
Aerobic plate count (CFU/g)	<10		23
Coliform (MPN/g)	1.3 ± 0.63	0 – 3	23
Escherichia coli (MPN/g)	<10		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[e]	5.1 ± 1.77	2.1 – 8.8	23
N-Nitrosodimethylamine (ppb)[e]	2.0 ± 0.91	1.1 – 5.1	23
N-Nitrosopyrrolidine (ppb)[e]	3.1 ± 1.35	1.0 – 5.6	23
Pesticides (ppm)			
α-BHC	<0.01		23
β-BHC	<0.02		23
γ-BHC	<0.01		23
δ-BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23

TABLE K4
Contaminant Levels in NTP-2000 Rat and Mouse Ration

	Mean ± Standard Deviation	Range	Number of Samples
Pesticides (ppm) (continued)			
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl chlorpyrifos	0.094 ± 0.087	0.020 – 0.368	20
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.209 ± 0.213	0.020 – 0.826	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfan sulfate	<0.03		23

[a] All samples were irradiated. 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] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX L
SENTINEL ANIMAL PROGRAM

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SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 3-month and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. Samples were processed appropriately and sent to Microbiological Associates, Inc. (Rockville, 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	
3-Month 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
Immunofluorescence Assay	
Helicobacter hepaticus	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	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE	
3-Month Study	
ELISA	
Ectromelia virus	Study termination
EDIM (epizootic diarrhea of infant mice)	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus-FL	Study termination
MHV (mouse hepatitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
H. hepaticus	Study termination
Hemagglutination Inhibition	
K (papova virus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination
2-Year Study	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
LCM	6 months
MCMV (mouse cytomegalovirus)	6 months, study termination
MHV	6 months
Parvovirus	6, 12, and 18 months, study termination
Sendai	12 months

RESULTS

For the 2-year studies in rats and mice, all serology tests were negative. At the end of the 3-month studies, one rat had an equivocal result and one mouse a positive result for *H. hepaticus*. There was no evidence of infection by viral or parasitic organisms in these animals, and *H. hepaticus* was not isolated from any of the animals.

APPENDIX M
TOXICOKINETIC STUDIES

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TOXICOKINETIC STUDIES

INTRODUCTION

The single exposure inhalation study was designed to estimate toxicokinetic parameters relevant to the elimination of decalin from the blood of F344/N rats and $B6C3F_1$ mice. Male and female F344/N rats and $B6C3F_1$ mice received a single 6-hour whole body inhalation exposure to 25, 100, or 400 ppm decalin. Postexposure blood samples were analyzed for decalin, and the results were used to estimate toxicokinetic parameters.

MATERIALS AND METHODS

The test chemical, decahydronaphthalene (decalin; approximately 215 kg; lots 12426EN and 07347LG were mixed, divided, and assigned lot nos. 8359-84-01 and 8359-84-02 by the supplier), a mixture of *cis*-decalin (35%) and *trans*-decalin (65%), was obtained from Research Triangle Institute (Research Triangle Park, NC) and stored under nitrogen at approximately 18° C in 55-gallon drums. The system for generation and monitoring of the test article vapor is described in Appendix J.

Male and female F344/N rats with an average weight of 237 and 156 g, respectively, and male and female $B6C3F_1$ mice with an average weight of 28.5 and 24.0 g, respectively, received whole-body inhalation exposures of 25, 100, or 400 ppm decalin for 6 hours plus T_{90}; rats and mice were 12 weeks old.

For determination of decalin concentrations in blood and kidney, decahydronaphthalene-d_{18} (decalin-d_{18}; Aldrich Chemical Company, Inc., Milwaukee, WI) was used as an internal standard. The internal standard was a mixture of *cis*-decalin-d_{18} (approximately 2.4%) and *trans*-decalin-d_{18} (approximately 97.6%). Internal standard corrections were completed using the response of the *trans* isomer.

For determination of 2-decalone concentrations in kidney, 2-decalone-1,1,3,3-d_4 (2-decalone-d_4) was synthesized by Seattle Biomedical Research Institute (Seattle, WA) and used as an internal standard. Small amounts of 2-decalone-d_3 (4.8%) and 2-decalone-d_2 (0.4%) were present as impurities. The synthesized material was a mixture of *cis*-2-decalone-d_4 (approximately 79.8%) and *trans*-2-decalone-d_4 (approximately 20.2%). Internal standard corrections were completed using the response of the *cis* isomer.

Heparinized blood was collected from the retroorbital plexus (rats) or supraorbital sinus (mice) under 70% carbon dioxide (in room air) anesthesia after exposure. Each animal was bled twice, once in each eye (except rats, which were sampled three times at less than 5 minutes after exposure, 60 minutes, and approximately 1440 minutes after exposure). Rats from all exposure groups were bled at 5 minutes or less and at 10, 20, 30, 60, 120, 240, 480, and 1440 minutes postexposure. Mice from the 25 ppm group were bled at 5 minutes or less and at 10, 20, 40, 60, 120, 240, and 360 minutes postexposure. Mice from the 100 and 400 ppm groups were bled at less than 5 minutes and at 10, 20, 40, 60, 180, 360, and 480 minutes postexposure. Samples were stored at –70° C until analyses.

Determination of Decalin in Whole Blood

Blood samples were thawed to room temperature. Aliquots of approximately 100 mg blood were diluted with an equal volume of 43 mM $NaHCO_3$ (pH 11) buffer; 160 ng; 1.2 nmole (*cis* + *trans*)-decahydronaphthalene-d_{18} (decalin-d_{18}) were added as an internal standard. The mixture was vortexed for 30 seconds, and 0.5 mL cyclohexane was added. The mixture was vortexed again for 30 seconds, centrifuged for 5 minutes, and the organic layer was transferred to automated liquid sampler vials for analyses.

Determination of decalin in blood was performed using gas chromatography/mass spectrometry with ion monitoring. A HP-5971A mass selective detector controlled by a HP Windows-based computer workstation interfaced to a HP-5890 Series II gas chromatograph was used. The injection port and the transfer line temperature were maintained at 275° C and 300° C, respectively. Separations were performed on a fused-silica capillary column (DB-5; 30 m × 0.25 mm ID, 0.25 µm film; J&W Scientific, Folsom, CA). The column temperature was initially increased from 50° C to 165° C at 20° C min^{-1} after 0.5 minutes at 50° C, and subsequently increased from 165° C to 300° C at 50° C min^{-1} for a total of 9 minutes. Helium was used as a carrier gas at an inlet pressure of 10 psi. Samples (2 µL) were injected using a HP-7673 automated liquid sampler via the splitless mode, and mass spectra were obtained using an electron impact ionization source at a potential of 70 eV and an electron multiplier voltage of 2200 V.

Selected ion-current profiles were obtained for each blank, solvent standard, and spiked blood standard by monitoring intense characteristic ions for *cis*- and *trans*-decalin (m/z 138) at retention times of 5.02 and 4.66 minutes, respectively, and the internal standard, *trans*-decalin-d_{18} (m/z 156) at a retention time of 4.56 minutes. There were no peaks for decalin or decalin-d_{18} in the solvent blanks or blank blood samples, therefore, data correction for blank response was unnecessary. For the calibration curves, relative response values were calculated as the ratio of peak area for *cis*- or *trans*-decalin at m/z 138 to peak area of *trans*-decalin-d_{18} at m/z 156. Total decalin blood concentrations were determined by addition of the *cis*- and *trans*-decalin, and concentrations of decalin were reported as total (*cis* + *trans*) unless stated otherwise.

The analytical method for determining decalin in blood was validated within a range of 0.00612 to 31.8 µg decalin/g blood. The limit of detection (LOD), limit of quantitation (LOQ), and experimental limit of quantitation (ELOQ) for *trans*-decalin were 0.0014, 0.0045, and 0.0079 µg/g blood, respectively. The LOD, LOQ, and ELOQ for *cis*-decalin were 0.00069, 0.0023, and 0.0043 µg/g blood, respectively. The LOD, LOQ, and ELOQ for (*cis* + *trans*)-decalin were 0.0011, 0.0036, and 0.012 µg/g blood, respectively.

Toxicokinetic Modeling and Parameter Estimates

Toxicokinetic parameters were determined by fitting Equation 1 to the data using a nonlinear least-squares fitting program (SAS PROC NLIN; SAS Institute, Inc., Cary, NC). In Equation 1, $C(t)$ is the blood concentration of decalin at any postexposure time (t), α and β are the hybrid rate constants (min^{-1}) obtained from the fit, and A_0 and B_0 are the intercepts on the ordinate (concentration) axis of the extrapolated initial (A_0) and terminal (B_0) phases. Estimates for these values, with their asymptotic standard errors and approximately 95% confidence intervals, were obtained directly from the model. The elimination half-lives for the initial and terminal phases of the concentration versus time profiles were calculated as ln 2/α or ln 2/β, respectively. The maximum blood concentration (C_0) was assumed to occur at $t = 0$ and was calculated as $A_0 + B_0$.

Equation 1: $$C(t) = A_0 e^{-\alpha t} + B_0 e^{-\beta t}$$

The area under the curve (AUC) was estimated using the trapezoidal rule in Equation 2 from the first to the last time point (AUC_t). In Equation 2, C_{n-1}, and C_n are the blood decalin concentrations measured at two consecutive time points, t_{n-1} and t_n, respectively. Areas under the curve were calculated from the data using Equation 2 for trapezoidal rule integration of the data points. The AUC extrapolated to infinity (AUC_∞) was estimated using Equation 3, where C_t is the concentration (µg decalin/g blood) measured at the final time point (t_n), and β is the rate constant for the terminal elimination phase.

Equation 2: $$AUC_t = \sum \frac{C_{n-1} + C_n}{2} \times (t_n - t_{n-1})$$

Equation 3: $$AUC_\infty = AUC_t + \frac{C_f}{\beta}$$

All data were used for estimation of the toxicokinetic parameters. The variability in blood concentrations appeared to increase with increasing exposure concentration. Therefore, in addition to an unweighted analysis, data were fitted using weighting schemes of [mean decalin blood concentration]$^{-1}$ and [mean decalin blood concentration]$^{-2}$. The toxicokinetic parameter estimates and fitted models were derived using a weighting factor of [mean decalin blood concentration]$^{-2}$ for rats and [mean decalin blood concentration]$^{-1}$ for mice. Toxicokinetic parameters were reported as the parameter estimate ± 0.5 of the 95% confidence interval (parameter estimate ± 0.5 confidence interval). For comparison purposes, differences in the estimates of the toxicokinetic parameters were considered statistically significant if the 95% confidence intervals did not overlap.

Separate parameter estimates were made for *cis*-, *trans*-, and total (*cis* + *trans*)-decalin. This allowed comparison of separate *cis*- and *trans*-decalin kinetic parameter estimates. Based on these analyses, rate constants (and half-lives) for the initial and terminal elimination phases were not statistically different for the two isomers. Therefore, kinetic parameters were reported only for total (*cis* + *trans*)-decalin.

Data Analyses

The data were statistically analyzed using PROC GLM in SAS 6.12 (SAS Institute, Inc., Cary, NC). Comparisons of the overall mean values as a function of exposure concentration and sampling time were performed. The data were first analyzed as a full three-way ANOVA, and the effects of sex, elimination time, and decalin exposure concentration and their possible interactions were evaluated. Subsequent analyses of two-way ANOVAs within each level of decalin exposure concentration were also conducted for more specific details. Finally, one-way ANOVAs were conducted within each sex and elimination time.

RESULTS

Decalin exhibited biexponential blood elimination kinetics in rats and mice after a single 6-hour whole body inhalation exposure. A rapid initial phase (α) representing elimination from blood and rapidly perfused tissues such as liver, lung, and kidney was followed by a slower phase (β) representing elimination from slowly perfused tissues such as muscle and fat.

The biexponential curves, weighted using [mean decalin blood concentrations]$^{-2}$, that were used to model the data and to estimate toxicokinetic parameters for rats are presented in Figures M1 and M2; parameter estimates, A_0, α, B_0, and β, were obtained from these models (Table M1). The biexponential curves, weighted using [mean decalin blood concentration]$^{-1}$, that were used to model the data and to estimate toxicokinetic parameters for mice are presented in Figures M2 and M3; parameter estimates, A_0, α, B_0, and β, were obtained from these models (Table M2). The parameter estimates, A_0, α, B_0, and β were used to calculate $t_{½}\alpha$, $t_{½}\beta$, C_0, and AUC_∞.

DISCUSSION

Decalin exhibited biexponential blood elimination kinetics in rats and mice following a single 6-hour whole body inhalation exposure to 25, 100, or 400 ppm decalin. Toxicokinetic parameters were reported for total (*cis* + *trans*)-decalin because analysis of rate constants (and half-lives) for the initial and terminal elimination phases were not statistically different for the two isomers.

Significant increases in the initial decalin blood concentration (C_0) in rats and mice occurred as a function of exposure concentration independent of sex. No significant differences in C_0 between sexes for rats or mice were observed.

The half-lives for the initial elimination phase were not significantly different between sexes for rats and mice. Differences in the terminal phase half-lives as a function of exposure concentration were also not significant between sexes for rats or mice. At each decalin exposure concentration, no significant differences in the initial or terminal half-lives as a function of sex for either species was observed. Half-lives for the initial elimination phase

were approximately 1.1 to 6.0 times shorter in mice than those in rats. Half-lives for the terminal elimination phase in mice were approximately 3.4 to 5.4 times shorter than those in rats. Shorter initial and terminal elimination phase half-lives indicated that mice metabolized and/or eliminated decalin faster than rats.

Dose-proportional elimination kinetics were not observed after comparison of C_0/exposure concentration or AUC_∞/exposure concentration estimates between exposure groups for rats and mice independent of sex, which suggested nonlinear toxicokinetic behavior at higher decalin exposure concentrations. The AUC_∞/exposure concentration for female rats was significantly higher than that for male rats at each exposure concentration, which suggested that male rats were more able to eliminate decalin from circulating blood than female rats, although the difference was smaller as the exposure concentration increased. However, the ratio of AUC_∞ female rats/AUC_∞ male rats decreased as a function of exposure concentration. No significant sex differences were observed in AUC_∞/exposure concentration for mice, which suggested that male and female mice eliminate decalin from circulating blood at a similar rate.

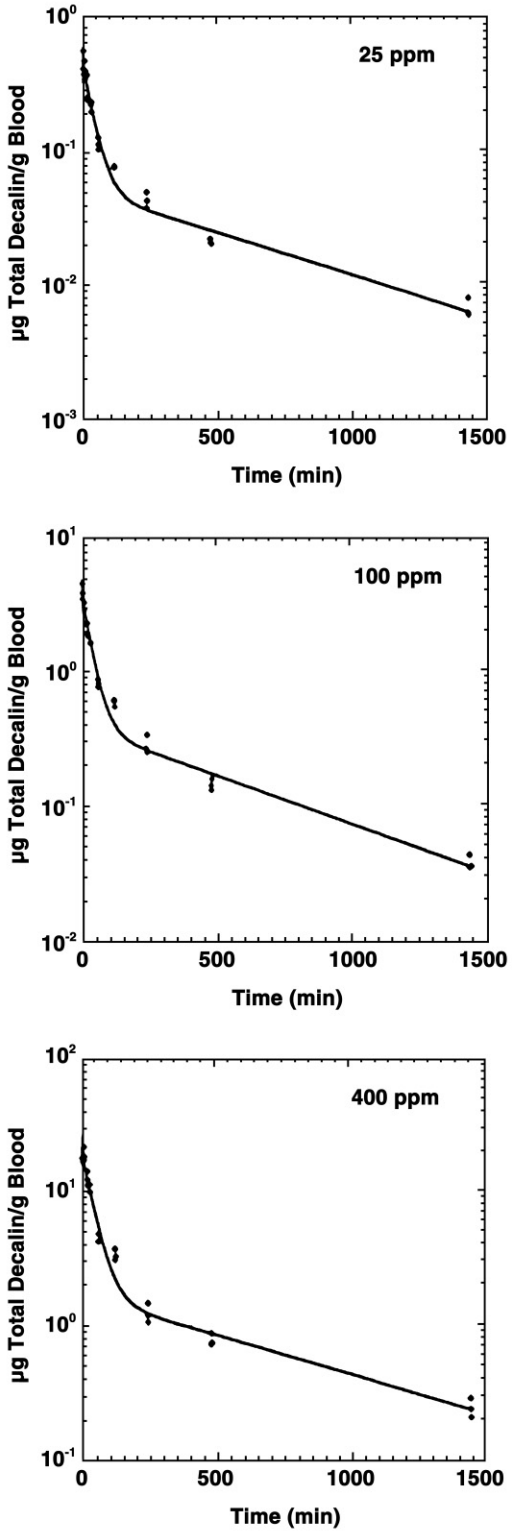

FIGURE M1
Blood Elimination Profiles for Male Rats in the Single-Exposure Toxicokinetic Studies of Decalin

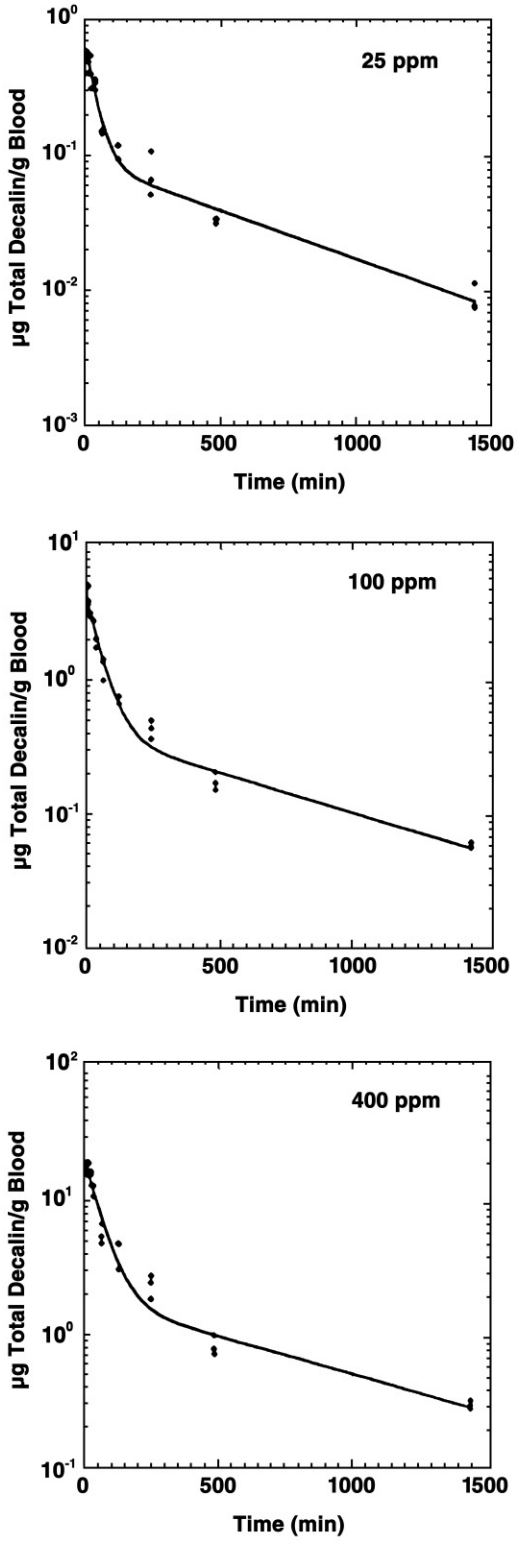

FIGURE M2
Blood Elimination Profiles for Female Rats in the Single-Exposure Toxicokinetic Studies of Decalin

TABLE M1
Toxicokinetic Parameter Estimates for the Elimination of Decalin in the Blood of Rats in the Single-Exposure Toxicokinetic Studies of Decalin

Parameter[a]	25 ppm	100 ppm	400 ppm
Male			
C_0 (μg•g^{-1})	0.501 ± 0.083	3.75 ± 0.64	20.2 ± 3.5
C_0/exposure concentration (μg•g^{-1}•ppm^{-1})	0.0200 ± 0.0033	0.0375 ± 0.0064	0.0505 ± 0.0087
α (min^{-1})	0.0276 ± 0.0062	0.0301 ± 0.0067	0.0260 ± 0.0057
$t_{½}$ (min)	25.1 ± 5.6	23.0 ± 5.1	26.6 ± 5.8
β (min^{-1})	0.00150 ± 0.00027	0.00166 ± 0.00026	0.00136 ± 0.00027
$t_{½}$ (min)	463 ± 84	418 ± 64	511 ± 100
Postexposure AUC_∞ (μg•min•g^{-1})	54.5 ± 2.1	370 ± 14	2,110 ± 90
AUC_∞/exposure (μg•min•g^{-1}•ppm^{-1})	2.18 ± 0.086	3.70 ± 0.14	5.28 ± 0.23
Female			
C_0 (μg•g^{-1})	0.639 ± 0.13	3.89 ± 0.61	19.5 ± 4.1
C_0/exposure concentration (μg•g^{-1}•ppm^{-1})	0.0256 ± 0.0052	0.0389 ± 0.0061	0.0488 ± 0.010
α (min^{-1})	0.0277 ± 0.0084	0.0199 ± 0.0044	0.0180 ± 0.0054
$t_{½}$ (min)	25.1 ± 7.6	34.9 ± 7.8	38.4 ± 11
β (min^{-1})	0.00163 ± 0.00032	0.00135 ± 0.00028	0.00127 ± 0.00039
$t_{½}$ (min)	426 ± 84	512 ± 100	546 ± 170
Postexposure AUC_∞ (μg•min•g^{-1})	80.3 ± 5.7	507 ± 25	2,680 ± 170
AUC_∞/exposure (μg•min•g^{-1}•ppm^{-1})	3.21 ± 0.23	5.07 ± 0.25	6.69 ± 0.43

[a] Estimate ± 0.5 of the 95% confidence interval (estimate ± 0.5 confidence interval); $C_0 = A_0 + B_0$

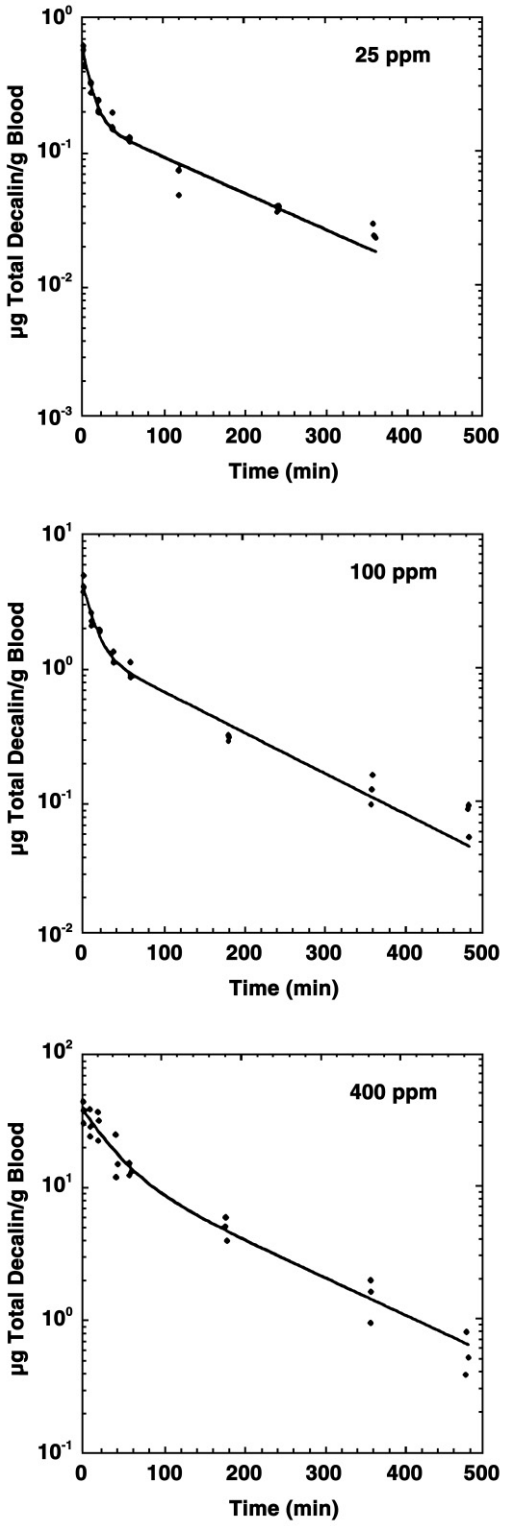

FIGURE M3
Blood Elimination Profiles for Male Mice in the Single-Exposure Toxicokinetic Studies of Decalin

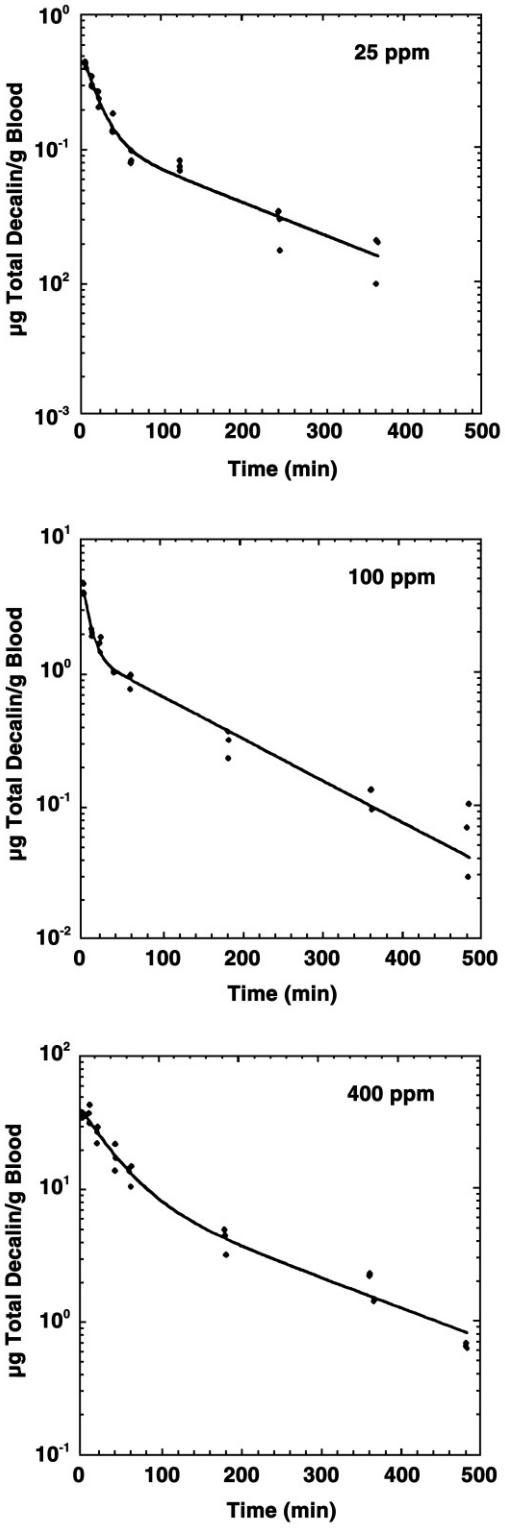

FIGURE M4
Blood Elimination Profiles for Female Mice in the Single-Exposure Toxicokinetic Studies of Decalin

TABLE M2
Toxicokinetic Parameter Estimates for the Elimination of Decalin in the Blood of Mice in the Single-Exposure Toxicokinetic Studies of Decalin

Parameter[a]	25 ppm	100 ppm	400 ppm
Male			
C_0 (μg/g^{-1})	0.649 ± 0.087	4.50 ± 0.59	39.3 ± 6.6
C_0/exposure concentration (μg/g^{-1}/ppm^{-1})	0.0260 ± 0.0035	0.0450 ± 0.0059	0.0983 ± 0.017
α (min^{-1})	0.0987 ± 0.033	0.0790 ± 0.033	0.0294 ± 0.031
$t_{½}$ (min)	7.02 ± 2.4	8.77 ± 3.7	23.6 ± 25
β (min^{-1})	0.00632 ± 0.0017	0.00706 ± 0.0019	0.00650 ± 0.0046
$t_{½}$ (min)	110 ± 29	98.2 ± 26	107 ± 75
Postexposure AUC_∞ (μg/min/g^{-1})	34.0 ± 2.0	250 ± 14	3,340 ± 260
AUC_∞/exposure (μg/min/g^{-1}/ppm^{-1})	1.36 ± 0.079	2.50 ± 0.14	8.36 ± 0.66
Female			
C_0 (μg/g^{-1})	0.582 ± 0.089	5.99 ± 1.1	42.7 ± 5.5
C_0/exposure concentration (μg/g^{-1}/ppm^{-1})	0.0233 ± 0.0036	0.0599 ± 0.011	0.107 ± 0.014
α (min^{-1})	0.0570 ± 0.019	0.120 ± 0.040	0.0267 ± 0.014
$t_{½}$ (min)	12.2 ± 4.1	5.79 ± 1.9	26.0 ± 14
β (min^{-1})	0.00561 ± 0.0019	0.00732 ± 0.0015	0.00527 ± 0.0033
$t_{½}$ (min)	124 ± 43	94.8 ± 20	131 ± 82
Postexposure AUC_∞ (μg/min/g^{-1})	31.3 ± 2.2	245 ± 16	3,430 ± 250
AUC_∞/exposure (μg/min/g^{-1}/ppm^{-1})	1.25 ± 0.088	2.45 ± 0.16	8.58 ± 0.63

[a] Estimate ± 0.5 of the 95% confidence interval (estimate ± 0.5 confidence interval); $C_0 = A_0 + B_0$

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PHARMACOKINETIC MODEL

INTRODUCTION

Commercially available decalin contains both *cis* and *trans* isomers, and it is extensively metabolized *in vivo* to *cis* and *trans* decalol isomers. The oxidation of decalols results in the production of decalones, and the decalones can be reduced back to decalols. A physiologically based pharmacokinetic model (PBPK) representing the uptake, distribution, and metabolism of decalin in rats and mice was developed to describe the processes involved in decalin toxicokinetics. This model was used to test several hypotheses regarding the decalin toxicokinetic data (Appendix M). Toxicokinetic data were available for male and female rats and mice, and the model was used to determine whether separate parameters for each species were required or whether one set of parameters was appropriate for both species. Similarly, the model was used to test whether separate parameters for each sex of a species were necessary. Finally, a model was used to determine if the data supported α2u-globulin binding to both decalols and decalones or to only one of these metabolites in male rats.

MODEL DEVELOPMENT

The PBPK model in these studies has separate compartments representing venous blood, arterial blood, liver, kidney, and fat tissue with all other tissue types grouped together as either slow or rapid perfused tissue (Figure N1). The model assumes that the liver, slow, and rapid tissue compartments are flow limited while the fat, kidney, and lung compartments are diffusion limited. The lung compartment includes alveolar space as the site of exchange between chamber air and lung blood. Decalin is metabolized in the liver to decalols, and the model assumes that this metabolism follows Michaelis-Menten kinetics. Urinary excretion of decalin from the kidney also follows Michaelis-Menten kinetics. This model does not include the decalols or decalones because there are too many unknown parameters. Decalones bind to α2u-globulin better than decalins, therefore, the metabolites of decalin could play a roll in the toxicokinetics of decalin. The number of unknown parameters in a PBPK model for the metabolites makes modeling them now unfeasible. The model results are for the total amount of the decalin, not the individual isomers. The model includes decalin binding to α2u-globulin. It is assumed that the binding removes free decalin from the blood and that the bound decalin ends up in the kidney. Once in the kidney, the bound decalin stays in the kidney or is excreted. The binding is set to zero for the mice since there is no α2u-globulin present.

The models consist of six differential equations for describing the rates of change of decalin in the tissues. There are also equations describing the amounts and concentrations of decalin in the blood and lung. All models were developed in MATLAB® (The Math Works, Inc., Natick, MA) using Simulink® code. Specific model equations are listed at the end of this section.

Physiological parameters such as tissue volumes, tissue blood flows, cardiac output, ventilation rate, and capillary volumes were obtained from the literature (Table N1; Brown *et al.*, 1997). Cardiac output and ventilation rates were derived from allometric relationships with body weight. Body weights were the mean body weights for male and female rats and mice used in the toxicokinetic studies.

The decalin blood to tissue partition coefficients for fat, liver, kidney, slow, rapid, and lung tissues were derived from the octanol:water partition coefficient for decalin (Table N2; Poulin and Krishnan, 1995). Decalin has an octanol:water partition coefficient of 4.2. The partition coefficients for fat, liver, kidney, slow, rapid, and lung tissues were 61.1, 3.8, 2.3, 11.7, 2.3, and 4.4, respectively. The octanol:water partition coefficient was used as an approximation of the fat:air partition coefficient. The ratio of the blood:air and fat:air partition coefficients was an approximation of the fat:blood partition coefficient; the fat:air partition coefficient was calculated given the fat:blood and fat:air partition coefficients. The blood:air partition coefficient was 256.6.

Eight parameters were estimated for rats and mice with an additional three parameters that described the binding of decalin to α2u-globulin in rats. The first two parameters were V_{maxc} and K_m in the Michaelis-Menten kinetics for metabolism. Estimates were needed for the four parameters that described the permeability of decalin from blood to fat, kidney, air, and lung. These constants described the movement of decalin from the tissue capillary space to the tissue or from the tissue back to the tissue blood. For rats and mice, the last two parameters that needed to be estimated were the Michaelis-Menten parameters for elimination. For the rat model only, the Michaelis-Menten parameters for binding to α2u-globulin and the elimination of bound decalin were also estimated. The details of how these parameters were estimated are given below.

Estimates for the unknown model parameters were obtained using maximum likelihood methods (Casella and Berger, 1990). Parameter estimates were based on fitting model output for blood concentration to toxicokinetic plasma data. A normal distribution was used for the likelihood function, and the data and model predictions were log transformed (so the ultimate likelihood function was log-normal). Some of the data were below the limit of quantitation (LOQ) and in this case, the LOQ data were compared to the model output with the cumulative distribution function in the likelihood rather than the probability distribution function (Koo *et al.*, 2002). This method allows all the data to be used for fitting purposes without making assumptions about the values below the LOQ. The residuals from the fit were examined with a QQ plot for evaluation. Each optimization was started with at least 12 different sets of initial values, and the parameter estimates were those from the optimization with the largest likelihood.

Differential Equations

$$\frac{dAMT_{slow}}{dt} = Q_{slow}C_{art} - Q_{slow} \cdot \frac{C_{slow}}{P_{slow}}$$

$$\frac{dAMT_{rapid}}{dt} = Q_{rapid}C_{art} - Q_{rapid} \cdot \frac{C_{rapid}}{P_{rapid}}$$

$$\frac{dAMT_{kidneytissue}}{dt} = C_{kidneycap} \cdot Perm_{kidney} - C_{kidneytissue} \cdot Perm_{kidney} - elim$$

$$elim = \frac{Vmax_{elim} \cdot C_{kidneytissue}}{Km_{elim} + C_{kidneytissue}}$$

$$\frac{dAMT_{kidneycap}}{dt} = Q_{kidney}C_{art} + C_{kidneytissue} \cdot Perm_{kidney} - Q_{kidneyt}C_{kidneycap} - C_{kidneycap} \cdot Perm_{kidney}$$

$$\frac{dAMT_{fattissue}}{dt} = C_{fatcap} \cdot Perm_{fat} - C_{fattissue} \cdot Perm_{fat}$$

$$\frac{dAMT_{fatcap}}{dt} = Q_{fat}C_{art} + C_{fattissue} \cdot Perm_{fat} - Q_{fat}C_{fatcap} - C_{fatcap} \cdot Perm_{fat}$$

$$\frac{dAMT_{liver}}{dt} = Q_{liver}C_{art} - Q_{liver} \cdot \frac{C_{liver}}{P_{liver}} - metab$$

$$metab = \frac{Vmax \cdot C_{liver}}{Km + C_{liver}}$$

Differential Equations (continued)

$$C_{tissue} = \frac{AMT_{tissue}}{Volume_{tissue}}$$

$$\frac{dAMT_{art}}{dt} = C_{lungcap}Q_{total} - C_{art}Q_{total}$$

$$\frac{dAMT_{ven}}{dt} = \sum C_{tissuecap}Q_{tissue} - C_{ven}Q_{total}$$

Definitions of Abbreviations

AMT_{tissue}	*amount in tissue (mg)*
C_{art}	*concentration in arterial blood (mg/mL)*
C_{fatcap}	*concentration in fat capillary blood (mg/mL)*
C_{tissue}	*concentration in tissue (mg/mL)*
$C_{tissuecap}$	*concentration in tissue capillary space (mg/L)*
Q_{tissue}	*blood flow to the tissue (L/hour)*
Perm	*capillary permeability in the fat*
P_{tissue}	*tissue:blood partition coefficient*
V_{max}	*maximum velocity of saturable metabolism (mg/L per hour)*
K_m	*Michaelis-Menten constant for metabolism (mg/L)*

RESULTS

The first test was to determine if different parameters were needed for each species. The full model for a test between species has 22 parameters (Table N3). There are 11 unknown parameters in the PBPK model and the full model estimates unique parameters for rats and mice. The reduced model estimates 11 parameters (Table N4) so that the rats and mice share common parameter values. The full and reduced models had log likelihood values of –797.9 and –809.6 respectively for a test statistic of 23.4. The Chi-squared distribution with 11 degrees of freedom at the 95% significance level has a value of 21.9, therefore, there was a statistically significant improvement to having species-specific parameter estimates.

For a test of sex differences within a species, the full model was used and each sex had different parameters, but with the same PBPK model structure. The reduced model is one parameter set for both sexes. For rats, there were 11 parameters, while for mice, there were eight parameters because the three binding parameters were not included (Table N5). For the rat, the full and reduced models have log likelihood values of –482.1 and –557.9, respectively. The likelihood ratio test statistic is 151.6, indicating that there is a significant improvement to sex-specific parameters for rats. For mice, the full and reduced models have log likelihood values of –239.9 and –240.0, respectively. The likelihood ratio test statistic is 0.2, therefore, a sex difference could not be detected for mice. The parameter estimates are shown in Tables N3 and N4.

The test for a sex difference for mice was not significant, but it was significant for rats. The model was used to test if the difference in male and female rats could be attributed only to a difference in binding to α2u-globulin. In this case, the full model was one in which each sex had unique binding parameters, but the sexes shared the other unknown parameters such as permeability constants and elimination rate constants. The reduced model had all the

parameters common to both sexes. The full model had a log likelihood value of –482.1, while the reduced model had a log likelihood value of –492.1. The test statistic was 20.0, while the Chi-squared distribution with eight degrees of freedom (22 parameters in the full model, 14 in the reduced) at the 95% significance level had a value of 17.5. Therefore, it was not possible to determine if the binding of decalin to α2u-globulin was the only difference between male and female rats using this PBPK model.

Error estimates from the optimizations came from the Hessian matrix. Because the Hessian matrix can be poorly approximated in this type of model (nonlinear system of differential equations), the accuracy of the errors may be poor. For this reason, the errors are not calculated or reported.

Figures N2 through N6 show the model predictions and data for blood concentration. Figure N2 is for rat blood decalin, and Figure N3 is for kidney decalin concentration when the parameters are unique to each sex (Table N1). Figure N4 is for the mouse blood decalin concentration with unique parameters for each sex. The figures show acceptable fits, but the model under predicts blood decalin in rats at 8 hours. This under prediction may be driven by the fit of the kidney data that is visually very good. There is no mouse kidney data, therefore, there is more flexibility to fit the blood concentration data. All of these predictions are better than the fits when one set of parameters is used for each species and sex (Figures N5 and N6). These poor fits are supported by the large test statistic for species-specific parameter estimates.

The model was used to make predictions about dose concentrations above 400 ppm. In mice, the values for the area under the curve scaled by exposure for the model closely match those from the data (Figures N7 and N8). The exponential rise of the curves indicates that the metabolism of decalin has been saturated.

Discussion and Conclusions

There are several conclusions that can be drawn from the PBPK model. First, it is not possible to detect any differences in the metabolism of decalin between male and female mice in these data. There are significant differences between male and female rats driven by the difference in kidney decalin concentrations. Second, the model predicts a higher rate of metabolism for mice, but this metabolism pathway saturates at a lower concentration than that in rats. Third, the model indicates that the highest dose (400 ppm) selected for the study was at a concentration where metabolism was saturated. Finally, it is not possible to determine if the metabolism and permeability parameters for male and female rats are the same; the only difference between the sexes were parameters associated with the binding to α2u-globulin.

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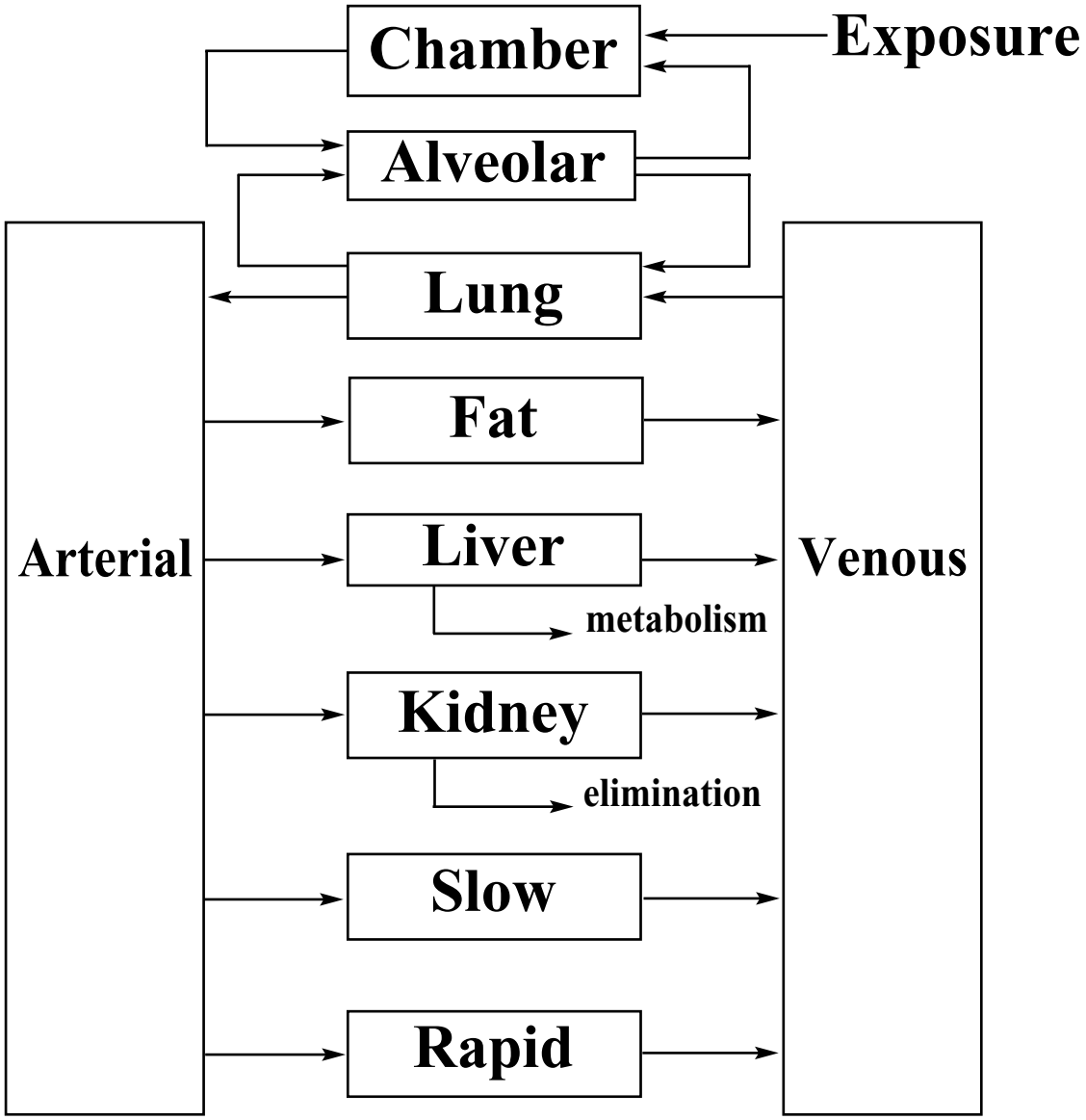

FIGURE N1
Physiologically Based Pharmacokinetic Model for Rats and Mice Exposed to Decalin by Inhalation

TABLE N1
Physiological Parameters of Rats and Mice for the Physiologically Based Pharmacokinetics Model of Decalin

Parameter	Rats		Mice	
	Male	Female	Male	Female
Body weight (kg)	0.237	0.156	0.029	0.024
Cardiac output (L/hour per kg body weight)	14.7	14.7	11.9	11.9
Ventilation rate (L/hour per kg body weight)	20.0	20.0	24.4	24.4
Tissue Volume as Fraction of Body Weight[a]				
Liver	0.037	0.037	0.055	0.055
Kidney	0.0148	0.0148	0.017	0.017
Fat	0.07	0.07	0.06	0.06
Slow	0.75	0.75	0.76	0.76
Rapid	0.0382	0.0382	0.018	0.018
Capillary Volume as Fraction of Tissue Volume[a]				
Kidney	0.14	0.14	0.14	0.14
Fat	0.03	0.03	0.03	0.03
Lung	0.11	0.11	0.11	0.11
Tissue Blood Flow as Fraction of Cardiac Output[a]				
Liver	0.174	0.174	0.162	0.162
Kidney	0.141	0.141	0.163	0.163
Fat	0.07	0.07	0.05	0.05
Slow	0.17	0.17	0.19	0.19
Rapid	0.445	0.445	0.435	0.435

[a] Brown *et al.* (1997)

TABLE N2
Partition Coefficients for Decalin for the Physiologically Based Pharmacokinetics Model of Decalin[a]

Partition Coefficient	Value
Fat:blood	61.1
Liver:blood	3.8
Kidney:blood	2.3
Lung:blood	4.4
Slow:blood	11.7
Rapid:blood	2.3
Blood:air	256.6

[a] Poulin and Krishnan (1995)

TABLE N3
Parameter Estimates of Rats and Mice for the Physiologically Based Pharmacokinetics Model of Decalin (Full Model)

Parameter[a]	Rats		Mice	
	Male	Female	Male	Female
V_{maxc} (mg/hour)	9.99	6.89	11.85	11.24
K_m (mg/L)	4.00	4.00	1.22	1.11
$Perm_{fat}$ ($hour^{-1}$)	0.20	0.32	0.46	0.09
$Perm_{air}$ ($hour^{-1}$)	10.10	6.19	11.02	8.89
$Perm_{lung}$ ($hour^{-1}$)	2.48	1.39	2.19	2.33
$V_{maxelim}$ (mg/hour)	2.98	11.82	1.59	1.32
K_{melim} (mg/L)	10.00	0.35	6.87	6.68
$Perm_{elim}$ ($hour^{-1}$)	4.02	0.20	2.36	2.65
Max binding (mg/hour)	0.007	0.18	NA	NA
Half binding (mg/L)	0.105	3.68	NA	NA
$k_{elim\text{-}bound}$ ($hour^{-1}$)	0.101	3.62	NA	NA

[a] V_{maxc} = maximum velocity of saturated metabolism; K_m = Michaelis-Menten constant for metabolism; NA=not applicable

TABLE N4
Parameter Estimates of Rats and Mice for the Physiologically Based Pharmacokinetics Model of Decalin (Reduced Model)

Parameter[a]	Rats	Mice	Rats and Mice
V_{maxc} (mg/hour)	5.58	11.43	6.72
K_m (mg/L)	13.11	0.50	4.26
$Perm_{fat}$ ($hour^{-1}$)	0.54	0.12	0.20
$Perm_{air}$ ($hour^{-1}$)	11.28	11.19	11.26
$Perm_{lung}$ ($hour^{-1}$)	7.98	2.17	3.09
$V_{maxelim}$ (mg/hour)	4.93	1.45	2.90
K_{melim} (mg/L)	17.31	8.41	6.89
$Perm_{elim}$ ($hour^{-1}$)	2.67	2.51	35.90
Max binding (mg/hour)	0.003	NA	0.004
Half binding (mg/L)	0.34	NA	0.14
$k_{elim\text{-}bound}$ ($hour^{-1}$)	0.6	NA	0.09

[a] V_{maxc} = maximum velocity of saturated metabolism; K_m = Michaelis-Menten constant for metabolism; NA=not applicable

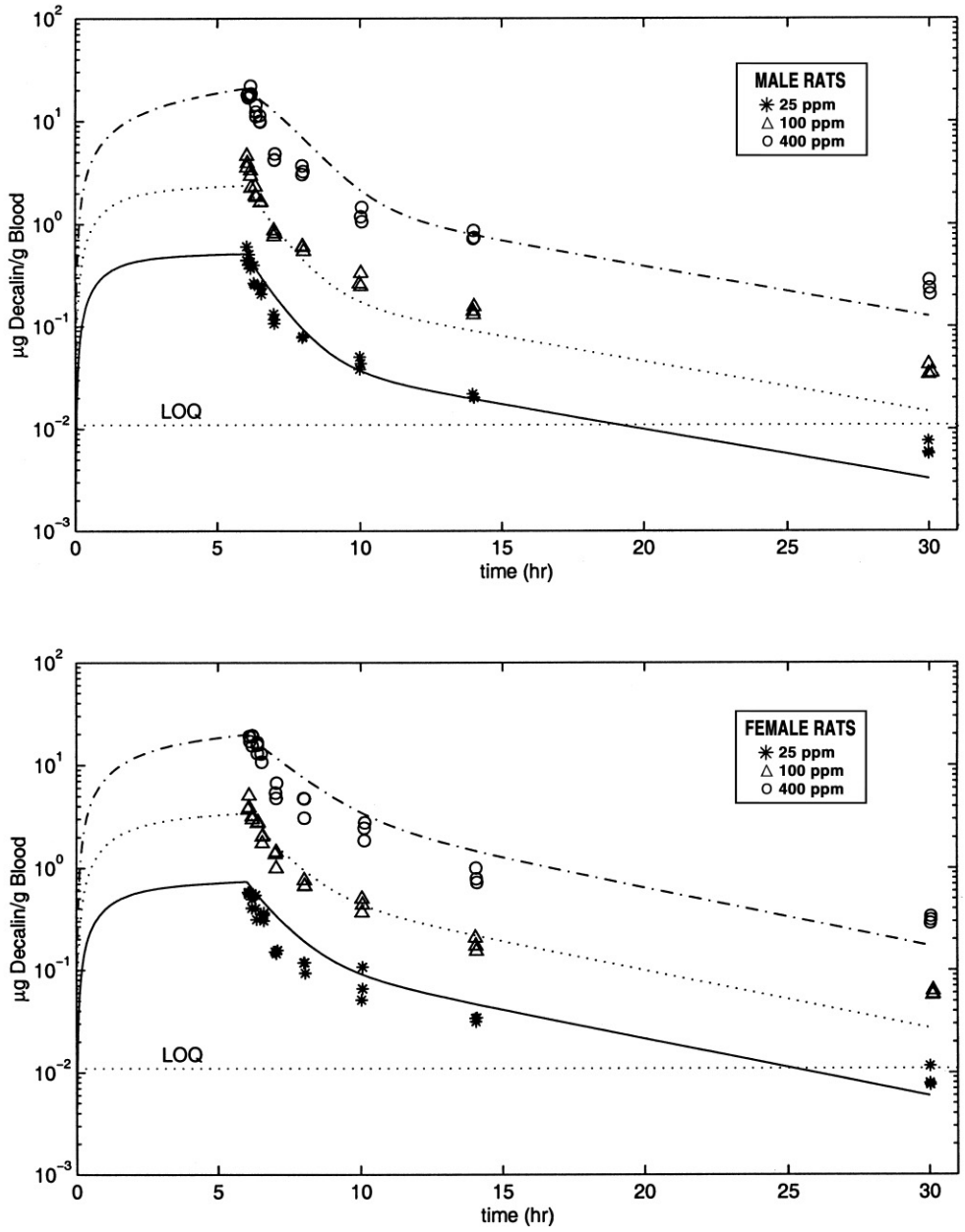

FIGURE N2
Blood Concentrations of Decalin in Rats after a Single 6-Hour Exposure to Decalin by Inhalation: Sex-Specific Model

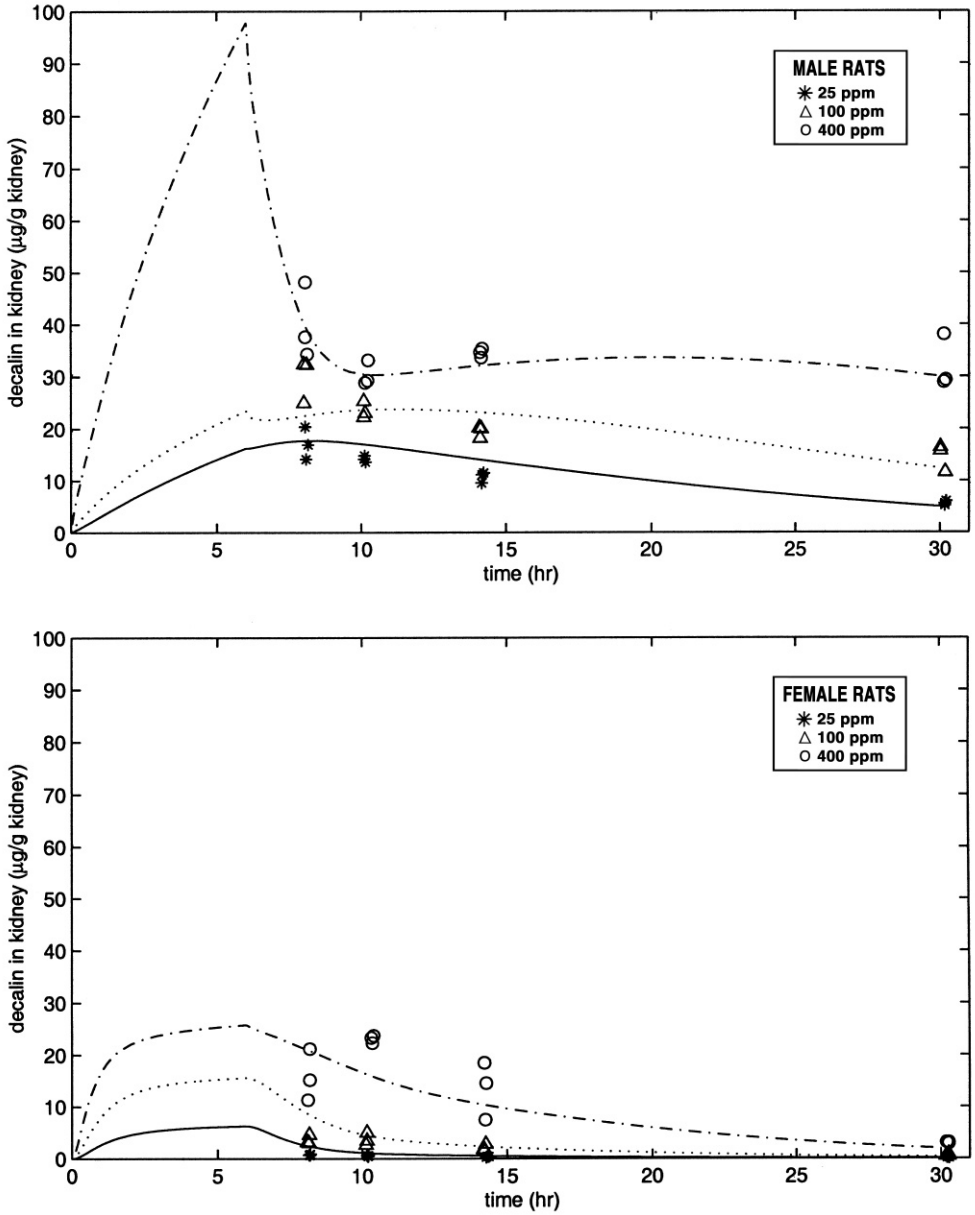

FIGURE N3
Kidney Concentrations of Decalin in Rats after a Single 6-Hour Exposure to Decalin by Inhalation: Sex-Specific Model

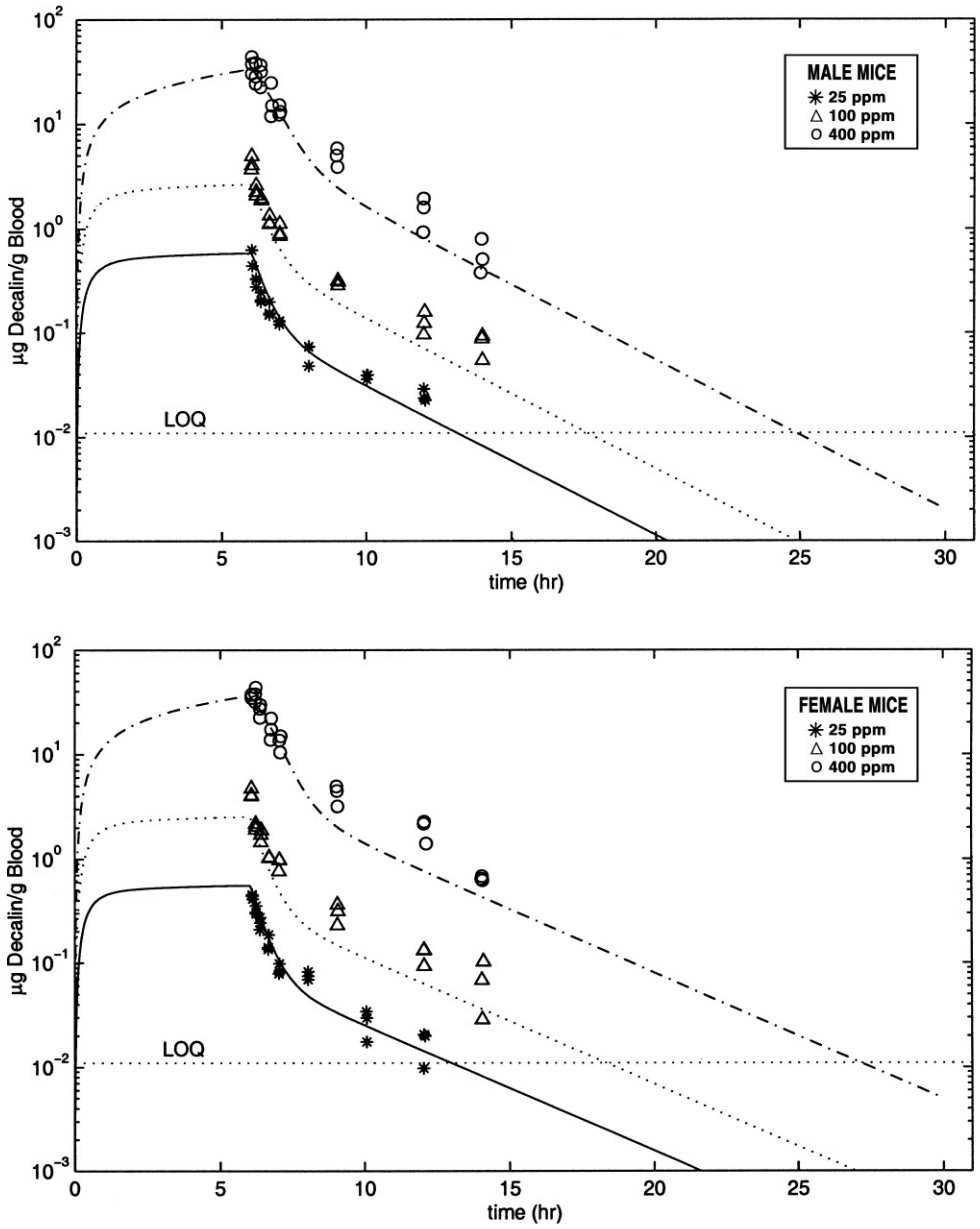

FIGURE N4
Blood Concentrations of Decalin in Mice after a Single 6-Hour Exposure to Decalin by Inhalation: Sex-Specific Model

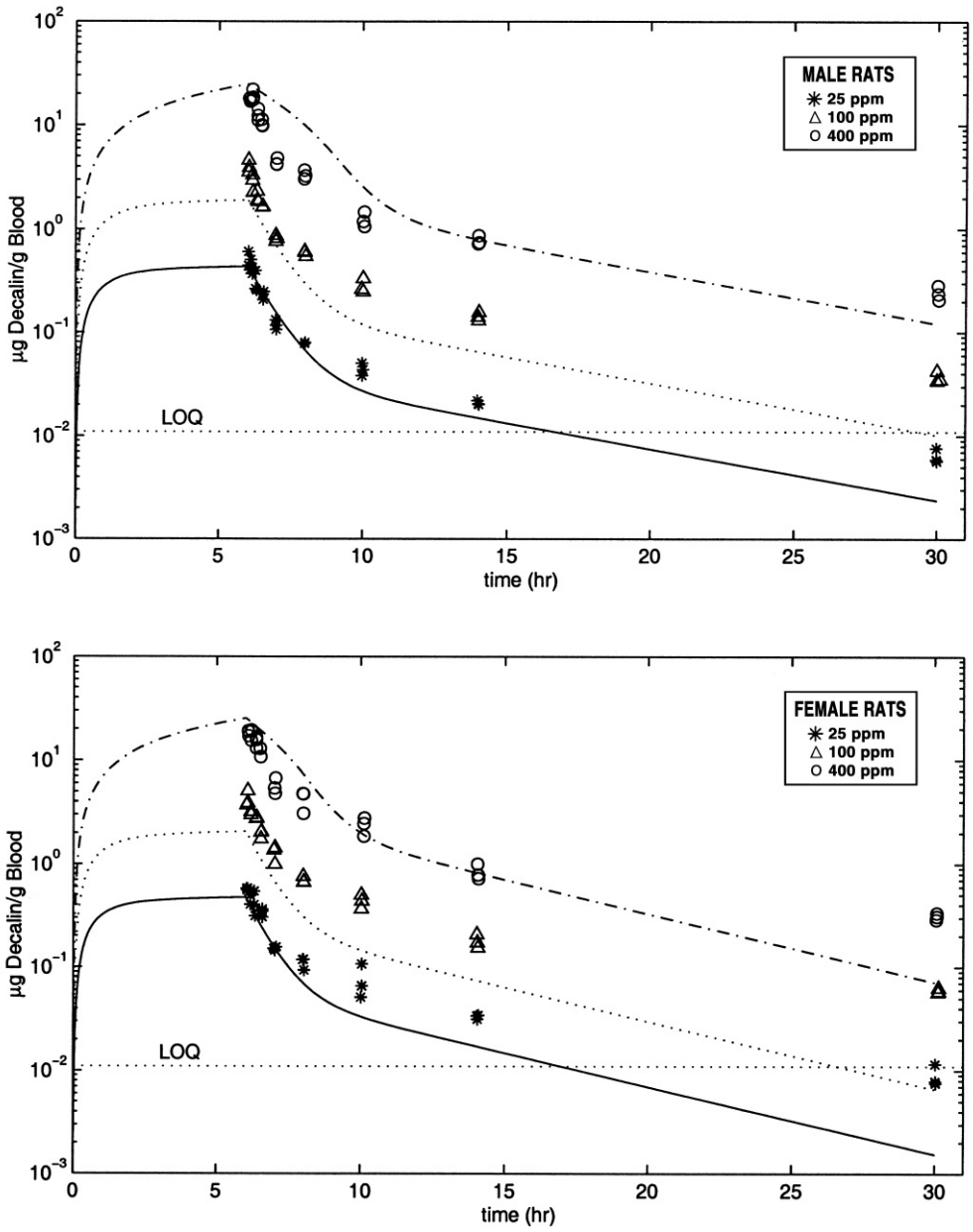

FIGURE N5
Blood Concentrations of Decalin in Rats after a Single 6-Hour Exposure to Decalin by Inhalation: Species- and Sex-Specific Model

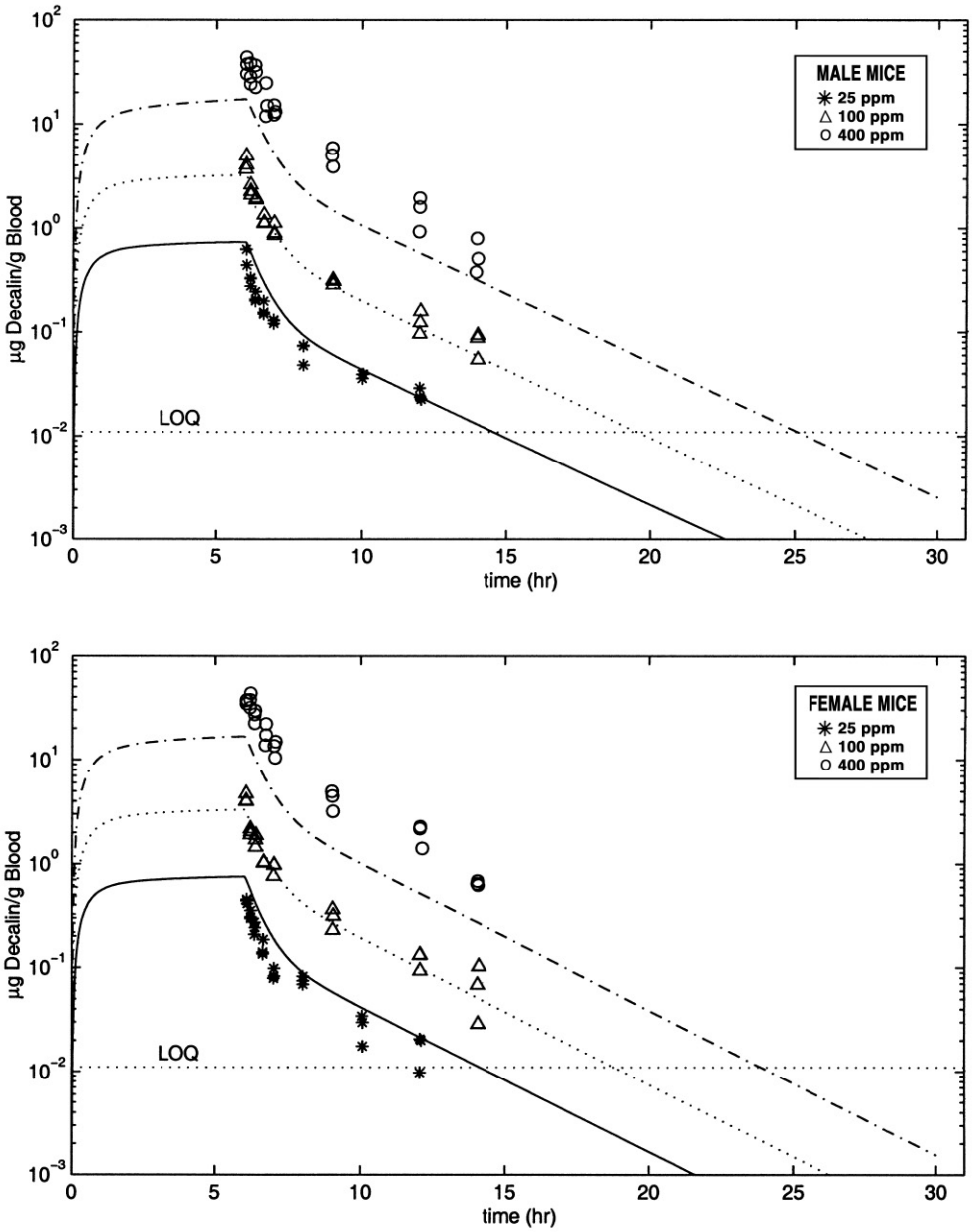

FIGURE N6
Blood Concentrations of Decalin in Mice after a Single 6-Hour Exposure to Decalin by Inhalation: Species- and Sex-Specific Model

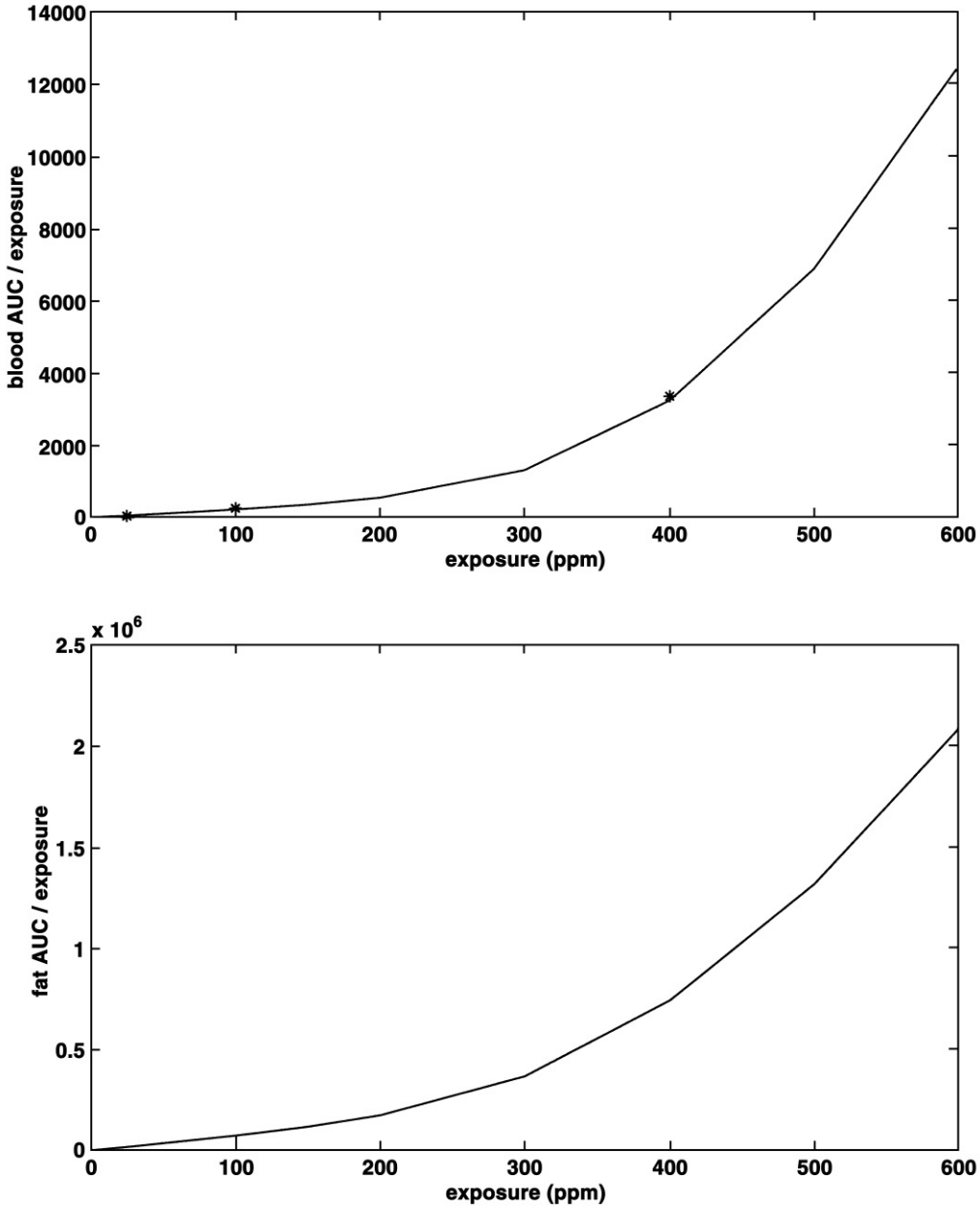

FIGURE N7
Predicted Area Under the Curve/Exposure and Calculated Area Under the Curve/Exposure Blood and Fat Concentrations of Decalin in Male Mice

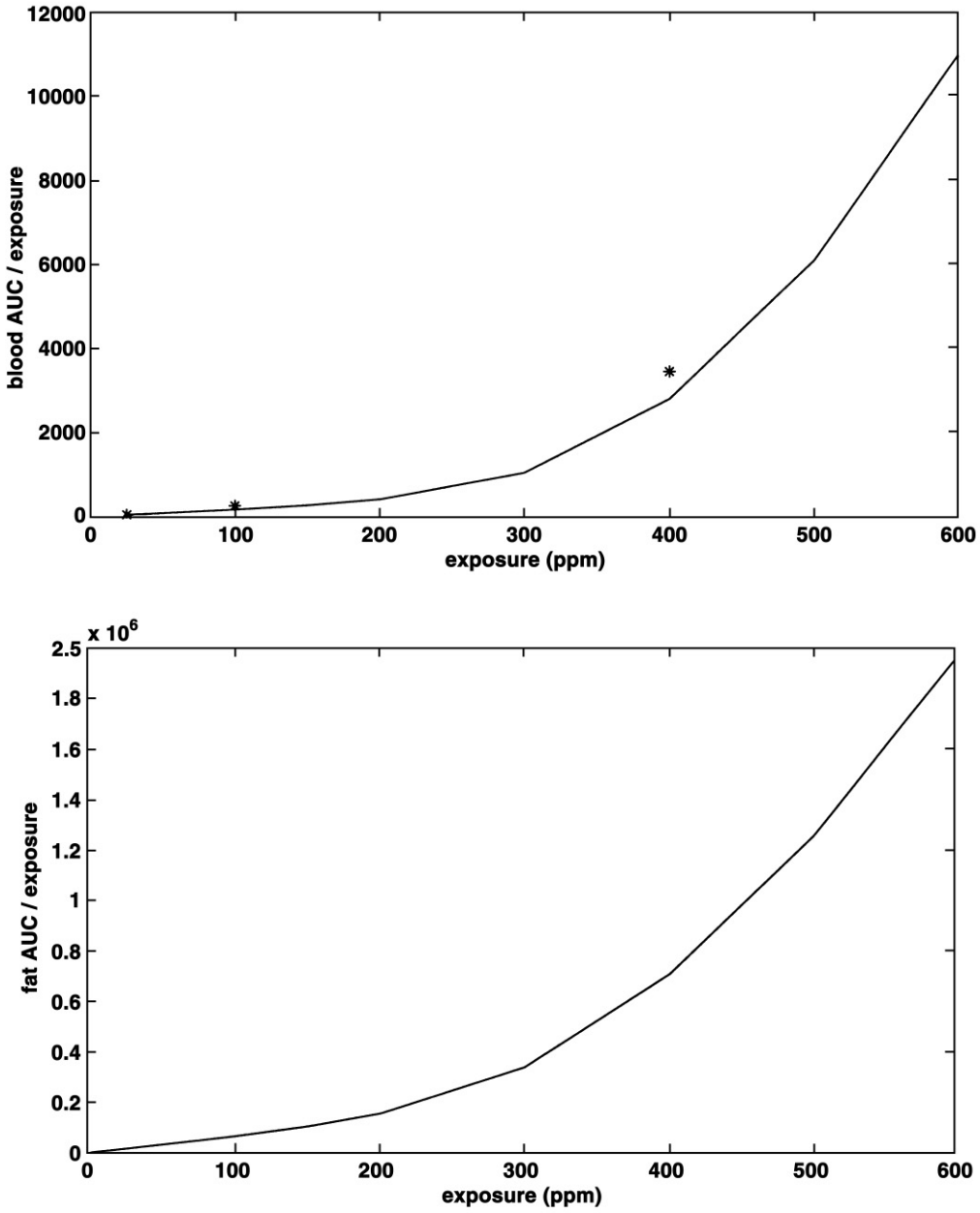

FIGURE N8
Predicted Area Under the Curve/Exposure and Calculated Area Under the Curve/Exposure Blood and Fat Concentrations of Decalin in Female Mice

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Chemical	TR No.
Acetaminophen	394
Acetonitrile	447
Acrylonitrile	506
Agar	230
Allyl Glycidyl Ether	376
Allyl Isothiocyanate	234
Allyl Isovalerate	253
1-Amino-2,4-Dibromoanthraquinone	383
2-Amino-4-Nitrophenol	339
2-Amino-5-Nitrophenol	334
11-Aminoundecanoic Acid	216
dl-Amphetamine Sulfate	387
Ampicillin Trihydrate	318
Asbestos, Amosite (Hamsters)	249
Asbestos, Amosite (Rats)	279
Asbestos, Chrysotile (Hamsters)	246
Asbestos, Chrysotile (Rats)	295
Asbestos, Crocidolite	280
Asbestos, Tremolite	277
L-Ascorbic Acid	247
AZT and AZT/α-Interferon A/D	469
Barium Chloride Dihydrate	432
Benzaldehyde	378
Benzene	289
Benzethonium Chloride	438
Benzofuran	370
Benzyl Acetate (Gavage)	250
Benzyl Acetate (Feed)	431
Benzyl Alcohol	343
o-Benzyl-*p*-Chlorophenol (Gavage)	424
o-Benzyl-*p*-Chlorophenol (Mouse Skin)	444
2-Biphenylamine Hydrochloride	233
2,2-Bis(Bromomethyl)-1,3-Propanediol	452
Bis(2-Chloro-1-Methylethyl) Ether	239
Bisphenol A	215
Boric Acid	324
Bromodichloromethane	321
Bromoethane	363
1,3-Butadiene	288
1,3-Butadiene	434
t-Butyl Alcohol	436
Butyl Benzyl Phthalate	213
Butyl Benzyl Phthalate	458
n-Butyl Chloride	312
t-Butylhydroquinone	459
γ-Butyrolactone	406
Caprolactam	214
d-Carvone	381
Chloral Hydrate	502
Chloral Hydrate	503
Chlorinated and Chloraminated Water	392
Chlorendic Acid	304
Chlorinated Paraffins: C_{23}, 43% Chlorine	305
Chlorinated Paraffins: C_{12}, 60% Chlorine	308
Chlorinated Trisodium Phosphate	294
2-Chloroacetophenone	379
p-Chloroaniline Hydrochloride	351
Chlorobenzene	261
Chlorodibromomethane	282
Chloroethane	346
2-Chloroethanol	275
3-Chloro-2-Methylpropene	300
Chloroprene	467
1-Chloro-2-Propanol	477
Chlorpheniramine Maleate	317
C.I. Acid Orange 3	335
C.I. Acid Orange 10	211
C.I. Acid Red 14	220
C.I. Acid Red 114	405
C.I. Basic Red 9 Monohydrochloride	285
C.I. Direct Blue 15	397
C.I. Direct Blue 218	430
C.I. Disperse Blue 1	299
C.I. Disperse Yellow 3	222
C.I. Pigment Red 3	407
C.I. Pigment Red 23	411
C.I. Solvent Yellow 14	226
trans-Cinnamaldehyde	514
Citral	505
Cobalt Sulfate Heptahydrate	471
Coconut Oil Acid Diethanolamine Condensate	479
Codeine	455
Comparative Initiation/Promotion Studies (Mouse Skin)	441
Corn Oil, Safflower Oil, and Tricaprylin	426
Coumarin	422
CS2	377
Cytembena	207
D&C Red No. 9	225
D&C Yellow No. 11	463
Decalin	513
Decabromodiphenyl Oxide	309
Diallyl Phthalate (Mice)	242
Diallyl Phthalate (Rats)	284
4,4′-Diamino-2,2′-Stilbenedisulfonic Acid, Disodium Salt	412
2,4-Diaminophenol Dihydrochloride	401
1,2-Dibromo-3-Chloropropane	206
1,2-Dibromoethane	210
2,3-Dibromo-1-Propanol	400
1,2-Dichlorobenzene (*o*-Dichlorobenzene)	255
1,4-Dichlorobenzene (*p*-Dichlorobenzene)	319
p,p′-Dichlorodiphenyl sulfone	501
2,4-Dichlorophenol	353
2,6-Dichloro-*p*-Phenylenediamine	219
1,2-Dichloropropane	263
1,3-Dichloropropene (Telone II)	269
Dichlorvos	342
Dietary Restriction	460
Diethanolamine	478
Di(2-Ethylhexyl) Adipate	212
Di(2-Ethylhexyl) Phthalate	217
Diethyl Phthalate	429
Diglycidyl Resorcinol Ether	257
3,4-Dihydrocoumarin	423
1,2-Dihydro-2,2,4-Trimethylquinoline (Monomer)	456
Dimethoxane	354
3,3′-Dimethoxybenzidine Dihydrochloride	372
N,N-Dimethylaniline	360
3,3′-Dimethylbenzidine Dihydrochloride	390
Dimethyl Hydrogen Phosphite	287
Dimethyl Methylphosphonate	323
Dimethyl Morpholinophosphoramidate	298
Dimethylvinyl Chloride	316
Diphenhydramine Hydrochloride	355
5,5-Diphenylhydantoin	404
Dipropylene Glycol	511
Elmiron®	512
Emodin	493
Ephedrine Sulfate	307
Epinephrine Hydrochloride	380
1,2-Epoxybutane	329
Erythromycin Stearate	338
Ethyl Acrylate	259

Chemical	TR No.
Ethylbenzene	466
Ethylene Glycol	413
Ethylene Glycol Monobutyl Ether	484
Ethylene Oxide	326
Ethylene Thiourea	388
Eugenol	223
FD&C Yellow No. 6	208
Fumonisin B_1	496
Furan	402
Furfural	382
Furfuryl Alcohol	482
Furosemide	356
Gallium Arsenide	492
Geranyl Acetate	252
Glutaraldehyde	490
Glycidol	374
Guar Gum	229
Gum Arabic	227
HC Blue 1	271
HC Blue 2	293
HC Red 3	281
HC Yellow 4	419
Hexachlorocyclopentadiene	437
Hexachloroethane	361
2,4-Hexadienal	509
4-Hexylresorcinol	330
Hydrochlorothiazide	357
Hydroquinone	366
8-Hydroxyquinoline	276
Indium Phosphide	499
Iodinated Glycerol	340
Isobutene	487
Isobutyl Nitrite	448
Isobutyraldehyde	472
Isophorone	291
Isoprene	486
Lauric Acid Diethanolamine Condensate	480
d-Limonene	347
Locust Bean Gum	221
60-Hz Magnetic Fields	488
Magnetic Field Promotion	489
Malachite Green Chloride and Leucomalachite Green	527
Malonaldehyde, Sodium Salt	331
Manganese Sulfate Monohydrate	428
D-Mannitol	236
Marine Diesel Fuel and JP-5 Navy Fuel	310
Melamine	245
2-Mercaptobenzothiazole	332
Mercuric Chloride	408
Methacrylonitrile	497
8-Methoxypsoralen	359
α-Methylbenzyl Alcohol	369
Methyl Bromide	385
Methyl Carbamate	328
Methyldopa Sesquihydrate	348
Methylene Chloride	306
4,4′-Methylenedianiline Dihydrochloride	248
Methyleugenol	491
2-Methylimidazole	516
Methyl Methacrylate	314
N-Methylolacrylamide	352
Methylphenidate Hydrochloride	439
Mirex	313
Molybdenum Trioxide	462
Monochloroacetic Acid	396
Monuron	266
Nalidixic Acid	368
Naphthalene (Mice)	410
Naphthalene (Rats)	500
Nickel (II) Oxide	451
Nickel Sulfate Hexahydrate	454
Nickel Subsulfide	453

Chemical	TR No.
p-Nitroaniline	418
o-Nitroanisole	416
p-Nitrobenzoic Acid	442
Nitrofurantoin	341
Nitrofurazone	337
Nitromethane	461
p-Nitrophenol	417
o-Nitrotoluene	504
p-Nitrotoluene	498
Ochratoxin A	358
Oleic Acid Diethanolamine Condensate	481
Oxazepam (Mice)	443
Oxazepam (Rats)	468
Oxymetholone	485
Oxytetracycline Hydrochloride	315
Ozone and Ozone/NNK	440
Penicillin VK	336
Pentachloroanisole	414
Pentachloroethane	232
Pentachloronitrobenzene	325
Pentachlorophenol, Purified	483
Pentachlorophenol, Technical Grade	349
Pentaerythritol Tetranitrate	365
Phenolphthalein	465
Phenylbutazone	367
Phenylephrine Hydrochloride	322
N-Phenyl-2-Naphthylamine	333
o-Phenylphenol	301
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Gavage)	244
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Feed)	398
Polysorbate 80 (Glycol)	415
Polyvinyl Alcohol	474
Primidone	476
Probenecid	395
Promethazine Hydrochloride	425
Propylene	272
Propylene Glycol Mono-*t*-butyl Ether	515
1,2-Propylene Oxide	267
Propyl Gallate	240
Pyridine	470
Quercetin	409
Riddelliine	508
Resorcinol	403
Rhodamine 6G	364
Rotenone	320
Roxarsone	345
Salicylazosulfapyridine	457
Scopolamine Hydrobromide Trihydrate	445
Sodium Azide	389
Sodium Fluoride	393
Sodium Nitrite	495
Sodium Xylenesulfonate	464
Stannous Chloride	231
Stoddard Solvent IIC	519
Succinic Anhydride	373
Talc	421
Tara Gum	224
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Dermal)	201
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Gavage)	209
1,1,1,2-Tetrachloroethane	237
Tetrachloroethylene	311
Tetracycline Hydrochloride	344
Tetrafluoroethylene	450
1-Trans-Delta^9-Tetrahydrocannabinol	446
Tetrahydrofuran	475
Tetrakis(Hydroxymethyl)Phosphonium Sulfate	296
Tetrakis(Hydroxymethyl)Phosphonium Chloride	296
Tetranitromethane	386
Theophylline	473
4,4-Thiobis(6-*t*-Butyl-*m*-Cresol)	435
Titanocene Dichloride	399
Toluene	371

Chemical	TR No.
2,4- & 2,6-Toluene Diisocyanate	251
Triamterene	420
Tribromomethane	350
Trichloroethylene	243
Trichloroethylene	273
1,2,3-Trichloropropane	384
Tricresyl Phosphate	433
Triethanolamine	449
Triethanolamine	518
Tris(2-Chloroethyl) Phosphate	391
Tris(2-Ethylhexyl) Phosphate	274
Turmeric Oleoresin (Curcumin)	427
Urethane, Ethanol, and Urethane/Ethanol	510
Vanadium Pentoxide	507
4-Vinylcyclohexene	303
4-Vinyl-1-Cyclohexene Diepoxide	362
Vinylidene Chloride	228
Vinyl Toluene	375
Xylenes (Mixed)	327
2,6-Xylidine	278
Zearalenone	235
Ziram	238